sciendo

ISSN 1820-8665

Vol. 22· No3· SEPTEMBER 2021

Serbian Journal of Experimental and Clinical Research

2000

Vol. 22 (3) 2021

Serbian Journal of Experimental and Clinical Research

2000

Print

Faculty of Medical Sciences, University of Kragujevac

Indexed in

EMBASE/Excerpta Medica, Index Copernicus, BioMedWorld, KoBSON, SCIndeks, Chemical Abstracts Service, Cabell's Directory, Celdes, CNKI Scholar (China National Knowledge Infrastructure), CNPIEC, EBSCO Discovery Service, Elsevier - SCOPUS, Google Scholar, J-Gate, Naviga (Softweco), Primo Central (ExLibris), ReadCube, SCImago (SJR), Summon (Serials Solutions/ProQuest), TDOne (TDNet), WorldCat (OCLC)

Address:

Serbian Journal of Experimental and Clinical Research, Faculty of Medical Sciences,
University of Kragujevac 69 Svetozara Markovica Street, 34000 Kragujevac, PO Box 124
Serbia

https:/medf.kg.ac.rs/sjecr

SJECR is published four times annually

Serbian Journal of Experimental and Clinical Research is categorized as a scientific journal of M51 category by the Ministry of Education, Science and Technological Development of the Republic of Serbia

ISSN 1820 8665

TABLE OF CONTENTS

PHYTOCHEMICAL AND PHARMACOLOGICAL PROPERTIES OF SOME SPECIES OF THE GENUS *GALIUM L. (GALIUM VERUM AND MOLLUGO)*

Jovana Bradic[1], Anica Petkovic[1] and Marina Tomovic[1]
[1] University of Kragujevac, Faculty of Medical Sciences, Department of Pharmacy, Kragujevac, Serbia

FITOHEMIJSKE I FARMAKOLOŠKE KARAKTERISTIKE NEKIH VRSTA IZ RODA *GALIUM L.* (BELO I ŽUTO IVANJSKO CVEĆE)

Jovana Bradić[1], Anica Petković[1] i Marina Tomović[1]
[1] Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Katedra za farmaciju, Kragujevac, Srbija

Received / Primljen: 10. 10. 2017. Accepted / Prihvaćen: 29. 10. 2017.

ABSTRACT

Galium verum L. and Galium mollugo L. are perennial herbaceous plants, belonging to the Rubiaceae family. Several classes of bioactive compounds, such as iridoid glycosides, phenolic compounds, anthraquinones and triterpenes, as well as small amounts of tannins, saponins, essential oils have been isolated from Galium species so far. Plants belonging to this genus have a long history of use in a traditional medicine for the treatment of many diseases and conditions. The main application of G. verum is as diuretic, choleretic and as the treatment for gout and epilepsy. On the other hand, G. mollugo has been used to treat hysteria, epilepsy, as vulnerary. Over the past decades, numerous papers have been published referring to the chemical constituents presented in G. verum and G. mollugo extracts. Additionally, chemical composition and pharmacological effects of G. verum have been investigated, however data related to the effects of G. mollugo is limited. In this review, we summarized the current knowledge on the phytochemical and pharmacological properties of G. verum and G. mollugo. Finally, we proposed directions for future research in this field, which can improve our understanding of the potential health benefits of Galium species.

Keywords: *Galium verum, Galium mollugo, biological activity, chemical composition*

SAŽETAK

Belo i žuto ivanjsko cveće su višegodišnje zeljaste biljke koje pripadaju porodici Rubiaceae. Do sada je iz roda Galium izolovano nekoliko vrsta bioaktivnih jedinjenja, kao što su iridoidni glikozidi, fenolna jedinjenja, antrahinoni, triterpeni, kao i male količine tanina, saponina i etarskih ulja. Biljne vrste iz ovog roda imaju dugu istoriju upotrebe u tradicionalnoj medicini u lečenju mnogih bolesti i stanja. Glavna primena belog ivanjskog cveća je kao diuretik, holeretik i u lečenju gihta i epilepsije. S druge strane, žuto ivanjsko cveće se koristi u lečenju epilepsije i histerije, za zarastanje rana. Tokom proteklih decenija objavljeni su brojni radovi koji se odnose na hemijska jedinjenja prisutna u ekstraktima žutog i belog ivanjskog cveća. Dodatno, hemijski sastav i farmakološki efekti belog ivanjskog cveća su proučavani, dok su podaci o efektima žutog ivanjskog cveća ograničeni. U ovom preglednom radu smo rezimirali trenutna saznanja o farmakološkim i fitohemijskim karakteristikama žutog i belog ivanjskog cveća. Konačno, predložili smo smernice za buduća istraživanja u ovoj oblasti, koja bi mogla poboljšati naše razumevanje potencijalnih zdravstvenih koristi roda Galium.

Ključne reči: *belo ivanjsko cveće, žuto ivanjsko cveće, biološka aktivnost, hemijski sastav*

INTRODUCTION

Galium genus belongs to the *Rubiaceae* family and comprises about 400 herbaceous plant species, 145 of which are distributed in Europe (1). Furthermore there are 37 species from *Galium* genus distributed in Serbian flora (2). Among them, the herb Lady`s Bedstraw (*G. verum* L.) is renowned for the most frequent use in traditional medicine (3). It is common throughout Europe, North Africa and Asia, tropical Asia and Europe, but it can occur in southern Canada and northern U.S. In addition, *G. mollugo* (hedge bedstraw or false baby's breath) is widely distributed in Europe and North Africa and it is naturalized in the Russian Far East, New Zealand, Norfolk Island and much of North America (4).

sciendo
UDK: 582.925.3:582.192
615.322:582.925.3
Ser J Exp Clin Res 2021; 22 (3): 187-193
DOI: 10.1515/sjecr-2017-0057

Corresponding author:
Assistant Professor Marina Tomovic, Ph.D.
Department of Pharmacy, Faculty of Medical Sciences,
University of Kragujevac,
Svetozara Markovica 69, 34 000 Kragujevac, Serbia
Phone: +381 64 14 14 910, Fax: +381 34 306800/ext 112;
E-mail: marinapop@gmail.com

Descripiton

G. verum L. is a perennial herbaceous plant, with elongated stems growing to 60-120 cm. Leaves are glossy and dark green, while flowers are golden yellow, grouped in many-flowered panicles. The aerial parts of this plant are collected during dry and sunny days of the blooming period. Its golden yellow *flowers* are present from *June* to *September.* It occurs at elevations between sea level and 2.600 m, at mountain meadows and temperate grasslands.

Galium mollugo L. is a perennial herb, with the stems growing to 15–100 cm, with bright green leaves and white to greenish white flowers. The *flowering* period extends from May to *September and arterial parts are collected during dry and sunny days of the blooming period (2-4).*

Since both *G. verum* and *G. mollugo* have a perennial habit they can be easily confused. What make them differ are stems, which are thinner and firmer in case of *G. verum*, while the panicles in *G. mollugo* are looser, almost leafless (4).

Chemical constituents

Several kinds of bioactive compounds have been isolated from *Galium* species so far. Previous phytochemical investigations of the *G. verum* and *G. mollugo* species reported the presence of iridoid glycosides, phenolic compounds, anthraquinones and triterpenes, as well as small amounts of tannins, saponins, essential oils, waxes, pigments and vitamin C (3).

Iridoids

It's been known that both *G. verum and G. mollugo* are rich in iridoids (Table 1). Secogalioside is marked as an important chemotaxonomic marker of the *G. mollugo* group (1).

Table 1. Iridoids in *G. verum* and *G. mollugo* species

Chemical name	Source *G. verum* References	Source *G. mollugo* References
Asperuloside	*Bojthe-Horvath K et al* [5,6] *Demïrezer* [7]	*Mitova MI*[1] *Iavarone C*[8] *Uesato S*[9]
Monotropein	*Bojthe-Horvath K et al* [5,6] *Demïrezer LO* [7]	*Mitova MI*[1] *Iavarone C*[8] *Uesato S*[9]
Scandoside	*Bojthe-Horvath K et al* [5,6]	*Iavarone C*[8] *Uesato S*[9]
Geniposidic acid	*Bojthe-Horvath K et al* [5,6]	*Uesato S*[9]
Deacetylasperulosidic acid	*Bojthe-Horvath K et al* [5,6] *Demïrezer LO*[7]	*Mitova MI*[1]
Asperulosidic acid	*Bojthe-Horvath K et al* [5,6] *Demirezer LO*[7]	*Mitova MI*[1] *Iavarone C*[8] *Uesato S*[9]
6-o-epi-acetylscandosid	*Demirezer LO*[7]	*Nf*
Daphylloside	*Demirezer LO*[7]	*Nf*
Apigenine glycosides	*Mitova MI*[1]	*Mitova MI*[1]
Luteoline glycosides	*Mitova MI*[1]	*Mitova MI*[1]
Diosmetin glycosides	*Mitova MI*[1]	*Mitova MI*[1]
Deacetyl-daphylloside	*Demirezer LO*[7]	*Nf*
6-O-epi-acetylscandosid	*Demirezer LO*[7]	*Nf*
Loganin	*Mitova MI*[1]	*Iavarone C*[8]
Secogaliosid	*Mitova MI*[1]	*Uesato S*[9]
6-acetylscandoside	*Mitova MI*[1]	*Mitova MI*[1] *Iavarone C*[8]
Galioside	*Nf*	*Mitova MI*[1] *Uesato S*[9]
Mollugoside	*Nf*	*Mitova MI*[1]
Secogalioside	*Nf*	*Mitova MI*[1] *Uesato S*[9]
Gardenosidic acid	*Nf*	*Uesato S*[9]
Scandoside methyl ester	*Nf*	*Iavarone C*[8] *Uesato S*[9]
Daphylloside	*Nf*	*Iavarone C*[8] *Uesato S*[9]
10-hydroxymorroniside	*Nf*	*Uesato S*[9]
10-hydroxyloganin	*Nf*	*Iavarone C*[8]

**Nf*-not found so far

Table 2. Phenolic compounds in *G. verum* and *G. mollugo* species

Chemical name	Source *G. verum* References	Source *G. mollugo* References
Isorhamnetin	*Zhao C et al*[10,11] *Matei AO et al* [12]	*Nf*
Isorhamnetin 3-O-α-L-rhamnopyranosyl-(1–6)-β-D-glucopyranoside	*Zhao C et al*[10,11]	*Nf*
Kaempferol	*Zhao C et al*[10,11] *Vlase L*[15]	*Nf*
Quercetin	*Zhao C et al*[10,11]	*Nf*
Diosmetin	*Zhao C et al*[10,11]	*Nf*
Diosmetin 7-O-β-D-glucopyranoside	*Zhao C et al*[10,11]	*Nf*
Diosmetin 7-O-β-D-xylopyranosyl-(1–6)-β-D-glucopyranoside	*Zhao C et al*[10,11]	*Nf*
Diosmetin 7-O-α-L-rhamnopyranosyl-(1-2)-[β-d-xylopyranosyl-(1-6)]-β-d-glucopyranoside	*Zhao C et al*[10,11]	*Nf*
3,5,7,3′,4′,3″,5″,7″,3‴,4‴-decahydroxyl-[8-CH(2)-8″]-biflavone	*Zhao C et al*[10,11]	*Nf*
Quercetin	*Matei AO et al*[12] *Vlase L et al*[15]	*Vlase L et al*[15] *Matei AO et al*[12]
Quercetin-3-O-β-D-glucopyranoside	*Zhao C et al*[11]	*Nf*
Fisetin	*Matei AO et al*[12]	*Nf*
Chrysin	*Matei AO et al*[12]	*Nf*
Catechin	*Matei AO et al*[12]	*Nf*
Epicatechin	*Matei AO et al*[12]	*Nf*
Coumaric acid	*Matei AO et al*[12] *Vlase L et al*[15]	*Vlase L et al*[15]
Ferulic acid	*Matei AO et al*[12] *Vlase L et al*[15]	*Vlase L et al*[16]
Hesperidin	*Matei AO et al*[12]	*Nf*
Astragalin	*Demirezer LO*[7] *Tamas M*[13]	*Demirezer LO*[7] *Tamas M*[13]
Rutin	*Demirezer LO*[7] *Matei AO et al*[12] *Tamas M*[13] *Vlase L*[15]	*Tamas M*[13] *Vlase L*[15]
Hyperozide	*Tamas M*[13]	*Tamas M*[13]
Rutoside	*Tamaș M et al*[13]	*Tamaș M et al*[13]
Hispidulin	*Mocan A et al*[14]	*Mocan A et al*[14]
Chlorogenic acid	*Matei AO et al*[11] *Tamas M*[13] *Mocan A et al*[14]	*Tamas M*[13] *Mocan A et al*[14]
Caffeic acid	*Matei AO et al*[12] *Tamas M*[13] *Mocan A et al*[14]	*Tamas M*[13] *Mocan A et al*[14] *Vlase L*[15]
Luteoline	*Nf*	*Vlase L*[15]
Chalcone	*Shafaghat A*[16]	*Nf*

Phenolic compounds

Phytochemical investigation of *G. verum L.* has led to the isolation of several phenolic compounds in *G. verum* and *G. mollugo* extracts (Table 2). Chemical analysis of ethanolic extracts [30, 50 and 70% (w/v)] of *G. verum* was observed and the results indicate that concentration of certain phenolic depends on the solvent (12). Qualitative differences in the flavonoid fractions between *G. verum* and *G. molugo* species exist, suggesting that the content of the flavonoids is about three times higher in *G. verum* (13). Regarding the amount of phenolics obtained by different extraction techniques (maceration, reflux and ultrasonic extraction), it was shown that the highest amount of phenolics from *G. mollugo* extracts has been obtained by the reflux extraction. Authors explained this fact by oxidation and degradation of some bioactive compounds during sonication of the aqueous solution. In addition, increased solubility of phenols and flavonoids in the extracting solvent at higher extraction temperatures may be an explanation for such composition of the extracts (17).

Terpenes and anthraquinones

Data suggests the presence of triterpenic saponins in *Gallium* species (18). However there is a lack of data referring to the amount of terpens in *G. verum* or *G. mollugo*. Two monoterpene glycosides, such as betulalbuside A and (2E)-2,6-dimethyl-2,7-octadien-1,6-diol-6-O-β-glucopyranoside were isolated from the aerial parts of *G.verum* (7). In the ethanolic extract of *G. verum* L 1,3-dihydroxy-2-methylanthraquinone, physcion, 2-hydroxy-1,3dimethoxyanthraquinone and 2,5-dihydroxy-1,3-dimethoxyanthraquinone were identified (19). It's been shown that anthraquinones are located in the vacuole of *G. mollugo* (20). In addition, anthraquinones production from *G. verum* lines of calus was proven as well (21). Unfortunately, data regarding the presense of anthraquinones and triterpenes in this *Galium* species is limited, thus suggesting that they are probably present in a smaller quantities compared to other bioactive compounds.

Mineral composition

A significant chemical compounds identified in white lady's bedstraw are certainly minerals such as potassium, calcium and magnesium (22, 23). Study which examined mineral composition of the extracts of *G. mollugo* flowers obtained by maceration, extraction under reflux and ultrasonic extraction, using *atomic absorption spectrometry, suggested that t*he *highest calcium and magnesium yield* could be *achieved* at the *ultrasonic extraction, while type of extraction didn't affect K yield (23).*

Phytosterols

Phytosterols, known as plant sterols structurally similar to cholesterol, may also be found in *Galium* species. It's been reported that *G. mollugo* was richer in β-sitosterol (19.02 ± 7.24 μg/g) and campesterol (15±0.08 μg/g) than *G. verum* (85.46 ± 1.24 μg/g for β-sitosterol and 9.86 ± 0.04 μg/g for campesterol) (14).

Essential oil

Essential oil obtained by hydro-distillation from the aerial parts of *G. verum* contains ß-caryophyllane, caryophyllene oxide, germacrene D, terpinene, benzyl alcohol, squalene and cis-3-Hexen-l-ol (24, 25). On the other hand, essential oil from the aerial parts of *G. mollugo* is yellow-green oil which was rich in palmetic acid, tetradecanal and ethyl linoleolate (26).

***G. verum* and *G. mollugo* usage**

Galium species have been traditionally used for the treatment of many diseases and conditions. Furthermore they are renowned for its usage in milk coagulation due to an enzyme in their chemical composition and that's the reason for knowing this plant as "Yogurt herb" (3, 14, 27). In Scotland the plant is still used in cheese manufacturing. Since the coumarin scent of the plants acted as a flea killer, dried plants were widely used to stuff mattresses (3, 27). Furthermore, *G. verum* may serve as a food additive and yellow and red pigments presented in its aerial parts and roots allow usage of this plant in dyeing (10). However there is a limited number of studies which examined the effects of *G. verum* and *G. mollugo* extracts both in animal models and humans.

Pharmacological effects of *G. verum* and *G. mollugo*

Studies which evaluated the effects of *Galium* species predominantly were conducted in Asian people. This is expected since traditional medicine is more present in their culture and everyday life compared to Europe and USA continents (27). *G. verum* has been studied both chemically and pharmacologically, however there is a little data related to the effects of *Galium mollugo* (17).

Anticancer effects

Recommendations for using *G. verum* in the treatment of tongue cancer are supported by the reports of patients with tongue and larynx carcinome successfully treated with the tea of this plant. *G. verum* decoction was proved to inhibit the chemo-sensitive and -resistant laryngeal carcinoma cell lines growth, thus suggesting its possible concomitant therapeutic use for oral or head and neck cancer (27). *Hartwells'* survey indicate that *G.verum* has been traditionally used in Europe and Northern America for the treatment of cancerous ulcers or breast cancer (28). In support of that, there is a data that its ethanolic extract may inhibit the proliferation of human breast cancer cells and induce cell death by apoptosis. Furthermore diosmetin, a flavon, extracted from the traditional Chinese herb *G. verum* L was tested on cervical cell lines and it was shown that it inhibit the tumor growth and protect tumor-induced apoptosis of thymus (29). To our knowledge there are no studies which proved anticancer effects of *G. mollugo* species.

Effects on central nervous system

The aerial parts of *G. verum* were traditionally used as sedative (3, 30, 31) and that was confirmed by an ethnobotanical study on the usage of wild medicinal herbs from Central Serbia (32). It's been proposed that chemical compounds such as iridioides (asperuloside) are responsible for sedative effects of *Galium* species (31). Upper herbaceous parts of *G. verum* have been renowned for beneficial effects on nervousness and phobias (3). Furthemore, both *G. verum* and *G. mollugo* species have been used in traditional medicine in the treatment of epilepsy and hysteria (14, 33, 34). There is an evidence that *G. mollugo* is used as a nerve relaxant (34). Hispidulin, which is proven benzodiazepine

receptor ligand, was recently discovered in some *Galium* species and may be responsible for the anticonvulsive effects of these plants (15, 35).

Effects on gastrointestinal, renal, hepatobiliary and urinary system

G. verum tea has diuretic effect and it may contribute to the cure of pyelitis or cystitis (14, 30, 33). It is effective in cases of bladder and kidney irritation, kidney stones and as anticolic as well (33, 36). *G. verum* may be used as spasmolytic, against diarrhea and in the treatment of some stomach complaints (3, 14, 17). In addition, upper herbaceous parts of *G. verum* exert effects on liver disorders and acts as choleretics and cholagogue (3, 7). In China it has been used to treat hepatitis (37). There is little data about the pharmacological effects of *G. mollugo* on the function of these systems, but taking into consideration similar chemical composition, we may assume that this species exert similar activity to *G. verum.*

Other pharmacological effects

It's been reported that both *G. verum* and *G. mollugo* may be useful in the treatment of skin disorders, exogenous treatment of psoriasis or wound healing (3, 27, 32). In addition *G. verum* is effective as diaphoretic and depurative, while *G. mollugo* as antiscorbutic (3, 30, 34). Among various therapeutic properties of these species, *G. verum* herba has beneficial effects on cardiovascular diseases, treatment of gout and rheumatic diseases in folk medicine (3, 17). *Galium verum* extract applied to the animals exposed to anakinetic stress led to a significant stimulation of secretory activity of thyroid and ovary, and to an increase in adrenal and glucocorticoid hormone synthesis (31, 38).

Antioxidant activity

There is an evidence that plants from *Gallium* genus possess natural antioxidants. Extracts from aerial parts of *G. verum* express very strong scavenger activity in a dose dependant manner. That antioxidant activity was determined via the neutralization of 2,2-diphenyl-1-pycrylhydrazyl (DPPH) radicals, hydroxyl (OH^-) radicals, hydrogen peroxide (H_2O_2) and inhibition of lipid peroxidation (3). These results are confirmed by several authors, thus qualifying *G. verum* as a promising natural source of antioxidants (15, 30, 39). Other researchers revealed that methanol extract had greater antioxidant activity than its water extract, while examining *G. verum* aqueous and methanolic extracts in the range 50-500 mg/L (39). Furthermore there was an investigation reporting that compounds found in methanol extract of *G. verum* exerted riboflavin-originated superoxide and xanthine-originated superoxide quenching activities (40). By comparing the antioxidant potential of different extracts, such as aqueous, 30%, 50% and 70% alcoholic, it was noticed that the highest potential may be expected from 50% alcoholic *G. verum* extract (41). Methanolic extract of *G. verum* exerted great antioxidant potential in tested models which included DPPH and nitric oxide radical scavenging, reducing power and H_2O_2 scavenging (42).

Antioxidant activity of aqueous-ethanolic *G. mollugo* extracts was revealed as well. It's important to emphasize that the activity was changing dependently of the extraction technique applied, where extracts obtained by extraction with reflux showed the best antioxidant activity (17). There is a data referring to the antioxidant potential of *G. mollugo* tested and proven by ferric ion reducing antioxidant power (FRAP) and trolox equivalent antioxidant capacity (TEAC) assays (43). Another study which aimed to compare the antioxidant potential of four *Galium* species suggested that *G. verum* extract exhibited higher antioxidant capacity compared to *G. mollugo* extract (15). Phenolic compounds isolated from *G. mollugo* may protect human fibroblast cells against oxidative stress (44).

Antibacterial and antifungal activity

Galium species have been used in the folk medicine for the treatment of infectious diseases, however antimicrobial activity of these plants is poorly reported. It was shown that chloroform extract of *G. verum* express antibacterial activity in comparison to aqueous and alcohol (70%) extracts, which possess no activity. In addition, *Candida albicans* was generally insensitive to the extracts of this plant. Confirmed antimicrobial activity of *G. verum* predominantly refers to its efficiency against Gram-positive microorganisms and less efficiency in reference to Gram-negative strains (45). Other authors noticed that *G. verum* and *G. mollugo* extracts exhibited effects mainly against the Gram-positive bacteria (*S. aureus, L. monocytogenes*) and low activity against Gram-negative bacteria (*S. typhimurium, E. coli*). Ethanolic extracts of these two G. species showed a weak antifungal capacity against *C. albicans* (46). Furthermore neither chloroform nor methanolic extract of *G. verum* has inhibitory effect against both clinical and standard strains of *Candida* spp (47). It may be hypothesized that the lack of antifungal activity of these plants may be the consequence of the insufficient quantity of compounds responsible for that activity.

CONCLUSION

Numerous studies proved that *G. verum* and *G. mollugo* contain chemical compounds with high therapeutic potential, which may be pharmaceutically exploited. Despite the centuries of successful traditional use in the treatment of many diseases, the number of studies referring to the effects of *G. verum* and *G. mollugo* is limited. This review provides available evidence on these two plants and may help to those intending to research further on these topics. Further researches regarding the effects of *G. verum* and *G.*

mollugo are necessary to make them a possible candidate for medicinal product.

ACKNOWLEDGMENT

The authors would like to express gratitude to the Faculty of Medical Sciences, University of Kragujevac for Grant No. JP 06/17.

REFERENCES

1. Mitova MI, Anchev ME, Handjieva NV et al. Iridoid patterns in Galium L. and some phylogenetic considerations. Z Naturforsch C. 2002; 57:226-34.
2. M. Gajić. Flora of Serbia. Belgrade: Serbian Academy of Sciences and Arts; 1973.
3. Lakic N, Mimica-Dukic N, Isak J et al. Antioxidant properties of Galium verum L. (Rubiaceae) extracts. Cent Eur J Biol. 2010; 5:331-7.
4. Mersereau D, DiTommaso A. The biology of Canadian weeds. 121. Galium mollugo L. Can. J. Plant Sci.. 2002; 2:453-466.
5. Bojthe-Horvath K, Hetenyi F, Kocsis A et al. Iridoid glycosides from Galium verum. Phytochemistry. 1980; 21-2917-2919.
6. Bojthe-Horvath K, Kocsis A, Parkany L et al. A new iridoid glycoside from Galium verum L. First X-ray analysis of a tricyclic iridoid glycoside. Tetrahedron Lett. 1982; 23- 965-966.
7. Demirezer LO, Gurbuz F, Guvenalp Z et al. Iridoids, flavonoids and monoterpene glycosides from Galium verum subsp. verum. Turk J Chem. 2006; 30- 525-534.
8. Iavarone C, Sen A, Trogole C et al. Mollugoside, an iridoid glucoside from Galium mollugo. Phytochemistry. 1983; 22:175-178.
9. Uesato S, Ueda M, Inouye H et al. Iridoids from Galium mollugo. Phytochemistry. 1984; 23:2535-2537.
10. Zhao C, Shao J, Li X et al. Flavonoids from Galium verum L. J Asian Nat Prod Res. 2008; 10:613-617.
11. Zhao C, Shao J, Cao D et al. Chemical constituents of Galium verum. Zhongguo Zhong Yao Za Zhi. 2009; 34:2761-2764.
12. Matei AO, Gatea F, Radu GL. Analysis of Phenolic Compounds in Some Medicinal Herbs by LC-MS. J Chromatogr Sci. 2015; 53:1147-1154.
13. Tamaș M, Stana D, Timiș S. Comparative phytochemical research of Galium verum L. and G. mollugo L. Not. Bot. Hort. Agrobot. Cluj. 2006; 34:18-20.
14. Mocan A, Gianina C, Laurian V et al. Phytochemical investigations on four Galium species (Rubiaceae) from Romania. Farmacia. 2016; 64:95-99.
15. Vlase L, Mocan A, Hanganu D. Comparative study of polyphenolic content, antioxidant and antimicrobial activity of four Galium species (Rubiaceae). Dig J Nanomater Biostruct. 2014; 9:1085-1094.
16. Shafaghat A, Salimi F, Aslaniyan N et al. Flavonoids and an ester derivative isolated from Galium verum L. World Appl Sci J. 2010; 11:473-477.
17. Milic PS, Stanojevic LP, Rajkovic KM. Antioxidant activity of Galium mollugo L. extracts obtained by different recovery techniques. Hem Ind. 2013; 67:89-94
18. de Rosa S, Iodice C, Mitova M et al. Triterpene saponins and iridoid glucosides from Galium rivale. Phytochemistry. 2000; 54:751-756.
19. Zhao CC, Shao JH, Li X et al. A new anthraquinone from Galium verum L. Nat Prod Res. 2006; 20:981-984.
20. Heide L, Leistner E. Enzyme activities in extracts of anthraquinone-containing cells of Galium mollugo. Phytochem. 1983; 22:659-662.
21. Banthorpe DV, White JJ. Novel anthraquinones from undifferentiated cell cultures of Galium verum. Phytochemistry. 1995; 38:107-111.
22. Milic PS, Bekric DM, Milic SM et al. A study of the extraction kinetics of the minerals from the white lady's bedstraw (Galium mollugo L.) by using an artificial neural network. Hem Ind. 2011; 65:313-321.
23. Milic PS, Rajkovic KM, Milicevic PM et al. Comparison, artificial neural network modeling and genetic algorithm optimization of the resinoid and potassium yields from white lady's bedstraw (Galium mollugo L.) by conventional, reflux and ultrasound-assisted aqueous-ethanolic extraction. Chem. In. Chem. Eng. Q. 2013; 19:141-152.
24. Mirzam M, Navaei MN, Dini M. Essential oil of Galium verum L. from Iran. Iran J Pharm Res. 2004; 3: 88-88.
25. Il'ina TV, Kovaleva AM, Goryachaya OV et al. Essential oil from Galium verum flowers. Chem Nat Compd. 2009; 45:587-588.
26. Ramdani M, Lograda T, Chalard P et al. Chemical composition of essential oils of Galium tunetanum Poiret and Galium mollugo L. in Algeria. Int. J. Med. Arom. Plants. 2013; 3:362-65
27. Schmidt M, Scholz CJ, Gavril GL et al. Effect of Galium verum aqueous extract on growth, motility and gene expression in drug-sensitive and -resistant laryngeal carcinoma cell lines. Int J Oncol. 2014; 44:745-60.
28. Hartwell JL. Plants used against cancer. A survey. Lloydia. 1971; 34:204-55.
29. Zhao R, Chen Z, Jia G et al. Protective effects of diosmetin extracted from Galium verum L. on the thymus of U14-bearing mice. Can J Physiol Pharmacol. 2011; 89:665-73.
30. Mitic VD, Stankov-Jovanovic VP, Ilic MD et al. The antioxidant, hemolytic and cholinesterase inhibition properties of Galium verum L. and Tragopogon pratensis subsp pratensis. Bulg Chem Commun. 2014; 46:269-276.
31. Roman I, Toma VA, Farcas AD. Protective effects of Galium verum L. extract on the hypothalamic--pituitary--adrenal axis under anakinetic stress conditions, in rats. histological aspects. Studia Universitatis Vasile Goldis Seria Stiintele Vietii (Life Sciences Series). 2015; 25:207-14

32. Jaric S, Popović Z, Macukanović-Jocic M et al. An ethnobotanical study on the usage of wild medicinal herbs from Kopaonik Mountain (Central Serbia). J Ethnopharmacol. 2007; 20:160-75.
33. Menkovic N, Savikin K, Tasic S et al. Ethnobotanical study on traditional uses of wild medicinal plants in Prokletije Mountains (Montenegro). J Ethnopharmacol. 2011; 133:97–107.
34. Popovic Z, Smiljanic M, Kostic M et al. Wild flora and its usage in traditional phytotherapy (Deliblato Sands, Serbia, South East Europe). Indian J Tradit Know. 2014; 13:9-35
35. Kavvadias D, Sand P, Youdim KA et al. The flavone hispidulin, a benzodiazepine receptor ligand with positive allosteric properties, traverses the blood-brain barrier and exhibits anticonvulsive effects. Br. J. Pharmacol. 2004; 142:811-20.
36. Al-Douri NA. A survey of medicinal plants and their traditional uses in Iraq. Pharm Biol. 2000; 38:74-9. ·
37. Bolivar P, Cruz-Paredes C, Hernandez LR et al. Antimicrobial, anti-inflammatory, antiparasitic, and cytotoxic activities of Galium mexicanum. J Ethnopharmacol. 2011; 137:141-7.
38. Roman I, Puica C. Effects of Anakinetic Stress and Galium verum Extract on the Thyroid and Ovary Morphology in Wistar Rats. Bulletin UASVM. 2013; 70:167-69.
39. Mavi A, Terzi Z, Ozgen U et al. Antioxidant properties of some medicinal plants: Prangos ferulacea (Apiaceae), Sedum sempervivoides (Crassulaceae), Malva neglecta (Malvaceae), Cruciata taurica (Rubiaceae), Rosa pimpinellifolia (Rosaceae), Galium verum subsp. verum (Rubiaceae), Urtica dioica (Urticaceae). Biol Pharm Bull. 2004; 27:702-5.
40. Kim DK. Superoxide Quenching Activity of Phenolic Compounds from the Whole Plant of Galium verum var. asiaticum. Nat Prod Sci. 2011; 17:261-66.
41. Danila AO, Gatea F and Radu GL. Polyphenol composition and antioxidant activity of selected medicinal herbs. Chem Nat Compd. 2011; 47(1): 22-26.
42. Layali I, Ebrahimzadeh MA, Joulaei M. Antioxidant properties of Galium verum. Int. J. Life Sci. Pharma Rres.. 2016; 6:31-37.
43. Csepregi R, Bencsik T, Papp N. Examination of secondary metabolites and antioxidant capacity of Anthyllis vulneraria, Fuchsia sp., Galium mollugo and Veronica beccabunga. Acta Biol Hung. 2016; 67:442-446.
44. Chaher N, Krisa S, Delaunay JC et al. Unusual compounds from Galium mollugo and their inhibitory activities against ROS generation in human fibroblasts. J Pharm Biomed Anal. 2016; 117:79-84.
45. Vasilevna IT, Volodymyrivna GO, Leonidivna TE et al. Antimicrobial Activity of the Genus Galium L. Pharmacogn. Commn. 2016; 6:42-47.
46. Ergun F, Deliorman D, Veliog IA et al. Antimicrobial activities of Galium species. J Fac Pharm Gazi. 199; 16-7–11
47. Yigit D, Yigit N, Ozgen U. An investigation on the anticandidal activity of some traditional medicinal plants in Turkey. Mycoses. 2009; 52:135-40.

GENDER DIFFERENCES IN HEALTH CARE UTILIZATION AMONG THE ELDERLY

Gordana Gajovic[1], Katarina Janicijevic[2], Dragana Andric[3], Olivera Djurovic[4] and Svetlana Radevic[2]
[1] *Health Center Arandjelovac, Serbia*
[2] *University of Kragujevac, Faculty of Medical Sciences, Department of Social medicine, Kragujevac, Serbia*
[3] *Department for organization, planning, evaluation and medical informatics, Clinical Center Kragujevac, Kragujevac, Serbia*
[4] *Special Hospital for Cerebrovascular Diseases "Sveti Sava", Belgrade, Serbia*

RODNE RAZLIKE U KORIŠĆENJU ZDRAVSTVENE ZAŠTITE MEĐU STARIJIM OSOBAMA

Gordana Gajović[1], Katarina Janićijević[2], Dragana Andrić[3], Olivera Đurović[4] i Svetlana Radević[2]
[1] *Zdravstveni centar Aranđelovac, Srbija*
[2] *Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Katedra za Socijalnu medicinu, Kragujevac, Srbija*
[3] *Služba za organizaciju, planiranje, evaluaciju i medicinsku informatiku, Klinički centar Kragujevac, Srbija*
[4] *Specijalna bolnica za cerebrovaskularne bolesti „Sveti Sava, Beograd, Srbija*

Received/Primljen: 11.02.2019. Accepted/Prihvaćen: 26.02.2019.

ABSTRACT

The unstoppable process of demographic aging of population has profound consequences on the economic, health, social and political spheres of society, because of the specific and diverse needs of the older population. The aim of the study was to examine gender differences of health care utilization among elderly in Serbia. The survey was conducted as a part of the national study "Health Survey of the Serbian population" in 2013. In the past year, 87.4% of the older population visited their chosen doctor. Women were significantly more likely to use primary health care compared to men, while the frequency of hospitalization is significantly higher in men. When it comes to female population, age, region of residence and financial situation stood out as the most important predictors of primary care services usage. In men, the residence stood out as the most important predictor of primary health care services usage. Multivariate binary logistic regression distinguishes gender, education and region of residence as the most important factors associated with hospital treatment.

Keywords: *elderly adults; gender; health care utilization; national health survey.*

SAŽETAK

Nezaustavljiv proces demografskog starenja stanovništva ima duboke posledice na ekonomsku, zdravstvenu, socijalnu i političku sferu društva zbog specifičnih i raznovrsnih potreba starog stanovništva. Cilj studije je bio da se ispitaju rodne razlike u korišćenju zdravstvene zaštite kod starijih osoba u Srbiji. Istraživanje je sprovedeno kao deo nacionalne studije „Istraživanje zdravlja stanovništva Srbije" 2013. godine. U poslednjih godinu dana 87,4% starog stanovništva je posetilo svog izabranog lekara. Žene značajno češće koriste usluge primarne zdravstvene zaštite u odnosu na muškarce, dok je učestalost hospitalizacija značajno veća kod muškaraca. Kada je u pitanju ženska populacija, kao najznačajniji prediktori korišćenja usluga primarne zdravstvene zaštite izdvajaju se godine starosti, regija stanovanja i materijalno stanje. Kod muškaraca se kao najvažniji prediktor korišćenja primarne zdravstvene zaštite izdvaja mesto stanovanja. Multivarijantna binarna logistička regresija kao najvažnije faktore koji su povezani sa bolničkim lečenjem izdvaja pol, stepen obrazovanja i regiju stanovanja.

Ključne reči: *stare osobe; rod; korišćene zdravstvene zaštite; nacionalno istraživanje zdravlja.*

sciendo
UDK: 614.2-053.9(497.11)
Ser J Exp Clin Res 2021; 22 (3): 195-203
DOI: 10.2478/sjecr-2019-0006

Corresponding author:
Svetlana Radevic, M.D., Ph.D.
Department of Social Medicine
Faculty of Medical Sciences University of Kragujevac, Serbia
Svetozara Markovica 69, 34000 Kragujevac, Serbia
E-mail: cecaradevic@yahoo.com
Tel: +381 34 306 800 ext 217
Fax: + 381 34 306 800

INTRODUCTION

The aging population is one of the biggest challenges that the world faces in the XXI century. Persons older than 65 already make up to 15% of the population in the developed countries and, according to projections, by 2025 they will represent 19% to 26% of the total population (1). Serbia's population is getting older and, in particular, the increase of very old population (over 75) is very significant. With an average age of 42.2 years, an aging index of 1.22 and the share of aged 65 years and over of 17.4%, Serbia is among the demographically oldest countries in the world, according to the last census (2011). The process of demographic aging will intensify so that, according to demographic projections, the number of population older than 65 in Serbia until 2030 will amount to more than 21%, which represents every fifth resident (2).

The unstoppable process of demographic aging of population has profound consequences on the economic, health, social and political spheres of society, because of the specific and diverse needs of the older population (1). As a result of biological manifestations of the aging process, there is a gradual increase in the incidence of patients with a chronic diseases (cardiovascular diseases, diabetes, malignant diseases, etc.), wherein the elderly tend to have more joint diseases (multimorbidity) (3). Older age increases the number of functionally dependent and cognitively changed persons. Extensive health problems of old people lead to increasing pressure on the health service and increasing costs of their health care (4).

The usage of health services is primarily motivated by a disease of an individual, but the quality and quantity of health service usage vary significantly based on socio-economic factors such as income and health insurance status (5, 6). Elderly people in their consumption of health care services are not a homogeneous group, as they may be particularly exposed to many factors such as personal income and social inequalities (7).

Specifics of gender model of aging are primarily the result of the impact of a number of factors that act in certain social circumstances and in the specific social environment. Therefore, gender is considered an important determinant of health, which further shapes the patterns of exposure to health risk factors and morbidity, access to health care services and access to treatment (8).

The aim of the study was to examine gender differences of health care utilization among elderly in Serbia.

METHODS

Study population and sample

As the basis for the analysis of the characteristics of the Serbian population older than 65, we used data from the Third national population health survey conducted by interviewing a random, representative sample of the population of our country. The testing was performed as the cross-sectional study on the territory of the Republic of Serbia and it did not include the population living in the AP Kosovo and Metohija. The target population did not include persons living in collective households and in institutions. The survey was conducted in accordance with the methodology and instruments of the European Health Survey - Second Wave (EHIS-wave 2) (9). The study was implemented by the Ministry of Health of the Republic of Serbia.

The sample included all households listed in all enumeration areas in the census conducted in 2011. The mechanism used to obtain the random sampling of the respondents and households was a combination of two sampling techniques: stratification and a multi-stage sampling. A stratified two-stage sample of the population of the Republic of Serbia has been chosen in such a way to provide a statistically reliable assessment of the indicators that indicate the health status of the population at the national level, as well as at the level of 4 geographic areas (Vojvodina, Belgrade, Šumadija and Western Serbia, Southern and Eastern Serbia) identified as the main strata in the sample. Their further division into urban and rural areas resulted in a total of 8 strata. In the first stage, a total of 670 enumeration areas were selected. The households were the units of the second stage. Within each enumeration area, 10 addresses were selected (+3 spare addresses) inhabited by households to be interviewed. Out of the total of 10089 households contacted, 6500 of them agreed to participate in the survey, so that the response rate of households was 64.4%. Out of the total of 16474 registered household members aged over 15, 14623 of them agreed to be interviewed, giving a response rate of 88.9%. Out of the number of people who agreed to be interviewed, 13756 of them accepted to fill in the questionnaire (response rate 94.1%). Data on the population aged over 65 were used for the purposes of this study (3540 respondents).

Instruments

The survey instrument used in this survey was standardized questionnaire prepared in accordance with the questionnaire of the European health research - the second wave (European Health Interview Survey - EHIS wave 2), according to internationally accepted defined indicators. Information on demographic, socio-economic characteristics, self-reported health and utilization of health services of respondents was obtained through three types of questionnaires: household questionnaire, face-to-face questionnaire and self-completion questionnaire (self-administered questionnaire). Data collection was conducted by specially trained teams of interviewers. The data collection process was standardized to ensure data quality. Participation in the survey was voluntary, and respondents, along with a questionnaire, signed informed consent with the previously received information about the study.

The dependent variable in this study was health services utilization. Predisposing factors related to the basic

characteristics of the population included gender, age, education, marital status type of settlement, financial status and region.

Statistical analysis

All the data of interest were presented and analyzed by adequate statistical methods appropriate for the data type. The Chi-square test was used to compare proportions between groups. The relations between the health services utilization, as a dependent variable, and a set of independent variables was examined by univariate and multivariate logistic regressions. All results with the probability that is equal to, or less than 5% ($p \leq 0.05$) were considered statistically significant. Statistical analysis was performed using a commercial, standard software package SPSS, version 19.0. (The Statistical Package for Social Sciences software (SPSS Inc., version 19.0, Chicago, IL).

RESULTS

The study included 3540 respondents aged over 65. 94.7% of the population had a chosen general practitioner in public health institutions and 2.7% of respondents had a doctor in private health institutions. According to gender, women significantly more likely had a chosen doctor (95.6%), as compared to men (93.6%) (χ^2=6.861, df=1, p=0.009). When it comes to private health care sector, a slightly higher number of men had their general practitioners compared to women (3.1% vs. 2.3%). This difference is not statistically significant (χ^2=1.846, df=1, p=0.174).

In the past year, 87.4% of the older population visited their chosen doctor. Women were significantly more likely to use primary health care compared to men (88.9% vs. 85.5%). The number of services was greater in the urban population compared to the rural environment (88.7% versus 85.8%), as well as in the richer population compared to the poor social class (89.6% vs. 85.4%). In the last year, 57% of the elderly visited a specialist, out of which proportion of women was slightly higher (58.4%) than of men (55.2%) (Table 1).

Table 1. Distribution of respondents who visited their general practitioner in relation to demographic and socio-economic characteristics

chosen doctor visit	men (%)	women (%)	total (%)	p*
Gender	85.5	88.9	87.4	0.009
Age (years)				
65-74	84.8	91.0	88.3	
75-84	87.6	87.6	87.6	< 0.001
85+	70.4	78.7	76.1	
Education				
No schooling	89.9	88.7	89.3	
incomplete primary education	82.9	87.4	86.0	
elementary school	84.7	91.3	89.0	0.323
middle school	85.4	88.1	86.6	
high school or higher	87.4	88.8	87.4	
Marital status				
single	91.7	77.3	82.4	
married	85.5	90.4	87.6	0.319
widowed	84.1	87.7	86.8	
separated/divorced	91.2	93.3	92.6	
Place of residence				
Urban	87.2	89.8	88.7	0.013
Rural	83.2	87.8	85.8	
Well-being index				

chosen doctor visit	men (%)	women (%)	total (%)	p*
I (the poorest)	84.6	85.5	85.4	
II	86.5	85.1	87.9	
III	87.6	86.1	88.8	0.014
IV	89.0	87.2	90.6	
V (the richest)	88.5	87.1	89.6	
Region				
Vojvodina	86.6	88.4	87.6	
Belgrade	85.3	82.4	83.6	0.001
Šumadija and W. Serbia	83.8	91.7	88.2	
Southern and Eastern Serbia	86.2	92.8	89.9	

* Chi-square test

Results of univariate binary logistic regression showed that the usage of primary care services is under the influence of gender, age, financial status and place of residence. Multivariate logistic regression signifies gender, age and place of residence as the most important predictors of usage of primary health care services. Women more frequently use the services of the selected physician for 28.7% as compared to men (OR=0.713). The process of aging decreases the usage of primary health care services; every year of age reduces the usage of these services by 2.2% respectively (OR=0.978). Elderly people who live outside the city visited their chosen doctor by 29.4% less (OR=0.706), while those in the South area visited their chosen doctor 1.5 times more compared to those living in the North (OR=1.508) (Table 2).

Table 2. Cross Odds Ratio (OR) and 95% confidence intervals (CI) for usage of PHC services related to demographic and socio-economic characteristics

Variable	Univariate model		Multivariate model	
	OR	p	OR	p
age	0.981 (0.965 – 0.997)	0.018	0.978 (0.962 – 0.995)	0.009
male	0.729 (0.594 – 0.894)	0.002	0.713 (0,580 – 0,875)	0.001
material state	1.096 (1.015 – 1.184)	0.019		
southern region	1.382 (1.126 – 1.695)	0.002	1.508 (1.221 – 1.861)	< 0.001
rural settlements	0.768 (0.626 – 0.942)	0.011	0.706 (0.571 – 0.875)	0.001

When it comes to the female population, age, region of residence and financial situation stood out as the most important predictors of primary care services usage. The reduced usage of primary care services comes with the older age (OR=0.953). Women who lived in the Southern parts of Serbia, 1.9 times more frequently visited their doctors, compared to those living in the North (OR=1.938), and women who, according to the index of well-being, belong to the rich class of the population, 1.2 times more frequently visited a chosen doctor (OR=1.238).

In men, the residence stood out as the most important predictor of primary health care services usage, so those who lived in rural villages rarely visited their chosen doctors (OR=0.717) compared to those who lived in the city (Table 3).

Table 3. The cross ratios (OR) and 95% confidence intervals (CI) for primary health care services usage related to gender and socio-economic characteristics

Variable	Gender	Univariate model		Multivariate model	
		OR	p	OR	p
rural settlements	men	0.727 (0.542 – 0.975)	0.033	0.717 (0.522 – 0.984)	0.033
age	women	0.958 (0.937 – 0.979)	< 0.001	0.953 (0.930 – 0.975)	< 0.001
southern region	women	2.070 (1.544 – 2.775)	< 0.001	1.938 (1.398 -2.688)	< 0.001
material status	women	1.117 (1.001 – 1.245)	0.048	1.238 (1.085 – 1.413)	0.002

516 persons (14.6%) aged over 65 were hospitalized in the last 12 months. There is a statistically significant correlation between gender and hospitalization, but it is noted that the frequency of hospitalization is significantly higher in men (16.1%) than in women (13.4%) (χ^2=4.797 df =1 p=0.026).

The incidence of hospitalization was significantly higher in people with no schooling (19.1%) and with incomplete primary education (17.8%), especially in people with the lowest incomes (18.3%), who lived in Šumadija and Western Serbia (18.1%), as well as in population in the age group 75-84 (16.3%) (Table 4).

Table 4. Distribution of respondents who use hospital care related to demographic and socio-economic characteristics

hospital care	men (%)	women (%)	total (%)	p*
Age (years)				
65-74	15.9	11.7	13.6	
75-84	16.6	16.1	16.3	0.058
85+	14.1	11.8	12.5	
Education				
No schooling	23.5	18.8	19.1	
incomplete primary education	23.8	15.0	17.8	
elementary school	18.1	11.6	13.9	< 0.0005
middle school	13.6	12.1	13.0	
high school	12.0	9.9	11.3	
Marital status				
single	14.3	3.4	7.0	
married	15.7	12.9	14.5	0.071
widowed	16.9	14.0	14.7	
separated/divorced	21.1	15.9	17.8	
Place of residence				
Urban	14.0	13.3	13.6	0.410
Rural	18.5	13.6	15.8	
Well-being index				

hospital care	men (%)	women (%)	total (%)	p*
I (the poorest)	17.3	14.1	15.4	
II	15.7	14.0	14.7	
III	21.3	13.2	16.6	0.097
IV	12.7	11.3	11.9	
V (the richest)	10.1	13.8	12.1	
Region				
Vojvodina	10.6	13.3	12.2	
Belgrade	14.6	8.7	11.2	< 0.0005
Šumadija and W. Serbia	21.9	15.0	18.1	
Southern and Eastern Serbia	15.2	16.5	15.9	

Multivariate binary logistic regression distinguishes gender, education and region of residence as the most important factors associated with hospital treatment. Quotient of chance for males was 1.319, and men are 1.319 times more likely to be hospitalized than women, respectively. Quotient of chance for education level was 0.759. The table shows that with an increase of education by one level, the chance of hospitalization decreases by 24.1%. Participants living in the southern parts of Serbia were 1.4 times more likely to be clinically treated than those who lived in the North (OR=1.481) (Table 5).

Table 5. The cross ratios (OR) and 95% confidence intervals (CI) for primary health care services usage related to gender and socio-economic characteristics

Variable	Univariate model		Multivariate model	
	OR	p	OR	p
male	1.238 (1.027 – 1.493)	0.025	1.319 (1.071 – 1.624)	0.009
education	0.793 (0.691 – 0.910)	0.001	0.759 (0.648 -0.887)	0.001
southern region	1.562 (1.287 – 1.894)	< 0.001	1.481 (1.204 – 1.822)	< 0.001

In the male population, multivariate logistic regression distinguishes the level of education and region of residence as the most significant factors associated with hospitalization. Men with the highest level of education are 29.6% less likely to be clinically treated in comparison to their peers with the lowest level of education (OR=0.704), while those in the South were 1.48 times more likely to be hospitalized compared to those who lived in the North (OR=1.483). Multivariate logistic regression distinguishes the region of residence as the most important predictor of hospitalization in women, and women living in the South had a 1.54 times higher risk (OR=1.544) to be hospitalized compared to women from the North (Table 6).

Table 6. Cross Odds Ratio (OR) and 95% confidence intervals (CI) for the use of hospital care by gender

Variable	Gender	Univariate model		Multivariate model	
		OR	p	OR	p
age	women	1.017 (0.997 – 1.037)	0.093		
material status	men	0.902 (0.814 – 0.999)	0.048		
type of settlement	men	1.394 (1.060 – 1.834)	0.017		
education	men	0.687 (0.567 – 0.833)	< 0.001	0.704 (0.571 -0.867)	0.001
education	women	0.815 (0.658 – 1.010)	0.062		
southern region	men	1.566 (1.179 – 2.081)	< 0.001	1.483 (1.092 – 2.013)	0.012
southern region	women	1.544 (1.186 – 2.010)	0.001	1.544 (1.186 – 2.010)	0.001

DISCUSSION

The results of this study indicate that women, in general, are more likely to use health services than men. A number of studies conducted all around the world support these results, but also offer different explanations for the higher rates of use of health services by women (10), such as differences in social roles, health status, susceptibility to symptoms, willingness to report health problems, willingness to seek for help, agreement with the choice of treatment (11).

Women have a greater need for a health care services because of their poorer health (higher rates of morbidity, worse perception of health, poorer quality of life and a greater degree of disability than men) and different social constructor of diseases (roles, attitudes, beliefs and behaviors of men and women when they are sick or concerned about health), which leads to different processes of seeking for health care and to differences between women and men in the provision of these services (12, 13).

Gender differences in attitudes towards health and in reporting of symptoms and diseases can also cause differences between men and women regarding the use of health care. It is believed that women are easier to adapt to the role of the patient; they recognize and experience more health problems than men because it is socially and culturally acceptable for a woman to be sick and to seek professional help (14). Higher consultation rates among women reflect greater awareness and concern about issues related to health (15), which is basically related to gender psychosocial and behavioral influences (16), or to the perception of symptoms (17-21). According to cultural characteristics, females are more likely to address health professionals for help. They are more open and willing to show the symptoms they feel, verbally as well as behaviorally. They more often complain on psychosomatic ailments and emotional instability, which is why they more frequently use health care services. Health disorders are less stigmatizing for females, because lower standards of health are accepted for them, while the strength and health are traditional male values (2).

The trend of more frequent use of health care among women is not constant data and depends on the level of health care and the types of health services. The results of this research that suggest that women more often use the services of primary health care services and that men more often use services of hospital treatment, are in accordance with the results of other studies based on national probability samples. Women more likely use outpatient, preventive and diagnostic services, while men more often visit specialists, have a higher rate of hospitalization compared with women (22) and stay longer in the hospital (23-25).

Mutran and Ferraro (14) suggested that the reasons for this lie in the nature of the diseases affecting aging men (e.g., cardiovascular and respiratory diseases) in comparison to those that women often experience (musculoskeletal and mental diseases), i.e. men suffer from more serious and complicated health problems. The fact that women report poorer health, more frequent use of primary health care services and less specialist' services, supports the argument that women are healthier, but have a poorer perception of their health.

Globally, there are good evidences that older women disproportionately suffer from chronic diseases that incapacitate, but are not life-threatening and do increase the need for health care (16). However, as gender differences remain after controlling for self-assessment of health or of chronic conditions, the explanation could not be so simple (15).

The results that indicate a high rate of female morbidity and its links to the increased use of health services, vary in

different studies. Portraid and colleagues argued that the age and chronic morbidity were the most important factors that have determined the need for long-term care. Furthermore, after eliminating the age and number of chronic diseases as factors, the women were institutionalized less frequently than men (19).

Ladvig and colleagues also described the positive relationship between the frequency of the chronic diseases and the overall utilization of the health services, including the frequency of visits to physician, hospitalization during the previous 12 months, as well as the number and frequency of drugs taken (20). In contrast to this, in the study that was conducted by Dunlop and colleagues, which examined gender differences in health care use in patients aged over 70, gender differences in the number of medical contacts in the last 2 years were not observed, although women required more frequent medical care at home than men. However, men were more frequently admitted to the hospital and more often used the services of ambulatory surgery than women (21).

Older people, both men and women, with lower income, reported worse indicators of the health status and of the physical functioning, and they used medical services less than those with better economic situations, regardless of age (16). Poorer and less educated people, despite higher morbidity and mortality, often have difficulties getting to the appropriate specialists and preventive services, they are less likely to use health services, and some of them must pay proportionately more in relation to their income than richer people. As people live longer in stressful economic and social conditions, it is less likely to enjoy good health during the old age. Therefore, the socio-economic position of people is the main determinant of health in adulthood and this effect also persists later in life (18).

The research conducted in China indicates that socio-economic status plays an important role in the use of outpatient services, but does not play a significant role in the use of hospital services (23). The research conducted in Finland and Norway showed that the usage of health services among older individuals varied with health status, socio-economic factors and gender, and that these three factors were independently connected with the use of health care in later life (15).

A study conducted in China as a part of a larger study of global aging and adult health (Study on global AGEing and adult health – SAGE), which included 4185 people aged over 50 with a diagnosis of cardiovascular disease, showed that older women more often used outpatient primary health care services than older men, and that the use of these services depended on the age, gender and financial situation of users household. Compared to persons aged 50-59, age group 70-79 (OR=1.26), and group aged over 80 (OR=1.38), significantly more frequently used ambulatory services. Female patients used more outpatient services than male patients (OR=1.30). Wealthy patients were more likely to use outpatient services than poorer. The average number of visits to the doctor of the general practice among wealthy patients was 7.3, while the average number of visits in the poorest population group was 2.4. Patients who had health insurance were more likely to use outpatient services than those who did not have health insurance (57.0% vs. 41.4%). The study did not find significant disparities in the provision of hospital services among men and women (25).

It is obvious that we can talk about gender differentiated quality of age, and more of such evidences could help informing of policies and programs aimed to reduce gender differences in the quantity and quality of years to live, providing equal opportunities for both men and women.

CONCLUSION

Women are significantly more likely to use primary health care compared to men, while the frequency of hospitalization is significantly higher in men. Integrating a gender perspective in public health refers to the recognition of these differences and inequalities, taking them into consideration during the process of designing various policies and in developing programs of health promotion and prevention strategies, taking into account the specific needs of women and men of this age.

ACKNOWLEDGMENTS

The study is a part of the 2013 National Health Survey for the population of Serbia carried out by the Ministry of Health of the Republic of Serbia and professional support of the Institute of Public Health of Serbia ‘Dr Milan Jovanovic Batut’.

REFERENCES

1. United Nations: World Population Ageing 1950-2050: Department of Economic and Social Affairs, Population Division. New York: United Nations Publication, 2007.
2. Devedžić M, Stojilković Gnjatović J. Demographic profile of the old population of Serbia. Belgrade: Statistical Office of the Republic of Serbia, 2015.
3. Afshar S, Roderick PJ, Kowal P, Dimitrov BD, Hill AG. Multimorbidity and the inequalities of global ageing: a cross-sectional study of 28 countries using the World Health Surveys. BMC Public Health 2015; 13:15:776.
4. World Population Ageing 2013. New York: United Nations, Department of Economic and Social Affairs, Population Division, 2013.
5. Gelberg L, Andersen RM, Leake BD. The behavioral model for vulnerable populations: application to medical care use and outcomes for homeless people. Health Serv Res 2000; 34(6):273–1302.

6. Peltzer K, Williams JS, Kowal P, Negin J, Snodgrass JJ, Yawson A. Universal health coverage in emerging economies: findings on healthcare utilization by older adults in China, Ghana, India, Mexico, the Russian Federation, and South Africa. Glob Health Action 2014; 7:25314.
7. Srakar A, Hren R, Prevolnik Rupel V. Health Services Utilization in Older Europeans: an Empirical Study. Organizacija 2016 49 (2) 127-136.
8. Sobot A. Demographic framework of gender inequality and quality of life in old age. Gerontology, 2011; 38(1):30-50.
9. European Health Interview Survey wave 2 – Conceptual Guidelines and Instructions, Eurostat, 2012.
10. Ladwig KH, Marten-Mittag B, Formanek B, Dammann G. Gender differences of symptom reporting and medical health care utilization in the German population. Eur J Epidemiol 2000; 16:511-518.
11. Gerritsen AM, Devillé W. Gender differences in health and health care utilisation in various ethnic groups in the Netherlands: a cross-sectional study. BMC Public Health 2009; 20(9):109.
12. Macintyre S, Hunt K, Sweeting H. Gender differences in health: are things really as simple as they seem? Soc Sci Med 1996; 42:617–24.
13. Gómez GE. Género, equidad y acceso a los servicios de salud: una aproximación empírica. Rev Panam Salud Publica 2002; 11:327–334.
14. Mutran E, Ferraro KF. Medical need and use of services among older men and women. J Gerontology: Social sciences 1998; 5(suppl 1):62-171.
15. Suominen-Taipale AL, Martelin T, Koskinen S, Holmen J, Johnsen R. Gender differences in health care use among the elderly population in areas of Norway and Finland. A cross-sectional analysis based on the HUNT study and the FINRISK Senior Survey. BMC Health Services Research 2006, 6:110.
16. Suominen-Taipale AL, Koskinen S, Martelin T, Holmen J, Johnsen R. Differences in older adults' use of primary and specialist care services in two Nordic countries. Eur J Publ Health 2004; 14:375-380.
17. Jakovljevic MB. Resource allocation strategies in Southeastern European health policy. The European Journal of Health Economics 2013; 14(2):153-159.
18. Kyoul K, Lee M. Factors associated with health services utilization between the years 2010 and 2012 in Korea: using Andersen's Behavioral model. Osong Public Health Res Perspect 2016; 7(1):18e25.
19. Portrait F, Lindeboom M, Deeg D. The use of long-term care services by the Dutch elderly. Health Econ 2000; 9:513–531.
20. Gelberg L, Andersen RM, Leake BD. The behavioral model for vulnerable populations: application to medical care use and outcomes for homeless people. Health Serv Res 2000; 34(6):273–1302.
21. Dunlop DD, Manheim LM, Song J, Chang RW. Gender and ethnic/racial disparities in health care utilization among older adults. J Gerontol B Psychol Sci Soc Sci 2002; 57:221–233.
22. Roy K, Chaudhuri A. Influence of socioeconomic status, wealth and financial empowerment on gender differences in health and healthcare utilization in later life: evidence from India. Social Science & Medicine 2008; 66:1951–1962.
23. Redondo-Sendino A, Guallar-Castillo'n P, Banegas JR, Rodriguez-Artalejo F. Gender differences in the utilization of health-care services among the older adult population of Spain. BMC Public Health 2006; 6:155.
24. Albanese E, Liu Z, Acosta D, Guerra M, Huang Y, Jacob KS, Jimenez-Velazquez IZ et al. Equity in the delivery of community healthcare to older people: findings from 10/66 Dementia Research Group crosssectional surveys in Latin America, China, India and Nigeria. BMC Health Serv Res. 2011; 11:153.
25. Lixia D, Xiaoyun L, Tuohong Z, Yangfeng W. Health care utilization in older people with cardiovascular disease in China. Int J Equity Health 2015; 14:59.

RETROSPECTIVE ANALYSIS OF REOPERATION RATE AFTER STANDARD LUMBAR DISCECTOMY AND MICRODISCECTOMY - SINGLE CENTER EXPERIENCE

Vojin Kovacevic[1,2] and Nemanja Jovanovic[2]
[1]*University of Kragujevac, Faculty of Medical Sciences, Department of Surgery, Kragujevac, Serbia*
[2]*Center for neurosurgery, Clinical Center Kragujevac, Kragujevac, Serbia*
**Authors Vojin Kovačević and Nemanja Jovanović contributed equally to this paper*

RETROSPEKTIVNA ANALIZA UČESTALOSTI REOPERACIJE LUMBALNE DISKUS HERNIJE NAKON STANDARDNE I MIKRODISKEKTOMIJE - ISKUSTVO JEDNOG CENTRA

Vojin Kovačević[1,2] i Nemanja Jovanović[2]
[1]*Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Katedra za Hirurgiju, Kragujevac, Srbija*
[2]*Centar za neurohirurgiju, Klinički Centar Kragujevac, Kragujevac, Srbija*
**Autori Vojin Kovačević i Nemanja Jovanović su podjednako učestvovali u istraživanju*

Received/Primljen: 24.04.2019. Accepted/Prihvaćen: 01.05.2019.

ABSTRACT

Discectomy is a surgical procedure in the treatment of lumbar disc herniation (LDH) if sciatica or neurological deficits occur and still persist after a course of conservative therapy. Standard discectomy (SD) and microdiscectomy (MD) are still equal in curent clinical practice. Many retrospective and prospective studies have shown that there is no clinically significant difference in the functional outcome after two treatment modalities.

The aim of our study was to determine whether there are differences in the incidence of reoperation after performing SD and MD.

The research included 545 patients with average period of postoperative follow-up of approximately 5.75 years. Standard discectomy was performed in 393 patients (72.11%), and microdiscectomy in 152 (27.8%) patients. The total number of reoperated patients was 37/545, or 6.78%. In the SD group, the number of reoperated patients was 33/393 (8.39%) and in the MD group 4/152 or 2.63%. Statistically significant difference (p <0.05) was recorded in favor of the MD group.

Although it has been proven that both SD and MD give good endpoints of treatment and similar functional recovery, the advantage is given to microdiscectomy due to statistically significantly lower rates of recurrent herniation. This result is attributed to better visualization of neural structures and pathological substrates, as well as their mutual relationship.

***Keywords**: hernia lumbar discus, microdiscectomy, standard discectomy, reoperation.*

SAŽETAK

Lumbalna diskektomija je hirurška metoda u lečenju pacijenata obolelih usled lumbalne diskus hernije (LDH) kada neurološki deficit i radikularni bol perzistiraju i nakon konzervativne terapije. Standardna diskektomija (SD) i mikrodiskektomija (MD) su u mnogim centrima još uvek dva ravnopravna modaliteta operativnog lečenja lumbalne diskus hernije. Većina dosadašnjih studija su došle do zaključka da nakon SD i MD nema značajne razlike u krajnjem funkcionalnom ishodu lečenja.

Naš cilj je bio da ustanovimo da li postoji razlika u učestalosti reoperacije u odnosu na inicijalno sproveden modalitet hirurškog lečenja.

Retrospektivnom analizom je obuhvaćeno ukupno 545 pacijenata, sa prosečenim periodom postoperatvinog praćenja od oko 5,75 godina. Standardna diskektomija je primenjena kod 393 pacijenta (72,11%), a mikrodiskektomija kod 152 (27,8%) pacijenta. Ukupan broj reoperisanih pacijenata je bio 37 (6,78%). U SD grupi broj reoperisanih pacijenata je bio 33 (8,39%), a u MD grupi 4 (2,63%). Zabeležena razlika se pokazala kao statistički značajna (p<0,05) u korist MD grupe.

Iako je dokazano da SD i MD daju podjednako dobre krajnje rezultate lečenja, prednost dajemo mikrodiskektomiji zbog uočene statistički značajno niže stope rekurentne diskus hernije. Ovaj rezultat pripisujemo boljoj vizuelizaciji neuralnih struktura i patološkog supstrata, kao i njihovog međusobnog odnosa.

***Ključne reči:** lumbalna diskus hernija, mikrodiskektomija, standardna diskektomija, reoperacija.*

sciendo
UDK: 616.711-007.43-089
Ser J Exp Clin Res 2021; 22 (3): 205-211
DOI: 10.2478/sjecr-2019-0023

Corresponding author:
Vojin Kovacevic, Department of Surgery,
Faculty of Medical Sciences, University of Kragujevac, Serbia
vojincnh@gmail.com

INTRODUCTION

Intervertebral (iv) disc degeneration is usually the first step in the cascade of pathophysiological processes that lead to various forms of degenerative lumbar spine diseases (1). Further progression of disc degeneration leads to a lumbar disc herniation (LDH), a disease that is the most common cause of low back pain and sciatica (2). Second most common cause for seeing a doctor (after respiratory diseases) is low back pain, according to sickness absence related studies (3). As a result, LDH is an enormous socio-economic problem in both developed and developing countries because it reduces population productivity.

Many pioneers of neurosurgery at the beginning of 20th century had an impact on creating modern way of understanding the influence of LDH in the occurrence of sciatica and neurological deficit (4-7). However, for definitive identification of degenerated disc as the cause of sciatica, as well as for viewpoint that surgical treatment can help the patient, we should be grateful to *William J. Mixter* and *Joseph S. Barr*. In 1932, in Massachusetts General Hospital, USA, they performed as a multidisciplinary team (neurosurgeon and orthopedic surgeon) the first planned lumbar discectomy using a transdural approach to the intervertebral disc (8, 9). In 1938, on the basis of their experience, the same authors concluded that interlaminar extradural surgical approach is more suitable for herniated lumbar disc (10).

Surgical approach presented by *Mixter* and *Barr*, nowadays known as SD, is still present today, accompanied by a number of technical improvements implemented over years, and includes partial hemilaminectomy and partial discectomy. A new era in the operative management of LDH began in the late 70s of the 20th century by introducing MD in clinical practice. MD as an improved surgical technique implying the use of operating microscope for surgical removal of herniated disc material (12). First results have shown that microdiscectomy was just as efficient as standard discectomy, having certain advantages over the latter (13). Compared with the standard open discectomy, microdiscectomy enabled better visualization of neural structures and their relationship to pathological substrate as well as less extensive hemilaminectomy (14). One of the main microdisectomy benefits is that patients nearly twice as fast return to ordinary life activities (15).

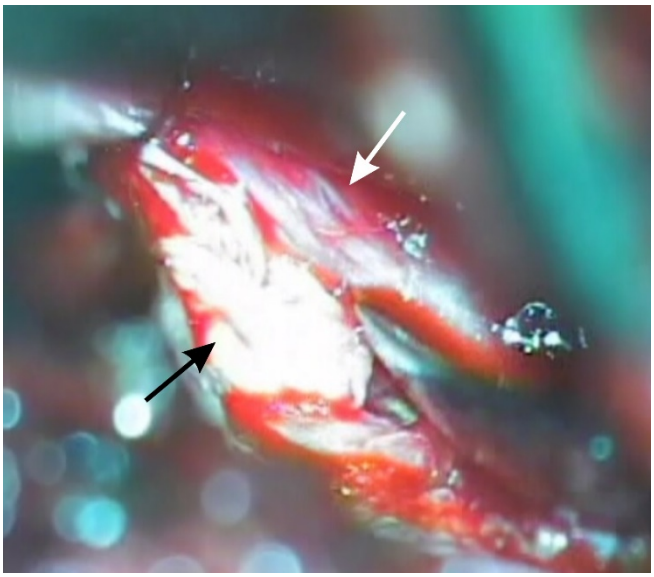
In the second half of the 20th century, many intradiscal techniques have been developed for the treatment of patients with LDH, but they have not become widely accepted into clinical practice due to having a limited range of indications and often unsatisfactory clinical results (16-21). Tubular and endoscopic discectomy, which appear to be generally accepted nowadays, have been proven to be a satisfactory alternative to microdiscectomy but also without significant difference in the treatment outcome (22).

In many medical centers, including our institution, it is still not rare for spinal surgeons to decide for standard discectomy. Therefore, these two treatment modalities in our clinical practice are equal and choice usually depends on the surgeon's familiarity with one of the two methods. Several retrospective and prospective randomized studies have been published so far (23, 24), analyzing the relative merits of MD and SD, which imposes a general conclusion that there is no clinically relevant difference in the functional outcome. Some studies, however, are favoring microdiscectomy in several parameters of clinical recovery (25). Although there are many studies that report reoperation rate after an initial LDH surgery, there are few studies that compare the same problem regarding these two operative treatment modalities.

THE AIM OF THE PAPER

The aim of our study was to determine whether there are differences in the incidence of reoperation after performing SD and MD. Our working hypothesis was that microdiscectomy was associated with a lower reoperation rate due to better visualization of the pathological substrate and neural structures, as well as their relationship (Figure 1).

Figure 1. Intraoperative view under magnification of the operating microscope, white arrow - spinal root, black arrow - extruded disc material



PATIENT AND METHODS

We conducted a retrospective analysis of recurrent disc herniation rate that required reoperation. Our research involved patients that were surgicaly treated in the period from July 2008 to February 2017 with folow-up period of 68,7±31 months (approximately 5,75 years). Patients underwent surgery by four experienced neurosurgeons and were classified into two groups, according to performed surgical procedure (MD or SD).

Operative procedures were performed under general anesthesia and patients were placed in the genupectoral position. The affected interlaminar space was localized by lateral x-ray fluoroscopy just before and with confirmation during surgery**.** Microdiscectomy was performed after a horizontal skin incision of approximately 4-5 cm in length above the lumbar spinal segments and incision of lumbodorsal fascia and subperiostal preparation to the interlaminar space. Using the operating microscope (Carl Zeiss Co., OPMI Vario/NC33, Oberkochen, Germany), the following aspects of the surgery were performed: partial hemilaminectomy of the superior and inferior lamina and partial flavectomy. After these aspects had been performed, the herniated disc was removed. In addition, all patients were mobilized during the first 24 hours after surgery.

The criteria for inclusion into the study were defined as: single level lumbar disc herniation; monoradicular symptoms with predominant sciatica compared to less severe lower back pain; conservative treatment failure or intolerable sciatica, or rapidly progressive neurological deficits (including motor deficits, bladder dysfunction, partial and complete cauda equina syndrome).

Exclusion criteria were defined as: a history of previous lumbar back surgery; signs of spinal instability or other spinal abnormalities and a history of psychiatric or addiction and mental disorders.

Indication for reoperation was recurrent radiculopathy resistant to conservative treatment followed by neuroradiological finding of a compressive lesion.

For statistical analysis the commercial statistical program SPSS (version 22) was used.

RESULTS

The study covered a total of 545 patients, of whom 298 (54.7%) were men and 247 (45.3%) women. Standard discectomy was performed in 393 patients (72.11%), and microdiscectomy in 152 (27.8%) patients. The average age of patients was 46.55 ± 12.7 years (M-46.6, F-46.48). Of the total number of patients, only 8.7% (47/545) had a certain degree of preoperative neurological deficits. The most common level of treated disc herniation was L5/S1 in 48.4% of cases (264/545), followed by L4/L5 in 41.3% (225/545). Based on intraoperative findings it was detected that in 36.7% (200/545) patients had disc protrusion, in 59.3% (324/545) disc extrusion, and in 2% (11/545) seqestration of iv disc. (Table 1).

Table 1. Parameters by groups and reoperation rate

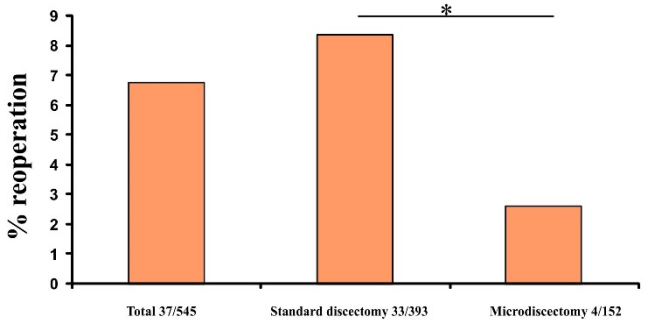
	Total	**Standard discectomy**	**Microdiscectomy**	
Number of patients	545	393	152	p>0,05
Male/female ratio	M - 298 (54,7%)	M - 215 (54,7%)	M - 83 (54,6%)	p>0,05
	F - 247 (45,3%)	F - 178 (45,3%)	F - 69 (45,4%)	
Years old	46,55±12,7	46,93±13	45,06±11,33	p>0,05
Preoperative neurological disability	8,7% (47/545)	9,4% (37/393)	6,5% (10/152)	p>0,05
Spinal level	L5/S1 - 48,4%	L5/S1 - 49,61%	L5/S1 - 50,6%	p>0,05
	L4/L5 - 41,3%	L4/L5 - 39,9%	L4/L5 - 44,7%	
Reoperation rate	6,78% (37/545)	8,39% (33/393)	2,63% (4/152)	p<0,05

The total number of reoperated patients in this retrospective group was 37/545, or 6.78%. In the SD group, the number of reoperated patients was 33/393 (8.39%) and in the MD group 4/152 or 2.63%. (Figure 2). According to reoperation rate, a statistically significant difference ($p < 0.05$) was recorded in favor of the MD group. Of the total number of reoperated patients, 22 (59.45%) patients had a verified disc extrusion during the first surgery and in remaining 15 (40.55%) disc protrusion was diagnosed.

Reoperations were most often performed in the first 6 months after the initial operation in 54.05% (20/37) of cases and in the period 6-12 months after the operation 8/37 patients were reoperated, or 21.6% (Figure 3A).

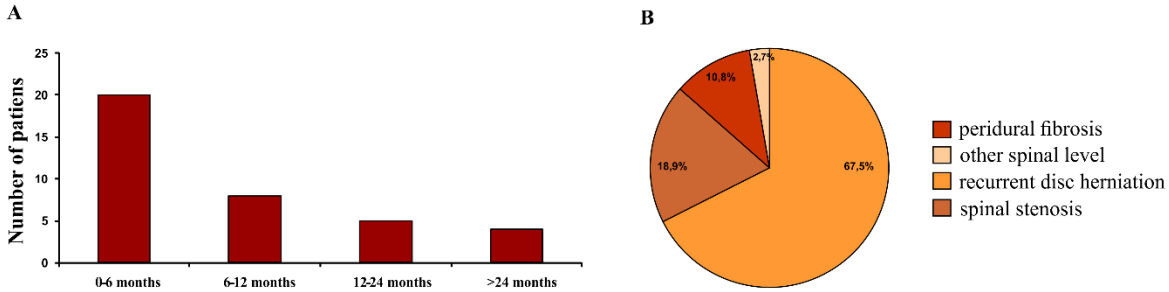
The most common cause of reoperation was recurrent disc herniation in 67.56% (25/37) of cases. In 18.91% (7/37) of patients, need for additional decompression due to central or lateral stenosis was indicated as a cause of reoperation. Peridural fibrosis was identified as a pathological substrate in 4 (10.81%) patients and one patient (2.7%) was reoperated due to disc herniation at different spinal level (Figure 3B).

Figure 2. Reoperation rate in relation to the examined groups and total number of patients



The most commonly surgically retreated spinal level was L5/S1 in 70.2% (26/37) of cases, followed by L4/L5 in 29.8% (11/37). Two patients were re-reoperated and both were initially surgically treated with standard discectomy

Figure 3. **A** - Number of reoperated patients in relation to time elapsed from primary LDH surgery; **B** - Frequency of pathology that required reoperation



DISCUSSION

Almost all the papers that analyze the recurrence rate of lumbar disc herniation give an answer to this question including one or more modality of discectomy, but without comparing two surgical procedures. According to them, the recurrence rate, depending on the monitoring period, is 6-24% [26-29]. A study with a similar follow-up period reported a rate of reoperation of about 10% [26], which is slightly higher than in our study. This difference in the rate of reoperation does not, however, prove our superior performance in the treatment of lumbar disc herniation, but the reasons may need to be sought in a different set of indications for reoperation. According to a single meta analysis in 2016 [30], the incidence of revision operations, which did not include other reasons than repeated disc-radicular compression, amounted to 1.4-11.4%, while in older patients' series the incidence was lower and amounted to 6% after a ten-year follow-up period [31]. Our results showed that the total reoperation rate in lumbar disc herniation was 6.78% (37/545) with an average follow-up period of about 5.75 years. In the SD group, the rate of reoperation was 8.39% (33/393), while in the MD group it was 2.63% (4/152). The observed difference was statistically significant in favor of the MD group ($p < 0.05$).

By reviewing the literature, we managed to find only one paper from 2000, which dealt with the comaparison of standard and microdiscectomy with respect to the mentioned problem [32]. According to the aforementioned South Korean group of authors, on a sample of 173 patients, microdiscectomy is associated with a higher rate of reoperation and perioperative infections, which is a conclusion contrary to our results. However, the limitation of this study is that all operations were taken by one surgeon.

The reason for repeated operations in our series, in most cases, was the recurrent disk herniation at the same level in 67.56% (25/37). Some form of spinal stenosis was the next

most common cause of reoperation, 18.91% (7/37), and other reasons were peridural fibrosis (4/37; 10.81%) and discus herniation at the second spinal level (1/37; 2.7%). According to other authors [33], the most frequent reason for the repeated operation of discus hernia was recurrent discus hernia (78%), followed by epidural fibrosis (12.2%), and in other cases: adhesive arachnoiditis, lateral spinal stenosis and iatrogenic instability.

Risk factors of the recurrent disc herniation mentioned in the literature arelarge anular defect, the degree of degeneration of the iv disc, male sex, the consumption of nicotine and the lifting of heavy objects [34, 35]. According to a prospective study conducted by Carragee et al. [36] the lowest risk of re-herniation (1%) were found in patients with extrusion of the fragment of the disc due to fissure on the fibrous ring. Patients with a major defect on the anulus had a significantly higher risk (27%), while the highest risk of reherniation was found in a patients with intervertebral disc protrusion (36%). It should be noted that these are not percentages of reoperation due to the re-herniations of the disk, but only symptomatic re-herniations. In our study of 37 reoperated patients due to a recurrent discus hernia, 21 had iv disc extrusion, and 16 patients had protruded iv disc preoperatively.

In obese patients with a BMI over 30, results are pretty contraversal. According to several authors, obesity does not significantly affect the occurrence of recurrent disc herniation [38, 39], while the results of several other studies claim that the obesity still has an effect [37]. We did not examine the influence of obesity on reoperation rate.

In the study group, which analyzed the rate of recurrent disc herniations in large patient groups, two studies highlighted. A large study that retrospectively analyzed the incidence of reoperation after discectomy in 7520 patients with an average follow-up period of 7 years resulted in an incidence of about 6.2% [40]. According to the second large retrospective study that included 13654 patients from the United States, the incidence of reoperation was higher after 4 years of follow-up and it amounted to 12.2%, and in almost half of the cases (5.9%), lumbar fusion surgery was performed [41]. The data on the high incidence of need for lumbar fusion after initial discectomy may indicate an incorrect treatment algorithm for these patients or the result of inadequate operating techniques that have caused the spinal column instability.

In our group of patients, as much as 75% of the reoperation was performed during the first year after the primary LDH operation. If we look at the frequency of reoperation within the first year after surgery, it was 5.23% (28/535). According to the literature data, the rate of early re-herniation, i.e. within one year after surgery is about 1-2% [31, 42]. It has been shown that the recurrence of the disc herniation is correlated with the degree of degeneration of the disc, as well as with the patient's age at the time of the first operation. More precisely, the recurrence of disk re-herniation is much more common in people in the third and fourth decade of life, as well as in the group with disc protrusion in the first operation [28]. In our study, the average age of reoperated patients did not deviate significantly from the average of the entire study group.

Among reoperated patients the best results of post-operative recovery can be expected in patients with recurrent disc herniation [33]. In general, good treatment result in reoperated patients is recorded in 50-70% of cases [43-45]. Lateral decompression is advised in order to achieve better results when reintervention is caused by lumbar disc re-herniation, i.e. removing the medial half of the facete joint all the way to the upper facet surface and then the microdiscectomy [46]. Factors that contribute to the poor outcome of post-operative treatment are: reoperation on the same side of the first operation and less than one year after the first operation [43]. Although the revision surgery in which was not found reherniated disc does not have such a good outcome, it significantly reduces the pain syndrome [27]. However, before making a decision on reoperation, the clinical and neuroradiological findings should be carefully analyzed and the operation should be indicated if the preoperative evaluation clearly indicates the existence of surgicaly corrective compression. The incidence of complications during LDH revision operations according to different authors is 0-34.6%, and the most common complication is the incidental durotomy [30].

CONCLUSION

Despite evident progress in the treatment of lumbar disc herniation, both by conservative methods and operative techniques, this disease still represents a major problem of the modern world.

As a special problem, criteria for the selection of patients for surgical treatment are imposed as there are no clearly adopted criteria that can be universally applied to each patient. This applies, first of all, to patients who do not have a neurological deficit, and to the group of patients whose pain partially or completely interferes with everyday life activities.

This decision is further aggravated by the relatively high frequency of recurrent complaints, that is, the unfavorable outcome of surgical treatment.

Although it has been proven that both SD and MD give good endpoints of treatment and similar functional recovery, the advantage is given to microdiscectomy due to statistically significantly lower rates of recurrent herniation. This result is attributed to better visualization of neural structures and pathological substrates, as well as their mutual relationship.

REFERENCE

1. M. Joković. Degenerativna oboljenja lumbosakralnog dela kičme. In: M Samardzic. Savremena neurohirurgija. 1st ed. Beograd: IP Obelezja plus; 2013; 174.
2. Schwarzer AC, Aprill CN, Derby R, Fortin J, Kine G, Bogduk N. The prevalence and clinical features of internal disc disruption in patients with chronic low back pain. Spine (Phila Pa 1976) 1995; 20:1878-1883.
3. Winn H. In: Youmans & Winn Neurological Surgery. 7th ed. Elsevier. 2016; 4.
4. Goldthwait JE. The lumbosacral articulation. An explanation of many cases of “lumbago”,”sciatica” and paraplegia. Boston Medical and Surgical Journal 1911; 164:365-372.
5. Dandy WE. Loose cartilage from intervertebral discs simulating tumour of the spinal cord. The Archives of Surgery 1929; 19:660-672.
6. Middleton GS, John TH. Injury of the spinal cord due to rupture of an intervertebral disc due to muscular effort. The Glasgow Medical Journal 1911; 76:1-6.
7. Mixter W, Barr J. Rupture of the intervertebral disc with involvement of the spinal canal. The New England Journal of Medicine 1934; 211:210-215.
8. Parisien RC, Ball PA. William Jason Mixter (1880-1958). Ushering in the "dynasty of the disc". Spine (Phila Pa 1976) 1998; 23:2363-2366.
9. Howard S. An. Principles and techniques of spine surgery. Philadelphia. Williams&Wilkins. 1997.
10. Truumees E. A history of lumbar disc herniation from Hippocrates to the 1990s. Clinical Orthopaedics and Related Research 2015; 473:1885-1895.
11. Peul WC, et al. Surgery versus prolonged conservative treatment for sciatica. The New England Journal of Medicine 2007; 356:2245–2256.
12. Caspar W. A new surgical procedure for lumbar disc herniation causing less tissue damage through a microsurgical approach. Advances and Technical Standards in Neurosurgery 1977; 4:74–80.
13. Williams RW. Microlumbar discectomy: a conservative surgical approach to the virgin herniated lumbar disc. Spine 1978; 3:175–182.
14. M. Samardžić i sar. Osnovi neurohirurgije za sve lekare. Beograd. Zavod za udžbenike i nastavna sredstva; 1998.
15. Wilson DH, Harbaugh R. Microsurgical and Standard Removal of the Protruded Lumbar Disc: A Comparative Study. *Neurosurgery* 1981; 8:422–427.
16. Greenberg MS. Spine and spinal cord in Handbook of Neurosurgery. 8th Edition. New York Thieme 2016; 1102.
17. Schreiber A, Yoshinori S, Hansjoerg L. Does Percutaneous Nucleotomy With Discoscopy Replace Conventional Discectomy? Eight Years of Experience and Results in Treatment of Herniated Lumbar Disc. Clinical Orthopaedics and Related Research 1989; 238:35-42.
18. Yeung AT, Tsou PM. Posterolateral Endoscopic Excision for Lumbar Disc Herniation: Surgical Technique, Outcome, and Complications in 307 Consecutive Cases. Spine 2009; 27:722-731.
19. Chatterjee S, Foy PM, Findlay GF. Report of a Controlled Clinical Trial Comparing Automated Percutaneous Lumbar Discectomy and Microdiscectomy in the Treatment of Contained Lumbar Disc Herniation. Spine 1995; 20:734-738.
20. Jaikumar S, Kim DH, Kam AC. History of minimally invasive spine surgery. Neuorsurgery (Suppl5) 2002; 51:S1-14.
21. Muto M, Andreula C, Leonardi M. Treatment of herniated lumbar disc by intradiscal and intraforaminal oxygen-ozone (O2-O3) injection. Journal of Neuroradiology 2004; 31:183-189.
22. Gempt J, Jonek M, Ringel F, Preuß A, Wolf P, Ryang Y. Long-term follow-up of standard microdiscectomy versus minimal access surgery for lumbar disc herniations. Acta Neurochirurgica 2013; 155:2333–2338.
23. Burkhardt WB, Grimm M, Schwerdtfeger K, Oertel Joachim MK. 318 Lumbar Disc Surgery: Clinical Outcome of 85 Patients With a Mean Follow-up of 32 Years. Neurosurgery 2016; 63:192.
24. Schmid SL, Wechsler C, Farshad M, Antoniadis A, Ulrich NH, Min K, et al. Surgery for lumbar disc herniation: Analysis of 500 consecutive patients treated in an interdisciplinary spine centre. Journal of Clinical Neuroscience 2016; 27:40–43.
25. Porchet F, Bartanusz V, Kleinstueck FS, Lattig F, Jeszenszky D, Grob D, et al. Microdiscectomy compared with standard discectomy: An old problem revisited with new outcome measures with in the framework of a spine surgical registry. Euro Spine Journal (Suppl 3) 2009; 18:360–366.
26. Kim CH, Chung CH, Park CS, Choi B, Kim MJ, Park BJ. Reoperation Rate After Surgery for Lumbar Herniated Intervertebral Disc Disease: Nationwide Cohort Study. Spine 2013, 38:581–590.
27. Erbayraktar S, Acar F, Tekinsoy B, Acar U, Guner EM. Outcome Analysis of Reoperations after Lumbar Discectomies: a Report of 22 Patients. Kobe Journal of Medical Sciences 2002; 48:33-41.
28. Kim MS, Park KW, Hwang C, Lee YK, Koo KH, Chang BS, Lee CK, Lee DH. Recurrence Rate of Lumbar Disc Herniation After Open Discectomy in Active Young Men. Spine 2009; 34:24-29.
29. Thome C, Barth M, Scharf J, Schmiedek P. Outcome after lumbar sequestrectomy compared with microdiscectomy: a prospective randomized study. Journal of Neurosurgery Spine *2005;* 2:271-278.
30. Yoshihara H, Chatterjee D, Paulino CB, Errico TJ. Revision Surgery for “Real” Recurrent Lumbar Disk Herniation: A Systematic Review. Clinical Spine Surgery 2016; 29:111–118.

31. Davis RA. A long-term outcome analysis of 984 surgically treated herniated lumbar discs. Journal of Neurosurgery *1994*; 80:415-421.
32. Kang YH, Lee WS, Yune SH. Comparison of the Results between Standard Discectomy and Microdiscectomy of the Herniated Lumbar Disc. Journal of Korean Society of Spine Surgery 2000; 7:228-233.
33. Serdar O, Sait N, Memet MO, Necmettin PM. Findings and Outcome of Revision Lumbar Disc Surgery. Journal of Spinal Disorders 1999; 12:287-292.
34. Miwa S**,** Yokogawa A**,** Kobayashi T**,** Nishimura T**,** Igarashi K**,** Inatani H**,** et al**.** Risk Factors of Recurrent Lumbar Disk Herniation**:** A Single Center Study and Review of the Literature**.** Journal of Spinal Disorders and Techniques 2015; 28:265–269.
35. Kyoung-Tae K, Dong-Hyun L, Dae-Chul C, Joo-Kyung S, Young-Baeg K. Preoperative Risk Factors for Recurrent Lumbar Disk Herniationin L5–S1. Journal of Spinal Disorders and Techniques 2015; 28:571–577.
36. Carragee EJ, Han MY, Suen PW, Kim D. Clinical Outcomes After Lumbar Discectomy for Sciatica: The Effects of Fragment Type and Anular Competence. The Journal of Bone and Joint Surgery 2003; 85:102-108.
37. Meredith DS, Huang RC, Nguyen J, Lyman S. Obesity increases the risk of recurrent herniated nucleus pulposus after lumbar microdiscectomy. Spine 2010; 10:575-580.
38. Rihn JA, Kurd M, Hilibrand AS, Lurie J, Zhao W, Albert T, et al. The influence of obesity on the outcome of treatment of lumbar disc herniation: analysis of the Spine Patient Outcomes Research Trial (SPORT). The Journal of Bone and Joint Surgery 2013; 95:1–8.
39. Quah C, Syme G, Swamy GN, Nanjayan S, Fowler A, Calthorpe D. Obesity and recurrent intervertebral disc prolapse after lumbar microdiscectomy. Annals of The Royal College of Surgeons of England 2014; 96:140-143.
40. Virk SS, Diwan A, Phillips FM, Sandhu H, Khan SN. What is the Rate of Revision Discectomies After Primary Discectomy on a National Scale? Clinical Orthopaedics and Related Research 2017; 475:2752-2762.
41. Heindel P, Tuchman A, Hsieh PC, Pham MH, D'Oro A, Patel NN, et al. Reoperation Rates After Single-level Lumbar Discectomy. Spine (Phila Pa 1976) 2017; 42:496-501.
42. Wera GD, Marcus RE, Ghanayem AJ, Bohlman HH. Failure within one year following subtotal lumbar discectomy. The Journal of Bone and Joint Surgery 2008; 90:10-15.
43. Silvers HR, Lewis P, Asch HL, Clabeaux DE. Lumbar Diskectomy for Recurrent Disk Herniation. Journal of Spinal Disorders 1994; 7:408-419.
44. Herron L. Recurrent Lumbar Disc Herniation: Results of Repeat Laminectomy and Discectomy. Journal of Spinal Disorders 1994; 7:161-166.
45. Li-Yang D, Qing Z, Wei-Fang Y, Lei S. Recurrent lumbar disc herniation after discectomy: outcome of repeat discectomy. Surgical Neurology 2005; 64:226-231.
46. Albayrak S, Ozturk S, Durdag E, Ayden O. Surgical management of recurrent disc herniations with microdiscectomy and long-term results on life quality: Detailed analysis of 70 cases. Journal of Neurosciences in Rural Practice 2016; 7:87-90.

sciendo

RISK FACTORS FOR THE OCCURRENCE OF POTENTIAL DRUG-DRUG INTERACTIONS IN SURGICAL PATIENTS

Milos N. Milosavljevic[1], Aleksandar G. Kocovic[1], Slobodan M. Jankovic[2], Dragce M. Radovanovic[3], Slobodan S. Milisavljevic[3] and Srdjan M. Stefanovic[1]
[1]*University of Kragujevac, Serbia, Faculty of Medical Sciences, Department of Pharmacy*
[2]*University of Kragujevac, Serbia, Faculty of Medical Sciences, Department of Pharmacology and Toxicology*
[3]*University of Kragujevac, Serbia, Faculty of Medical Sciences, Department of Surgery*

FAKTORI RIZIKA ZA POJAVU POTENCIJALNIH INTERAKCIJA LEKOVA KOD HIRURŠKIH PACIJENATA

Miloš N. Milosavljević[1], Aleksandar G. Kočović[1], Slobodan M. Janković[2], Dragče M. Radovanović[3], Slobodan S. Milisavljević[3] i Srđan M. Stefanović[1]
[1]*Univerzitet u Kragujevcu, Srbija, Fakultet medicinskih nauka, Katedra za farmaciju*
[2]*Univerzitet u Kragujevcu, Srbija, Fakultet medicinskih nauka, Katedra za farmakologiju i toksikologiju*
[3]*Univerzitet u Kragujevcu, Srbija, Fakultet medicinskih nauka, Katedra za hirurgiju*

Received/Primljen: 18.04.2019. Accepted/Prihvaćen: 26.05.2019.

ABSTRACT

Background: *Drug-drug interactions are defined as modifications of the drug action that result from the simultaneous administration of another individual drug or several drugs. Nowadays, potential drug-drug interactions (DDIs) are most frequently detected and analyzed using personal digital assistant software programs (online interaction checker tools).*

Objective: *To determine the risk factors for the emergence of all drug-drug interactions in surgical patients with particular emphasis on clinically significant interactions.*

Patients and methods: *This was a retrospective cohort analysis of patients treated at the Surgical Clinic of the Clinical Center Kragujevac. Three interaction checkers were used to reveal drug-drug interactions: Medscape, Epocrates and Micromedex.*

Results: *The study included total of 200 patients, aged 58.54±17.08 years. Average number of drug-drug interactions per patient was between 10.50±9.10 (Micromedex) and 18.75±17.14 (Epocrates). Number of prescribed drugs, antidepressive therapy, antiarrhythmic therapy, number of pharmacological/therapeutic subgroups (2nd level of ATC classification) prescribed, delirium or dementia, diabetes, heart failure, and number of physicians who prescribed drugs to single patient were identified as risk factors for drug-drug interactions while length of hospitalization in days and age of patient in years emerged as protective factors.*

Conclusion: *Drug-drug interactions are relatively common in surgical patients and predisposed by factors such as number of prescribed drugs or drug group per patient, number of physicians who prescribed drugs, antidepressive therapy, antiarrhythmic therapy, presence of delirium or dementia, diabetes and heart failure. On the other hand, prolonged hospitalization and higher age are factors that reduce the risk of interactions in surgical patients.*

Keywords*: Drug-drug interactions, Risk factors, Surgery patients, Micromedex, Epocrates, Medscape.*

SAŽETAK

Uvod: *Interakcije lekova se mogu definisati kao promene u delovanju leka koje nastaju kao posledica istovremene primene dva ili više leka. U današnje vreme, potencijalne interakcije lekova se najčešće identifikuju i analiziraju primenom odgovarajućih softverskih programa (online Internet čekera).*

Cilj: *Cilj rada bio je da se odrede faktori rizika za nastanak interakcija između lekova kod hirurških pacijenata sa posebnim osvrtom na klinički značajne interakcije.*

Pacijenti i metode: *Studija je dizajnirana kao retrospektivna kohortna studija kojom su analizirani pacijenti lečeni na hirurškoj klinici Kliničkog centra Kragujevac. Za otkrivanje interakcija korišćena su tri različita čekera: Medscape, Epocrates i Micromedex.*

Rezultati: *Studija je uključila ukupno 200 pacijenata prosečne starosti 58.54 ± 17.08 godina. Prosečan broj potencijalnih interakcija lekova bio je između 10.50 ± 9.10 (Micromedex) i 18.75 ± 17.14 (Epocrates). Broj propisanih lekova, primena antidepresiva, primena antiaritmika, broj propisanih farmakoloških/terapeutskih podgrupa (drugi nivo ATC klasifikacije lekova), prisustvo delirijuma ili demencije, dijabetes, srčana insuficijencija i broj lekara koji su propisali lekove su se izdvojili kao faktori rizika za nastanak interakcija između lekova, dok su se dužina hospitalizacije u danima i starost pacijenata izdvojili kao protektivni faktori.*

Zaključak: *Interakcije lekova su relativno česte kod hirurških pacijenata i predisponirane su faktorima kao što su broj propisanih lekova ili grupa lekova, broj lekara koji su propisali lekove, antidepresivna terapija, antiaritmijska terapija, prisustvo delirijuma ili demencije, dijabetes melitusa i srčane insuficijencije. S druge strane, produžena hospitalizacije i starija životna dob su faktori koji smanjuju rizik od pojave interakcija kod hirurških pacijenata.*

Ključne reči: *interakcije lekova, faktori rizika, hirurški pacijenti, Micormedex, Epocrates, Medscapeinterakcije lekova, faktori rizika, hirurški pacijenti, Micormedex, Epocrates, Medscape.*

sciendo
UDK: 615.015.2:617-089-052
Ser J Exp Clin Res 2021; 22 (3): 213-223
DOI: 10.2478/sjecr-2019-0032

Corresponding author:
Aleksandar G. Kocovic
Faculty of Medical Sciences
University of Kragujevac
Svetozara Markovica 69
34000 Kragujevac, Serbia
+381646603606
salekkg91@gmail.com

INTRODUCTION

Drug-drug interactions (DDIs) are defined as modifications in the drug action resulting from the simultaneous administration of another individual drug or several drugs (1-2). DDIs could be of pharmacokinetic or pharmacodynamics nature, when absorption, distribution, metabolism or elimination of the drug are being altered as a consequence of the concurrent use of another drug or drugs, when interacting drugs have an additive, synergistic or antagonistic effect, respectively (1). A particular attention should be paid to classification of DDIs according to severity. The highest clinical importance have contraindicated and major (avoid to use) DDIs, although moderate and minor interactions could also suggest necessary changes in patient's pharmacotherapy (2-3). Nowadays, potential DDIs (pDDIs) are most frequently detected and classified using personal digital assistant software programs, which function as applications that are regularly updated (4). There are several online available tolls for such purpose and among them, the most important and the most commonly used are Micromedex Drug Interactions (5), Pharmavista (6), Epocrates (7) Lexi-Interact (8) and Medscape (9).

Epidemiological data on the incidence of pDDIs in hospitalized patients are inconsistent, with quite variable detection of interactions in previous studies ranging from 5 to 80 percent (10). However, it seems that clinically significant interactions are not so common (11-12) given their incidence of up to 4% (10). Clinically significant interactions are the reason for hospitalization in 3% of patients (13), and when occur during hospitalization they could be associated with the prolonged stay in hospital, increased morbidity (14) and mortality (15), and the significant higher cost of treatment (16).

Previous studies have pointed several risk factors that are associated with a higher incidence of interactions in hospitalized patients, such as patients older age, prolonged hospital treatment (17), presence of comorbidities (18), polypharmacotherapy and greater number of physicians prescribing drugs to patients (3). Available data on pDDIs in surgical patients indicate that interactions often include drugs such as H2 receptor blockers, warfarin, digoxin and anesthetics (19-20). These data are available from the studies that were carried out before the onset of the Interaction checkers and before the implementation of many novel drugs in clinical practice, so it could be said that the predisposing factors and the clinical significance of pDDIs in surgical patients are quite unknown. Therefore, the aim of this study was to determine the risk factors for the emergence of all pDDIs in surgical patients with particular emphasis on clinically significant interactions.

PATIENTS AND METHOD

Study design

We conducted a retrospective cohort study on patients who were treated at the Surgical Clinic of the Clinical Center Kragujevac (CCK), during the period from March 1st to August 31st 2018. According to structural organization of a Surgery clinic of CCK the patients that have been hospitalized at following departments were observed: Department of chest surgery, Department of general and endocrine surgery, Department of biliopancreatic surgery, Department of gastrointestinal surgery and Department of colorectal surgery. The study was approved by the Ethics Committee of CCK. The main outcome was number of pDDIs by each interaction checker tool.

Data collection

Data were collected by reviewing the medical files of patients. The complete medical documentation of the patients during their hospitalization i.e.: discharge papers, temperature-therapeutic lists, the laboratory analysis of blood and urine, data from all consultative examinations and other useful documentation, were available to research investigators. Within our study we have analyzed a large number of variables: basic socio-demographic data of the patients (age, gender, data on the consumption of alcohol and cigarettes), clinical history data (main diagnosis, length of hospitalization in days, transfer from other departments to the Surgical Clinic, presence of mechanical ventilation, conducted operations, state of consciousness), qualitative presentation of comorbidities (presence of dementia or delirium, renal failure, liver cirrhosis, diabetes mellitus, chronic obstructive pulmonary disease, bronchial asthma, hypertension, heart failure), Charlson Comorbidity Index to quantify the effect of comorbidities , number of physicians who prescribed therapy to a particular patient, data on prescribed medication during hospitalization of a particular patient (total number of prescribed drugs, number of different pharmacological/therapeutic subgroups prescribed according to Anatomical Therapeutic Chemical Classification codes, prescribing certain groups of drugs such as antidepressants, anticonvulsants, anticoagulants, antiarrhythmic and antiaggregation drugs) and interaction checker data (number and description of the DDI).

Checking of DDI

The presence of potential interactions and their classification was determined for each hospital day for each patient using three relevant interaction checker databases which operate on the principle of Internet applications: Medscape (9), Epocrates (7) and Micromedex (5). Given that these checkers have their own systems of classification of interactions based on severity, according to Medscape, DDI could be categorized as Contraindicated, Serious- Use alternative, Monitor closely and Minor, while Epocrates classifies them as Contraindicated, Avoid/use alternative, Monitor/modify therapy and Caution advised, and Micromedex separates them into

Contraindicated, Major, Moderate and Minor drug-drug interactions.

Data analysis

The study data were analyzed by descriptive statistics and presented in tables. Mean and standard deviation was used as a measure of central tendency and dispersion for continuous variables. Values of categorical variables were presented as rates or percentages. Influence of potential risk factors on number of drug-drug interactions per patient was evaluated by multiple linear regression analysis. Statistical validity of the regression was checked by analysis of variance (F value) and percentage of outcome (number of DDIs per patient) variability explained (R^2). Influence of potential risk factors on number of DDIs per patient was assessed by their B coefficients within the regression equation, including confidence intervals (CIs). All calculations were performed by the Statistical Program for Social Sciences (SPSS version 20).

RESULTS

The study included 200 patients who were hospitalized in five surgery departments. Characteristics of the patients are shown in the Table 1. Twenty two patients (11%) didn't have a single drug-drug interaction detected by any of the used interaction checkers. Average number of potential drug-drug interactions detected by each of the interaction checkers is shown in the Table 2.

The largest number of potential drug-drug interactions was detected by Epocrates (3749), followed by Medscape (3466) and Micromedex (2100). Number of Contraindicated and Avoid/use alternative interactions detected by Epocrates was 681 (18.1% of pDDIs), Contraindicated and Serious-Use alternative interactions detected by Medscape was 553 (16.0% of pDDIs) and Contraindicated and Major interactions detected by Micromedex was 1492 (71.0% of pDDIs).

Table 1. Characteristics of the study sample

Variable	Mean ± standard deviation (range) or number (%)
Age (years)	58.54 ± 17.08 (18 92)
Gender	Male: 97 (48.5%)
	Female: 103 (51.5%)
Length of hospitalization (days)	6.63 ± 4.14 (1 29)
Transfer from another ward	2 (1.0%)
Transfer from emergency department	130 (65.0%)
Transfer from intensive care unit	2 (1.0%)
At least one day of immobilization because of agitation	7 (3.5%)
Inability to stand up from the bed	10 (5.0%)
Number of prescribed drugs	15.36 ± 7.16 (3–38)
Number of pharmacological/therapeutic subgroups (2nd level of ATC classification) prescribed	11.17 ± 5.03 (2 24)
Number of physicians who prescribed drugs to single patient	2.05 ± 0.996 (1 7)
Surgery	112 (56.0%)
Charlson Comorbidity Index	1.58 ± 2.37 (0–10)
Delirium or dementia	5 (2.5%)
Renal failure	3 (1.5%)
Liver cirrhosis	1 (0.5%)
Diabetes	29 (14.5%)
Chronic obstructive pulmonary disease	12 (6.0%)
Asthma	3 (1.5%)
Hypertension	101 (50.5%)
Heart failure	30 (15.0%)
Anticoagulant therapy	100 (50.0%)
Drug allergy	13 (6.5%)
Antidepressants	5 (2.5%)
Antiarrhythmic drugs	9 (4.5%)
Mechanical ventilation	3 (1.5%)
Coma	1 (0.5%)

Table 2. Average number of potential drug-drug interactions per patient by checker

Type of interaction	Mean ± standard deviation (range)
Medscape	
Contraindicated	0.00 ± 0.00 (0-0)
Serious – Use alternative	2.81 ± 2.66 (0-10)
Monitor closely	11.76 ± 10.66 (0-49)
Minor	2.75 ± 3.12 (0-17)
Total	17.33 ± 15.34 (0-67)
Epocrates	
Contraindicated	0.29 ± 0.47 (0-2)
Avoid/use alternative	3.13 ± 3.09 (0-12)
Monitor/modify therapy	10.41 ± 10.02 (0-41)
Caution advised	4.92 ± 5.15 (0-17)
Total	18.75 ± 17.14 (0-67)
Micromedex	
Contraindicated	0.60 ± 0.63 (0-2)
Major	6.92 ± 6.46 (0-27)
Moderate	2.75 ± 3.03 (0-15)
Minor	0.22 ± 0,50 (0-2)
Total	10.50 ± 9.10 (0-38)

Results of the last step of the backward multiple linear regression analysis are presented in the Tables 3–5. Comparing all significant independent factors that entered the final regression model 18 different factors were identified from a total of 21. These factors in descending order and the number of times when factor entered the final model are: number of prescribed drugs (7), surgery (6), number of pharmacological/therapeutic subgroups (2nd level of ATC classification) prescribed (5), length of hospitalization (days) (5), hypertension (5), antiarrhythmic therapy (4), chronic obstructive pulmonary disease (4), Charlson comorbidity index (3), transfer from emergency department (3), delirium or dementia (3), diabetes (3), antidepressive therapy (2), heart failure (2), anticoagulant therapy (2), number of physicians who prescribed drugs to single patient (2), inability to stand up from the bed (1), age (years) (1) and drug allergy (1).

Eight factors were positively correlated with number of DDIs, i.e. in other words, we can say that they contribute to the occurrence of DDIs: number of prescribed drugs, antidepressive therapy, antiarrhythmic therapy, number of pharmacological/therapeutic subgroups (2nd level of ATC classification) prescribed, delirium or dementia, diabetes, heart failure, and number of physicians who prescribed drugs to single patient. Two factors were negatively correlated with number of DDIs (protective factors): length of hospitalization in days and age of patient in years.

Surgery was positively correlated with number of Serious – Use alternative interactions by Medscape (Table 3), number of Avoid/use alternative, Monitor/modify therapy and Caution advised interactions by Epocrates (Table 4) and number of Major interactions by Micromedex (Table 5) but was found to be negatively correlated with the number of Minor interactions by Micromedex (Table 5). It was shown that hypertension was a risk factor for higher number of Monitor closely and Minor interactions by Medscape (Table 3), higher number of Monitor/modify therapy interactions by Epocrates (Table 4) and higher number of Moderate interactions by Micromedex (Table 5) but in same time was protective factor for the occurrence of Caution advised interactions by Epocrates (Table 4). Patients with chronic obstructive pulmonary disease had lower number of Avoid/use alternative and Monitor/modify therapy interactions by Epocrates (Table 4) and number of Major interactions by Micromedex (Table 5) but also had a higher number of Minor interactions by Micromedex (Table 5). Charlson Comorbidity Index was associated with less Minor interactions by Medscape (Table 3) and Minor interactions by Micromedex (Table 5) and with more Monitor/modify therapy interactions by Epocrates (Table 4). Transfer from emergency department was positively correlated with number of Serious – Use alternative interactions by Medscape (Table 3), but was negatively correlated with the number of Monitor closely interactions by Medscape (Table 3) and number of Moderate interactions by Micromedex (Table 5). Positive association was shown between anticoagulant therapy and number of Major interactions by Micromedex (Table 5), and negative association between anticoagulant therapy and number of Caution advised interactions by Epocrates (Table 4).

Table 3. Variables included in the last step of the model for potential drug-drug interactions detected by Medscape

Variables	B	P	95% CI
Serious – Use alternative interaction			
Constant	-1.852	<0.001*	-2.435 to -1.269
Number of prescribed drugs	0.206	<0.001*	0.165 to 0.248
Transfer from emergency department	0.461	0.037*	0.029 to 0.893
Surgery	1.932	<0.001*	1.308 to 2.557
Antidepressive therapy	1.315	0.037*	0.078 to 2.552
Antiarrhythmic therapy	1.697	<0.001*	0.756 to 2.638
R^2; F (p)	0.750; 116.144 (<0.001*)		
Monitor closely interaction			
Constant	-4.520	<0.001*	-6.840 to -2.201
Number of prescribed drugs	0.565	<0.001*	0.269 to 0.860
Number of pharmacological/therapeutic subgroups (2nd level of ATC classification) prescribed	0.835	<0.001*	0.408 to 1.263
Delirium or dementia	5.208	0.029*	0.548 to 9.869
Length of hospitalization (days)	-0.351	<0.001*	-0.547 to -0.156
Transfer from emergency department	-2.206	0.010*,	-3.879 to -0.533
Diabetes	3.878	0.001*	1.683 to 6.073
Hypertension	2.079	0.008*	0.543 to 3.615
Antiarrhythmic therapy	6.657	<0.001*	3.123 to 10.190
R^2; F (p)	0.783; 85.907 (<0.001*)		
Minor interaction			
Constant	-1.845	<0.001*	-2.535 to -1.156
Number of prescribed drugs	0.257	<0.001*	0.216 to 0.298
Delirium or dementia	1.898	0.044*	0.052 to 3.744
Charlson Comorbidity Index	-0.279	<0.001*	-0.416 to -0.143
Diabetes	2.601	<0.001*	1.695 to 3.507
Hypertension	1.302	<0.001*	0.685 to 1.920
Drug allergy	-1.057	0.070	-2.203 to 0.089
Antidepressants	3.281	<0.001*	1.456 to 5.106
R^2; F (p)	0.606; 42.152 (<0.001*)		
B – unstandardized coefficient; CI – confidence interval; p – statistical significance. * Statistically significant.			

Table 4. Variables included in the last step of the model for potential drug-drug interactions detected by Epocrates

Variables	B	p	95% CI
Avoid/use alternative interaction			
Constant	-0.288	0.610	-1.401 to 0.824
Age (years)	-0.016	0.067	-0.033 to 0.001
Number of prescribed drugs	0.197	<0.001*	0.137 to 0.258
Surgery	2,281	<0.001*	1.411 to 3.152
Chronic obstructive pulmonary disease	-2,189	<0.001*	-3.330 to -1.047
Heart failure	0.833	0.043*	0.026 to 1.641

Variables	B	p	95% CI
Antiarrhythmic therapy	1,257	0.056	-0.034 to 2.547
R^2; F (p)	0.649; 59.465 (<0.001*)		
Monitor/modify therapy interaction			
Constant	-6.076	<0.001*	-7.954 to -4.197
Number of prescribed drugs	0.617	<0.001*	0.316 to 0.918
Number of pharmacological/therapeutic subgroups (2nd level of ATC classification) prescribed	0.511	0.023*	0.071 to 0.950
Charlson Comorbidity Index	0.426	0.009*	0.108 to 0.744
Length of hospitalization (days)	-0.373	<0.001*	-0.561 to -0.184
At least one day of immobilization because of agitation	4.245	0.050	0.004 to 8.486
Inability to stand up from the bed	-3.129	0.077	-6.605 to 0.347
Surgery	3.681	0.004*	1.209 to 6.153
Chronic obstructive pulmonary disease	-3.458	0.030*	-6.576 to -0.340
Hypertension	2.474	0.002*	0.903 to 4.045
R^2; F (p)	0.784; 76.477 (<0.001*)		
Caution advised interaction			
Constant	-2.930	<0.001*	-4.007 to -1.852
Number of prescribed drugs	0.297	<0.001*	0.133 to 0.462
Number of pharmacological/therapeutic subgroups (2nd level of ATC classification) prescribed	0.391	0.002*	0.146 to 0.635
Length of hospitalization (days)	-0.197	<0.001*	-0.304 to -0.089
Surgery	1.983	0.007*	0.536 to 3.430
Hypertension	-0.906	0.041*	-1.777 to -0.036
Anticoagulant therapy	-1.194	0.019*	-2.192 to -0.196
Drug allergy	1.662	0.040*	0.074 to 3.251
Antidepressants	2.332	0.070	-0.190 to 4.854
R^2; F (p)	0.726; 63.187 (<0.001*)		
B – unstandardized coefficient; CI – confidence interval; p – statistical significance. * Statistically significant.			

Table 5. Variables included in the last step of the model for potential drug-drug interactions detected by Micromedex

Variables	B	p	95% CI
Major interaction			
Constant	-0.352	0.723	-2.312 to 1.608
Age (years)	-0.032	0.033*	-0.060 to -0.003
Number of prescribed drugs	0.457	<0.001*	0.337 to 0.577
Length of hospitalization (days)	-0.164	0.009*	-0.287 to -0.042
Surgery	3.390	<0.001*	1.783 to 4.996
Chronic obstructive pulmonary disease	-2.821	0.005*	-4.801 to -0.841
Anticoagulant therapy	2.615	<0.001*	1.450 to 3.781
Antiarrhythmic therapy	3.193	0.006*	0.928 to 5.457
R^2; F (p)	0.756; 84.890 (<0.001*)		
Moderate interaction			
Constant	-0.934	0.033*	-1.793 to -0.074
Number of pharmacological/therapeutic subgroups (2nd level of ATC classification) prescribed	0.319	<0.001*	0.262 to 0.376

Variables	B	p	95% CI
Number of physicians who prescribed drugs to single patient	0.332	0.020*	0.053 to 0.611
Delirium or dementia	2.198	0.009*	0.559 to 3.836
Charlson Comorbidity Index	-0.113	0.069	-0.234 to 0.009
Length of hospitalization (days)	-0.132	<0.001*	-0.203 to -0.061
Transfer from emergency department	-0.904	0.003*	-1.488 to -0.321
Diabetes	2.337	<0.001*	1.546 to 3.129
Hypertension	1.132	<0.001*	0.575 to 1.690
Heart failure	0.884	0.020*	0.138 to 1.629
R^2; F (p)	0.690; 47.032 (<0.001*)		
Minor interaction			
Constant	-0.155	0.096	-0.337 to 0.028
Number of pharmacological/therapeutic subgroups (2nd level of ATC classification) prescribed	0.030	0.005*	0.009 to 0.050
Number of physicians who prescribed drugs to single patient	0.089	0.016*	0.017 to 0.161
Charlson Comorbidity Index	-0.031	0.031*	-0.060 to -0.003
Inability to stand up from the bed	0.373	0.015*	0.072 to 0.674
Surgery	-0.276	0.006*	-0.472 to -0.081
Chronic obstructive pulmonary disease	0.503	<0.001*	0.229 to 0.776
Antiarrhythmic drugs	0.409	0.010*	0.097 to 0.722
R^2; F (p)	0.242; 8.758 (<0.001*)		
B – unstandardized coefficient; CI – confidence interval; p – statistical significance. * Statistically significant.			

The Table 6 shows the most common contraindicated/serious/major interactions detected by the interaction checkers. The most frequently occurring interaction was between fentanyl and sevoflurane which was detected by Medscape interaction checker in 98 (49.0%) patients.

Table 6. The most frequent contraindicated/serious/major potential interactions detected by the interaction checkers

Drug combinations	Description	Number (%) of patients
Medscape		
Serious – Use alternative		
1. Fentanyl + sevoflurane	Either increases effects of the other by pharmacodynamic synergism	98 (49.0%)
2. Fentanyl + propofol	Either increases effects of the other by pharmacodynamic synergism	95 (47.5%)
3. Fentanyl + rocuronium	Either increases effects of the other by pharmacodynamic synergism	81 (40.5%)
4. Fentanyl + tramadol	Either increases effects of the other by pharmacodynamic synergism	74 (37.0%)
5. Diclofenac + ketorolac	Either increases toxicity of the other by pharmacodynamic synergism.	23 (11.5%)

Drug combinations	Description	Number (%) of patients
Epocrates		
Contraindicated		
1. Atropine + potassium chloride	Combo may delay solid potassium passage through GI tract, increased risk of ulcerative/stenotic lesions	44 (22.0%)
2. Potassium chloride + scopolamine	Combo may delay solid potassium passage through GI tract, increased risk of ulcerative/stenotic lesions	8 (4.0%)
3. Aspirin + ketorolac	Combo may increase risk of GI bleeding,	6 (3.0%)
Avoid/use alternative		
1. Ondansetron + sevofluran	Combo may increase risk of QT prolongation, cardiac arrhythmias	78 (39.0%)
2. Fentanyl + midazolam	Combo may increase risk of profound CNS and resp. depression, psychomotor impairment	73 (36.5%)
3. Fentanyl + tramadol	Combo may increase risk of profound CNS and resp. depression, psychomotor impairment	73 (36.5%)
4. Ondansetron + tramadol	Combo may increase risk of QT prolongation, cardiac arrhythmias	59 (29.5%)
5. Fentanyl + potassium chloride	Combo may delay solid potassium passage through GI tract, increased risk of ulcerative/stenotic lesions	53 (26.5%)
Micromedex		
Contraindicated		
1. Atropine + potassium chloride	Concurrent use may result in risk of gastrointestinal lesions.	78 (39.0%)
2. Diclofenac + ketorolac	Enhanced gastrointestinal adverse effects	23 (11.5%)
3. Aspirin + ketorolac	Gastrointestinal adverse effects	7 (3.5%)
4. Potassium chloride + scopolamine	Concurrent use may result in risk of gastrointestinal lesions.	7 (3.5%)
5. Haloperidol + metoclopramide	Concurrent use may result in an increased risk of extrapyramidal reactions and neuroleptic malignant syndrome.	1 (0.5%)
Major		
1. Fentanyl + propofol	Concurrent use may result in increased risk of CNS depression.	91 (45.5%)
2. Ondansetron + sevoflurane	Concurrent use may result in increased risk of QT-interval prolongation.	76 (38.0%)
3. Fentanyl + ranitidine	Concurrent use may result in increased risk of fentanyl toxicity.	75 (37.5%)
4. Ranitidine + tramadol	Concurrent use may result in increased tramadol exposure and increased risk of respiratory depression.	75 (37.5%)
5. Fentanyl + tramadol	Concurrent use may result in increased risk of respiratory and CNS depression; increased risk of serotonin syndrome.	74 (37.0%)

DISCUSSION

We showed that the occurrence of DDIs is predisposed by factors such as number of prescribed drugs, number of pharmacological/therapeutic subgroups, prescribed antidepressants, antiarrhythmic drugs, number of physicians who prescribed drugs to single patient, delirium or dementia, diabetes, and heart failure. On the other hand, length of hospitalization and age of patients are set as factors that reduce the risk of DDIs. There are also factors, such as surgery, hypertension, chronic obstructive pulmonary disease, Charlson Comorbidity Index, transfer from emergency department and anticoagulant therapy, whose impact is equivocal and depend

on the incidence of DDIs depends on the checker used for detection of DDIs as well as on the type of interaction.

The increase in the number of prescribed medication carries a higher risk for the occurrence of DDIs, and we could say that the results of our study are consistent with the results of other authors (12, 21-22). A significant risk factor for the occurrence of DDIs in our study is related to the use of antiarrhythmic drugs, which is also demonstrated in other studies (3). Most of antiarrhythmics are metabolized via the cytochrome P450 enzyme system, so they can interact with a number of cytochrome P450 inducers / inhibitors. Because of their narrow therapeutic window, interactions of antiarrhythmics generally have a serious clinical character (23). We also found that use of antidepressants is also related with higher risk od DDIs occurrence in surgical patients, which also can be easily explained by the basic pharmacological properties of these drugs. Fluoxetine and paroxetine are potent inhibitors of CYP2D6, fluvoxamine and nefazodone inhibit CYP3A4, while tricyclic antidepressants and monoamine oxidase inhibitors beside pharmacokinetic interactions, have a significant potential for pharmacodynamic interactions (24).

Most of patients included in our study had one or more comorbidities, which were mostly treated in the same way as before hospitalization. Presence of comorbidities in patients represents a significant risk factor for the occurrence of interactions (25). In our study, we found positive correlation between number of DDIs and presence of diabetes, heart failure and dementia/delirium. Hypertension was positively correlated with clinical significant interactions and negatively correlated with DDIs of minor clinical significance, while the presence of chronic obstructive pulmonary disease (COPD) paradoxically meant a lower risk of occurrence of clinically significant interactions. The results of previous studies (26-27) suggest that the presence of cardiac diseases represents a significant risk factor for the occurrence of interactions. This is due the fact that cardiovascular diseases, particularly heart failure and severe hypertension, are treated with a combination of drugs such as beta-blockers, ACE inhibitors, diuretics and digoxin, which have a notable potential to interact with other drugs (28). Additionally, anticoagulation and antiaggregation drugs are often used to prevent unwanted cardiovascular events. Among these drugs, a particularly high potential for interaction has warfarin due to it is metabolized via the cytochrome P450 enzyme system (29). We showed that use of anticoagulants increases the risk of major DDIs, and because of that, there is a necessity of special caution when prescribing these drugs. Of antidiabetic drugs, sulfonylurea derivatives have a serious potential for interactions with other drugs at the cytochrome P450 level in liver, whereas metformin should be used with caution in patients receiving nephrotoxic drugs, primarily NSAIDs (30). In this possible lies the explanation of the result of our study in which the presence of diabetes mellitus in surgical patients significantly increased the risk of DDIs. Patients with delirium in our study were treated with haloperidol, a typical antipsychotic that interacts with other CNS depressants (31), but also with metoclopramide (32), which was also commonly used antiemetic in patients enrolled in this study. This is in line with the finding we of our study, in which the presence of delirium was identified as a significant risk factor for the occurrence of interactions. When we talk about chronic obstructive pulmonary disease, we found that presence of COPD was protective factor for the occurrence of significant DDIs, but also factor which predispose the occurrence of minor DDIs. Similar results were reported by a group of authors from Slovenia (33-34), who showed that the interactions in patients with COPD are frequent, but that they were of minor clinical relevance.

Surgical intervention during hospitalization in our study was related to increased number of clinical significance DDIs. It is known that in surgical patients interactions typically occur during the use of warfarin, digoxin and drugs used for anesthesia of patients (19-20). In our study the most commonly clinical significant DDIs by all of three used checkers were interactions that involved drugs used for general anesthesia of patients. In addition to general anesthetics, opiod analgesics fentanyl and tramadol, antiemetic ondansetron and ranitidine were included within these interactions. Interactions between general anesthetics and clinical analgesics have been predicted and found to be useful in clinical practice due to the synergistic hypnotic and analgesic effect (35), but a great caution is needed when combining these drugs in order to avoid over-hypnosis of patients and the occurrence of a coma. The number of DDIs in patients who undergo surgical interventions is also increased due to the introduction of antibiotic prophylaxis as well as the treatment of postoperative pain (36). It has also been shown in our study, given that among the most common clinically significant DDIs were interactions involving NSAIDs, such as diclofenac and ketorolac. This combination of drugs can be considered as contraindicated due to the fact that such practice does not increase the effectiveness of analgesic therapy, while the toxic effects of NSAIDs on the kidneys and stomach become more pronounced.

The elderly takes a greater number of drugs in general, with consequently increased risk of DDIs (37). The results of our study, on the other hand, show that the risk of interaction is reduced with increasing age of patients. This phenomenon can be explained in several ways. Firstly, as we have previously stated, in the most commonly detected DDIs in our patients participated the drugs used for the preoperative anesthesia of patients. Despite significant progress in the field of anesthesiology and postoperative care of patients, it could be said that operations that are not essential to a patient's life are not routinely performed in elderly patients due to the more common occurrence of postoperative complications and a higher rate of morbidity and mortality (38). Also, in our study, we examined the risk factors for the emergence of interactions in surgical patients, while studies that showed an opposite effect of age on the incidence of DDIs (11, 37) were conducted on patients hospitalized in several different wards. Therefore, there is a necessity for conducting new studies on a larger sample of surgical patients in order to examine this phenomenon.

Increased duration of stay in the hospital is associated with a higher risk of DDIs (3, 15). However, in our study, we found that length of hospitalization could be a protective factor for the occurrence of DDIs in surgical patients. We could say that the length of hospitalization has an indirect impact on the incidence of DDIs, since the extension of the hospitalization increases the number of drugs that are prescribed to patients. Since the study by Jankovic et al (3) was also conducted on patients who were hospitalized at the Clinical Center Kragujevac but in the intensive care unit, the explanation of this phenomenon should be sought in the differences in the functioning of these departments. In the intensive care unit of the Clinical Center in Kragujevac are treated life-threatening condition in patients with indications that require the use of a large number of drugs and prolonged treatment. On the other hand, patients in the surgical department generally have better conditions and their extended stay is usually the consequence of a postoperative infection of the wound, which requires the introduction of antibiotic therapy. Antibiotics do not have such a great potential for interactions with other drugs, as shown in our research, since the interactions of antibiotics with other drugs were not so frequent.

Finally, it is important to emphasize that our study has significant limitations. The first limitation relates to a relatively modest sample size of patients who were surgically treated in a single center; therefore, there is a possibility that it did not reveal all factors which might be associated with the occurrence of DDIs in surgical patients. Second important shortcoming of our study relates to the disadvantages of the applications (online checkers) used for detection of DDIs. This applies in particular to Medscape and Epocrates, because these checkers do not offer the possibility of checking potential DDIs for drugs such as nadroparin and bromazepam, that were relatively frequently administered in our patients. Also, this study was related to the theoretical presentation of potential DDIs in surgical patients, while the practical significance of most of these interactions was not the subject of this study.

In conclusion, we could say that DDIs in surgical patients are relatively common and that their occurrence is predisposed by factors such as number of prescribed drugs or drug group per patient, number of physicians who prescribed drugs, antidepressive therapy, antiarrhythmic therapy, delirium or dementia, diabetes and heart failure. On the other hand, length of hospitalization and age are factors that reduce the risk of interactions in surgical patients. The most common interactions in surgical patients are those which include the drugs used for the preoperative anesthesia of patients, whose synergistic effect is mostly predictable and desirable. However, the combination of these drugs requires great caution because in case of overdose there is a risk of respiratory depression, coma and even death of the patient. The online applications widely used nowadays for detection potential DDIs are quite effective, but they have some disadvantages that need to be corrected.

ACKNOWLEDGEMENTS

This study was partially supported by bilateral scientific project between Serbia and Montenegro entitled “Risk factors for DDIs in tertiary care hospitals”.

REFERENCES

1. May JR, DiPiro JT, Sisley JF. (1987). Drug interactions in surgical patients. Am J Surg, 153(3):327-35.
2. Hasan SS, Lim KN, Anwar M, et al. (2012). Impact of pharmacists' intervention on identification and management of drug-drug interactions in an intensive care setting. Singapore Med J, 53(8):526-31.
3. Janković SM, Pejčić AV, Milosavljević MN, et al. (2018). Risk factors for potential drug-drug interactions in intensive care unit patients. J Crit Care, 43:1-6.
4. Kheshti R, Aalipour M, Namazi S. (2016). A comparison of five common drug-drug interaction software programs regarding accuracy and comprehensiveness. J Res Pharm Pract, 5(4):257-263.
5. Truven Health Analtytics LLC, Micromedex® Solutions,https://www.micromedexsolutions.com/home/dispatch/PFDefaultActionId/pf.LoginAction/ssl/true?redirected=true; 2019 [accessed 20.03.2019].
6. Pharmavista-information for healthcare proffesionals, http://www.pharmavista.ch/content/default.aspx?http://www.pharmavista.ch/content/NewsMaker.aspx?ID=4439&NMID=4421&LANGID=3; 2019 [accessed 20.02.2019].
7. Epocrates, Inc. Interaction Checker. https://online.epocrates.com/interaction-check; 2019 [accessed 20.02.2019].
8. Lexi-Comp OnlineTM, Pediatric Lexi-Drugs OnlineTM, Hudson, Ohio: Lexi-Comp, Inc.; 2019, www.lexi.com/institutions/products/online/;2019 [accessed 20.02.2019].
9. Medscape. Multi-Drug Interaction checker. http://reference.medscape.com/druginteractionchecker; 2019 [accessed 20.02.2019].
10. Lubinga SJ, Uwiduhaye E. (2011). Potential drug-drug interactions on in-patient medication prescriptions at Mbarara Regional Referral Hospital (MRRH) in western Uganda: prevalence, clinical importance and associated factors. Afr Health Sci, 11(3):499-507.

11. Bjerrum L, Gonzalez Lopez-Valcarcel B, Petersen G. (2008). Risk factors for potential drug interactions in general practice. Eur J Gen Pract, 14(1):23-9.
12. Gagne JJ, Maio V, Rabinowitz C. (2008). Prevalence and predictors of potential drug-drug interactions in Regione Emilia-Romagna, Italy. J Clin Pharm Ther, 33(2):141-51.
13. Lazarou J, Pomeranz BH, Corey PN. (1998). Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA, 279(15):1200-5.
14. Vonbach P, Dubied A, Krähenbühl S, Beer JH. (2008). Prevalence of drug-drug interactions at hospital entry and during hospital stay of patients in internal medicine. Eur J Intern Med, 19(6):413-20.
15. Moura CS, Acurcio FA, Belo NO. (2009). Drug-drug interactions associated with length of stay and cost of hospitalization. J Pharm Pharm Sci, 12(3):266-72.
16. Becker ML, Kallewaard M, Caspers PW, Visser LE, Leufkens HG, Stricker BH. (2007). Hospitalisations and emergency department visits due to drug-drug interactions: a literature review. Pharmacoepidemiol Drug Saf, 16(6):641-51.
17. Murtaza G, Khan MY, Azhar S, Khan SA, Khan TM. (2016). Assessment of potential drug-drug interactions and its associated factors in the hospitalized cardiac patients. Saudi Pharm J, 24(2):220-5.
18. Ahmad A, Khan MU, Haque I, et al. (2015). Evaluation of potential drug - drug interactions in general medicine ward of teaching hospital in southern India. J Clin Diagn Res, 9(2):FC10-3.
19. Durrence CW 3rd, DiPiro JT, May JR, Nesbit RR Jr, Sisley JF, Cooper JW. (1985). Potential drug interactions in surgical patients. Am J Hosp Pharm, 42(7):1553-6.
20. May JR, DiPiro JT, Sisley JF. (1987). Drug interactions in surgical patients. Am J Surg, 153(3):327-35.
21. Chatsisvili A, Sapounidis I, Pavlidou G, et al. (2010). Potential drug–drug interactions in prescriptions dispensed in community pharmacies in Greece. Pharm. World Sci, 32(2):187–193.
22. Janchawee B, Wongpoowarak W, Owatranporn T, Chongsuvivatwong V. (2005). Pharmacoepidemiologic study of potential drug interactions in outpatients of a university hospital in Thailand. J. Clin. Pharm. Ther, 30(1):13–20.
23. Trujillo TC, Nolan PE. (2000). Antiarrhythmic agents: drug interactions of clinical significance. Drug Saf, 23(6):509-32.
24. Spina E, Scordo MG. (2002). Clinically significant drug interactions with antidepressants in the elderly. Drugs Aging, 19(4):299-320.
25. Ko Y, Malone DC, D'Agostino JV, et al. (2008). Potential determinants of prescribers' drug-drug interaction knowledge. Research in Social and Administrative Pharmacy, 4(4):355-66.
26. Doubova Dubova SV, Reyes-Morales H, Torres-Arreola Ldel P, Suarez-Ortega M. (2007). Potential drug-drug and drug-disease interactions in prescriptions for ambulatory patients over 50 years of age in family medicine clinics in Mexico City. BMC Health Serv Res, 7:147.
27. Cruciol-Souza JM, Thomson JC. (2006). Prevalence of potential drug-drug interactions and its associated factors in a Brazilian teaching hospital. J Pharm Pharm Sci, 9(3):427–433.
28. Straubhaar B, Krähenbühl S, Schlienger RG. (2006). The prevalence of potential drug-drug interactions in patients with heart failure at hospital discharge. Drug Saf, 29(1):79-90.
29. Mateti U, Rajakannan T, Nekkanti H, Rajesh V, Mallaysamy S, Ramachandran P. (2011). Drug-drug interactions in hospitalized cardiac patients. J Young Pharm, 3(4):329–333.
30. May M, Schindler C. (2016). Clinically and pharmacologically relevant interactions of antidiabetic drugs. Ther Adv Endocrinol Metab, 7(2):69–83.
31. Ocaña-Zurita MC, Juárez-Rojop IE, Genis A, et al. (2016). Potential drug-drug interaction in Mexican patients with schizophrenia. Int J Psychiatry Clin Pract, 20(4):249-53.
32. Okuno MF, Cintra RS, Vancini-Campanharo CR, Batista RE. (2013). Drug interaction in the emergency service. Einstein (Sao Paulo), 11(4):462–466.
33. Roblek T, Trobec K, Mrhar A, Lainscak M. (2014). Potential drug-drug interactions in hospitalized patients with chronic heart failure and chronic obstructive pulmonary disease. Arch Med Sci, 10(5):920-32.
34. Roblek T, Trobec K, Mrhar A, Lainscak M. (2012). Drug-drug interactions in hospitalized patients with chronic obstructive pulmonary disease. European Respiratory Journal, 40(56):P2159.
35. Rosow CE. (1997). Anesthetic drug interaction: an overview. J Clin Anesth, 9(6 Suppl):27S-32S.
36. Zhou L, Ma J, Gao J, Chen S, Bao J. (2016). Optimizing Prophylactic Antibiotic Practice for Cardiothoracic Surgery by Pharmacists' Effects. Medicine (Baltimore), 95(9):e2753.
37. Cruciol-Souza JM, Thomson JC. (2006). Prevalence of potential drug-drug interactions and its associated factors in a Brazilian teaching hospital. J Pharm Pharm Sci, 9(3):427–433.
38. Desserud KF, Veen T, Søreide K. (2016). Emergency general surgery in the geriatric patient. Br J Surg, 103(2):e52-61.

RELATIONS BETWEEN FAMILIAL HYPERCHOLESTEROLEMIA AND EARLY ISCHEMIC HEART DISEASE: AN ANALYSIS OF MEDICAL DOCUMENTATION DATA

Olena Hrechanina[1], Ganna Isayeva [2], Olena Kolesnikova[2] and Yelisaveta Isakova[2]
[1]*Kharkiv Interregional Specialized Medico-Genetic Center – Center of Rare (Orphan) Diseases*
[2]*L.T. Mala National Institute of Therapy of the National Academy of Medical Sciences of Ukraine;*
Department of Complex Risk Reduction of Chronic Non-Communicable Diseases

ODNOSI PORODIČNE HIPERHOLESTEROLEMIJE I RANE ISHEMIJSKE BOLESTI SRCA: ANALIZA PODATAKA IZ MEDICINSKE DOKUMENTACIJE

Olena Hrechanina[1], Ganna Isaieva[2], Olena Kolesnikova[2] i Ielisaveta Isakova[2]
[1]*Harkovski interregionalni specijalizovani medicinsko-genetski centar - Centar retkih bolesti, Harkov, Ukrajina*
[2] *L.T. Mala Nacionalna ustanova za terapiju Nacionalne akademije medicinskih nauka Ukrajine;*
Odeljenje za smanjenje rizika od hronične nezarazne bolesti, Harkov, Ukrajina

Received/Primljen: 19.01.2019. Accepted/Prihvaćen: 26.05.2019.

ABSTRACT

Heterozygous familial hypercholesterolemia is associated with a high risk of early ischemic heart disease onset and cardiovascular death. There is almost no data about the prevalence of the disease in the Ukrainian population. The aim of the study was to assess the incidence of familial hypercholesterolemia among patients who were treated in "L.T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine" due to early ischemic heart disease. Medical records data of 600 patients treated in the Institute during 2015-2017 were analyzed. Early ischemic heart disease was diagnosed in 89 patients. The disease verification has been conducted either on the basis of coronarography data, or on the basis of previous myocardial infarction with Q wave. To identify patients with familial hypercholesterolemia, the Dutch lipid clinic network criteria were used. The presence of familial hypercholesterolemia was suspected in more than 14.8% of patients with early ischemic heart disease. Among these patients, 2 (2.2%) had definite diagnosis; 27 (30.3%) were likely to have diagnosis, 26 (29.7%) had possible diagnosis and in 34 (38,2%) patients it was unlikely to diagnose them with familial hypercholesterolemia. The term "familial hypercholesterolemia" was not mentioned in the hospital diagnosis. This paper demonstrates that despite frequent occurrence of familial hypercholesterolemia, doctors' alertness towards this disease has been noted to be quite low.

Keywords: *heterozygous familial hypercholesterolemia; early ischemic heart disease*

SAŽETAK

Heterorozna porodična hiperholesterolemija povezana je sa velikim rizikom od ranog nastanka ishemijske bolesti i kardiovaskularne smrti. Gotovo da nema podataka o rasprostranjenosti bolesti u ukrajinskoj populaciji. Cilj studije bio je proceniti učestalost porodične hiperholesterolemije kod pacijenata koji su lečeni od „L.T. Malaja terapija, Nacionalni institut Nacionalne akademije medicinskih nauka Ukrajine "zbog rane ishemijske bolesti srca. Analizirani su podaci medicinske evidencije za 600 pacijenata lečenih u Institutu tokom 2015-2017. Rana ishemijska bolest srca dijagnostikovana je kod 89 pacijenata. Verifikacija bolesti je izvršena ili na osnovu podataka koronarografije, ili na osnovu prethodnog infarkta miokarda sa K talasom. Da bi se identifikovali pacijenti sa porodičnom hiperholesterolemijom, korišćeni su mrežni kriterijumi holandske lipidne klinike. Sumnjalo se na prisustvo porodične hiperholesterolemije kod više od 14,8% pacijenata sa ranom ishemijskom bolešću srca. Među tim pacijentima, 2 (2,2%) je imala definitivnu dijagnozu; 27 (30,3%) verovatno će imati dijagnozu, 26 (29,7%) - imalo je moguću dijagnozu, a kod 34 (38,2%) pacijenata nije bilo verovatno da im se dijagnostikuje porodična hiperholesterolemija. Izraz "porodična hiperholesterolemija" nije spomenut u bolničkoj dijagnozi. Ovaj rad pokazuje da je uprkos učestaloj pojavi porodične hiperholesterolemije primećeno da je doktor lekara na ovu bolest prilično nizak.

Ključne reči: *heterorozna porodična hiperholesterolemija; rana ishemijska bolest srca*

ABBREVIATIONS

HDH-C - high density lipoproteins cholesterol
LDL-C - low density lipoproteins cholesterol
TC - total cholesterol
TG - Triglycerides
VLD-C - very low-density lipoproteins cholesterol

sciendo
UDK: 616.1(477)"2015/2017"
616-008.9-056.7:577.115(477)
Ser J Exp Clin Res 2021; 22 (3): 225-231
DOI: 10.2478/sjecr-2019-0056

Corresponding author:
Dr. Ganna Isayeva
Address: Prospekt Lyubovi Maloy 2a, 61039, Kharkiv, Ukraine
L.T. Mala National Institute of Therapy of the National Academy of Medical Sciences of Ukraine
Tel.: +380504006550; Fax: +380573739015
E-mail: anna isayeva 74@yahoo.co.uk

INTRODUCTION

Familial hypercholesterolemia is an autosomal dominant hereditary disease characterized by high levels of low-density lipoproteins and early development of ischemic heart disease, as well as by early atherosclerosis of other localization (1). The homozygous form of the disease is a rare condition and occurs with a frequency of 1: 1.000.000 in the general population. Conversely, the heterozygous form is one of the most widespread genetically determined human diseases. It was believed earlier that the heterozygous form of the disease occurs in 1 out of 500 subjects; now the ratio is about 1 per 200-300 subjects (2). One of the most common causes of this disease development is a mutation responsible for low-density lipoprotein receptors functioning. Besides, the disease can be caused by other rare mutations of genes encoding apolipoprotein B, pro-protein convertase subtilisin/kexin type 9 and LDL adaptor protein 1 (3).

The disease is associated with a high risk of early atherosclerosis and cardiovascular death. Nanchen D. et al. demonstrated that patients with heterozygous familial hypercholesterolemia and those with acute coronary syndrome have two times higher risk of recurrent event during the first year than patients without familial hypercholesterolemia (4).

One of the most optimal strategies is the creation of national registries and long-term monitoring of patients' families. Such an approach will allow to identify patients with suspected familial hypercholesterolemia and initiate therapy at an early age. Besides, maintenance of state registries will furnish possibility to examine relatives, especially children, and, again, allow to start the treatment early. Currently, there is no centralized system for registering patients with familial hypercholesterolemia in Ukraine. Gold standard for this disease diagnosis is a genetic study and confirmation of mutation carriage. At the same time, this method is expensive and not affordable for routine use in many countries. Therefore, many countries use clinical criteria to make up registry and detect patients at risk. There are several options for the diagnosis as per clinical criteria, but the most common diagnostic criteria are the following: Dutch Lipid Clinic Network, Simon Broome, Make Early Diagnosis to Prevent Early Deaths and American Heart Association (1). In their work, Chan et al. matched the data of clinical scales and the results of genetic study and demonstrated quite high diagnostic value of Dutch Lipid Clinic Network, Simon Broome, and Make Early Diagnosis to Prevent Early Deaths scales. The authors state that cholesterol level before the treatment start, family history and presence of xanthomas are quite strong criteria for detecting candidates for genetic study (5).

The objective of this study was to identify subjects with familial hypercholesterolemia among patients who sought care in "L.T. Mala National Institute of Therapy of the National Academy of Medical Sciences of Ukraine" due to ischemic heart disease during 2015 – 2017, according to clinical criteria.

MATERIALS AND METHODS

Data Source

Investigators analyzed the data from medical histories of patients who were treated in "L.T. Mala National Institute of Therapy of the National Academy of Medical Sciences of Ukraine" during 2015-2017. Only medical records of patients with verified ischemic heart disease were eligible for the analysis. Early ischemic heart disease involves disease onset before the age of 60 in women and 55 in men (6). Disease verification has been conducted either on the basis of coronary angiography data, or on the basis of previous myocardial infarction with Q wave. The total of 600 medical records were analyzed.

Identification of patients with Familial Hypercholesterolemia

To identify patients with familial hypercholesterolemia the investigators used Dutch lipid clinic network criteria (Table 1).

Ethics Statement

The study was approved by the Ethical Committee of "L.T. Mala National Institute of Therapy of the National Academy of Medical Sciences of Ukraine"

Statistical analysis

Statistical analysis was performed using SPSS software, version 17.0. χ^2 test was used for comparison of clinical characteristics between groups of patients.

RESULTS

From all the medical records for the period 2015-2017, early ischemic heart disease was revealed in 89 patients. Average age of the patients included in the analysis was 49±4.5 years. Evaluation by clinical criteria allowed to suspect the presence of familial hypercholesterolemia in more than 14.8% of patients with early ischemic heart disease. Upon that, among these patients, 2 (2.2%) had definite diagnosis; 27 (30.3%) were likely to have diagnosis, 26 (29.7%) had possible diagnosis and in 34 (38.2%) patients it was unlikely to diagnose them with familial hypercholesterolemia. The distribution of patients as per familial hypercholesterolemia diagnosis criteria is shown in Fig. 1.

Investigators compared the groups with different degrees of diagnosis probability on the basis of disease course, age and risk factors (Table 2).

The patients with definite diagnosis of familial hypercholesterolemia were younger than patients with probable, possible and unlikely diagnosis. Smoking and hypertension were observed significantly more frequently among patients with unlikely diagnosis of familial hypercholesterolemia (Table 3).

It is additionally notable that among the patients included in this study “familial hypercholesterolemia” was not mentioned anywhere in their diagnosis.

Table 1. Clinical criteria for identification patients with familial hypercholesterolemia (Dutch clinics criteria - Dutch Lipid Clinics Network Criteria)

Family history	
A. First degree relatives with known premature (men < 55 y.o.; women < 60 y.o.) coronary or vascular disease or first degree relatives with known LDL above the 95th percentile	1
B. First degree relatives with tendiunous xanthomata and/or arcus cornealis or children < 18 y.o. with LDL above the 95th percentile	2
Clinical history	
A. Patients with premature (men < 55 y.o.; women < 60 y.o.) coronary artery disease	2
B. Patients with premature (men < 55 y.o.; women < 60 y.o.) cerebral or peripheral vascular disease	1
Physical examination	
A. Tendinous xanthomata	6
B. Arcus cornealis before 45 y.o.	4
LDL-C level	
A. LDL-C > 8,5 mmol/l	8
B. LDL-C 6,5 – 8,5 mmol/l	5
C. LDL-C 5 – 6,4 mmol/l	3
D. LDL-C 4 – 4,9 mmol/l (normal TG)	1
DNA analysis	
A. Functional mutation in the LDL-receptors, ApoB or PCSK9 gene	8
Use onle one score of groups, the highest applicable Diagnosis (diagnosis is based on total number of points obtained)	
‘Definite’ FH diagnosis requires	>8 points
‘Probable’ FH diagnosis requires	6 – 8 points
‘Possible’ FH diagnosis requires	3 – 5 points

Table 2. Characteristics of patients with early ischemic heart disease. *

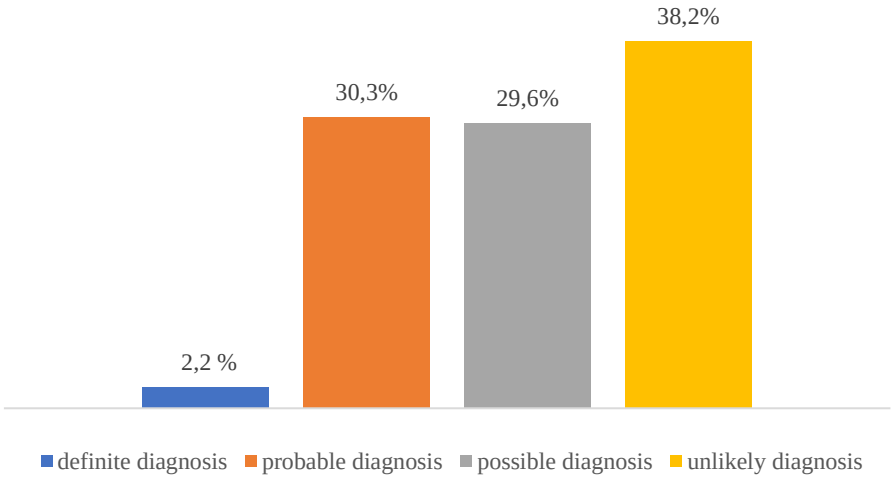
	Definite diagnosis n=2 (2,2 %) group 1	Probable diagnosis n=27 (30,3%) group 2	Possible diagnosis n=26 (29,7 %) group 3	Unlikely diagnosis n=34 (38,2 %) group 4	p
Age, years	37/39	41,2±5,7	51,4±6,3	50,3±8,7	P_{2-3}=0,001 P_{2-4}=0,001 p_{2-3}=0,588
Female, n (%)	1 male/ 1 female	17 (62,9%)	19 (73,1%)	4 (11,7%)	P_{2-3}=0,430 P_{2-4}=0,0001 P_{3-4}=0,0001
Smoking (%)	0	4 (14,8%)	5 (19,2%)	14 (41,7%)	P_{2-3}=0,669 P_{2-4}=0,025 P_{3-4}=0,070
Hypertension (%)	0	9 (33,3%)	11 (42,3%)	26 (76,5%)	P_{2-3}=0,500 P_{2-4}=0,002 p_{-3-4}=0,007
History of myocardial infarction (%)	0	12 (44,4%)	11 (42,3%)	19 (55,8%)	P_{2-3}=0,875 P_{2-4}=0,375 P_{3-4}=0,297
Clinically significant coronary atherosclerosis (%)	2	10 (37,1%)	7 (26,9%)	7 (20,5%)	P_{2-3}=0,430 P_{2-4}=0,155 P_{3-4}=0,565
Revascularisation (%)	0	4 (14,8%)	6 (23,1%)	2 (5,8%)	P_{2-3}=0,676 P_{2-4}=0,465 P_{3-4}=0,059
Stable angina (%)	2 (100%)	15 (55,5%)	15 (57,7%)	15 (44,1%)	P_{2-3}=0,875 P_{2-4}=0,375 P_{3-4}=0,297

*comparison was conducted between groups 2, 3 and 4, since in the first group there were only two patients.

Table 3. Values of cholesterol and its fractions in groups of patients with early ischemic heart disease.

	Definite n=2 (2,2 %) group 1	Probable n=27 (30,3%) group 2	Possible n=26 (29,7 %) group 3	Unlikely diagnosis n=34 (38,2 %) group 4	P
TC mmol/l	14,1/13,11	8,48±3,11	7,52±2,86	6,11±2,13	P_{2-3}=0,248 P_{2-4}=0,001 P_{3-4}=0,033
LDL – C, mmol/l	11,77/11,0	6,40±2,15	5,43±1,32	3,91±0,95	P_{2-3}=0,054 P_{2-4}=0,0001 P_{3-4}=0,0001
VLDL – C, mmol/l	0,62/0,42	1,07±0,38	0,76±0,29	1,12±0,35	P_{2-3}=0,002 P_{2-4}=0,596 P_{3-4}=0,0001
HDL –C, mmol/l	1,72/1,34	1,14±0,35	1,45±0,60	0,90±0,34	P_{2-3}=0,025 P_{2-4}=0,009 P_{3-4}=0,0001
TG, mmol/l	3,81/2,14	2,44±0,98	1,71±0,45	2,13±0,67	P_{2-3}=0,001 P_{2-4}=0,148 P_{3-4}=0,008

Fig. 1. Distribution of patients as per diagnosis of familial hypercholesterolemia based on Dutch Lipid Clinics Network Criteria



DISCUSSION

Clinical investigations have demonstrated that patients with early ischemic heart disease are also frequently diagnosed with familial hypercholesterolemia and doctors should therefore also consider this condition. Accordingly, further observation by family physicians has been conducted with slight alertness towards family members of the patients, and due to this, further examination of relatives was not performed and chances of disease were excluded. It has been shown that a diagnosis of familial hypercholesterolemia can increase patients' compliance with a healthy life style (7) and thus potentially improve outcomes.

Recent research has considered the incidence of familial hypercholesterolemia in the general population. Although studies were conducted in different ethnic groups and using different clinical criteria, most studies have demonstrated relatively high level of early ischemic heart disease among patients with known familial hypercholesterolemia. According to the United States National health and Nutrition Surveys, a personal history of early atherosclerotic disease was found in 59.1% of patients with a probable diagnosis and in 47.8% of patients with a definite diagnosis (8).

In addition, several studies have also showed that the frequency of familial hypercholesterolemia was significantly higher among the patients with ischemic heart disease than in the general population.

In our study, the incidence of familial hypercholesterolemia was 14.8% among patients with early ischemic heart disease. The reported prevalence of comorbidity varied according to the definition criteria. According the criteria of the American Heart Association, 2.5% of all patients with ischemic heart disease had familial hypercholesterolemia compared to 5.5% using Simone Broom's definition, and 1.6% patients according to the criteria of the Dutch Lipid Clinic (4). Among patients with stable coronary artery disease, 3.3% were diagnosed as having familial hypercholesterinemia (9).

The rate of familial hypercholesterolemia in our research was closer to the reported EUROASPIRE IV results. This registry enrolled only those patients with a diagnosed coronary pathology. Among 7044 patients included in EUROASPIRE IV, the prevalence of potential (considered to be both probable and possible) familial hypercholesterolemia was 8.35% in men and 11.4% in women (10). Faggiano P. et al. found that among patients that had survived acute coronary syndrome, 75% had a definite diagnosis of familial hypercholesterolemia and 60.9% of patients had a probable diagnosis. Among patients with stable coronary heart disease, a definite diagnosis of familial hypercholesterolemia was confirmed in 22.2% of the sample, and 29.1% had a probable diagnosis of the disease (11). In our study, the proportion of patients with a possible or probable diagnosis of familial hypercholesterolemia was significantly higher than these reported rates. According to our data, among patients with stable angina, 57.4% had a probable and 55.3% had a possible diagnosis of familial hypercholesterolemia. Furthermore, compared to the results of Nanchen et al. and Faggiano et al., our research suggests a significantly higher incidence of familial hypercholesteremia (4, 11). This high incidence of the disease in our study may be due to the fact that our study only included patients with early ischemic heart disease, while in the studies cited above, the data of patients with all forms of the condition were analyzed. The results reported by Cao et al. demonstrated that among patients with very early onset of coronary heart disease 38.1% had familial

hypercholesterolemia due to pathogenic mutations. According to the criteria of the Dutch Lipid Clinic Network, 26.7% of patients had a probable and 15.2% had a definite diagnosis of familial hypercholesterolemia (12). The data presented by Cao et al. are most similar to our results. Both studies included only patients with early ischemic heart diseases.

A relevant observation was presented by Pérez et al. in an analysis of a population of patients with molecularly defined familial hypercholesterolemia from the Spanish Familial Hypercholesterolemia Cohort Study (SAFEHEART). The median age of Spanish patients was similar to those of our patients who had a probable diagnosis (44,0 and 41,3). According to this study, atherosclerotic cardiovascular disease was present in 13.0% of patients with familial hypercholesterolemia and in only 4.7% of their unaffected relatives. The main difference between our study and Spanish registry was the age at which ischemic heart disease was diagnosed. The patients with confirmed ischemic heart disease included in our study were younger than patients with first manifestation of atherosclerotic events in the Spanish registry. In our study, the mean age of patients with early ischemic heart disease and probable familial hypercholesterolemia was 41,2±5,7 years old and in the Spanish study first manifestation of atherosclerotic events was at the age of 46,4±10,7 in male patients and 52±14,3 in female patients. One of the most controversial finding of the Spanish study was that familial hypercholesterolemia did not influence the rate of premature atherosclerotic cardiovascular disease. A premature atherosclerotic event was observed in 22.4% of patients with confirmed familial hypercholesterolemia and in 20.7% of their unaffected relatives (p=0,28). The authors rationalized this anomaly by suggesting that the relatively high prevalence of other cardiovascular risk factors was different from LDL-cholesterol in unaffected relatives (7).

Alternatively, the observed difference may be explained by the fact that familial hypercholesterolemia phenotype is highly variable, possibly due to both environmental and genetic factors (13, 14). Durst et al. suggested that this may be a result of the polygenic nature of the disorder, which, of course, can cause various clinical manifestations of the disease (15). Despite the recent emergence of modern methods of genetic analysis, it may still be impossible to determine the key mutation in all the cases. A pathogenic familial hypercholesteremia - causing mutation was detected in 30% of 885 patients tested. Elevated LDL-cholesterol and a personal or familial history of tendon xanthomata were independent predictors of a mutation (ORs range 5.32-15.2, P<0.001) (5).

Among patients with unlikely diagnosis of familial hypercholesterolemia, women prevailed significantly, and there were also significantly more patients with hypertension and smokers. Also, patients with unlikely diagnosis had significantly higher values of total cholesterol, LDL cholesterol and HDL cholesterol. Given that a larger number of patients with unlikely diagnosis of ischemic heart disease were females, it should be assumed that their disease had other development mechanisms, and it was not always due to high cholesterol (16). It should be noted that the prognosis in familial hypercholesterolemia may differ in men and women. Slack et al. in their study demonstrated that the risk of the first event differed in men and in women with family hypercholesterolemia. Results of this study demonstrated that the chances of fatal or nonfatal CHD for men and women were 5.4 and 0% by the age of 30, 51.4 and 12.2% by the age of 50, and 85.4 and 57% by the age of 60, respectively (17). Patients with likely diagnosis were significantly younger.

Summarizing the data, the rate of probable familial hypercholesterolemia among patients with early ischemic coronary disease was higher than 30%. These results demonstrated the needs of genetic confirmation and family members screening when suspected case of familial hypercholesterolemia is detected. Knowledge and perception of the diagnosis encourage patients to healthier life style.

CONCLUSION

Thus, this work demonstrated that despite frequent occurrence of familial hypercholesterolemia, doctors' alertness towards this disease has been noted to be quite low in Ukraine. It can be recommended to check all patients with early onset of ischemic heart disease in accordance to criteria of familial hypercholesterolemia. Development of the national register of patients with familial hypercholesterolemia is a crucial step in order to improve the situation with medical help to this group. Such register will allow to plan genetic testing in families where are members with familial hypercholesterolemia and treatment with statins and proprotein convertase subtilisin/kexin type 9 inhibitors.

CONFLICT OF INTEREST

Not declared.

REFERENCES

1. Pérez-Calahorra S, Sánchez-Hernández RM, Plana N, Marco-Benedi V, Pedro-Botet J, Almagro F, et al. Value of the Definition of Severe Familial Hypercholesterolemia for Stratification of Heterozygous Patients. Am J Cardiol 2017; 119(5): 742-8. PMID: 28081939 DOI: 10.1016/j.amjcard.2016.11.025
2. Singh S, Bittner V. Familial hypercholesterolemia--epidemiology, diagnosis, and screening. Curr Atheroscler Rep 2015; 17(2): 3-8. PMID: 25612857 DOI: 10.1007/s11883-014-0482-5
3. Amor-Salamanca A, Castillo S, Gonzalez-Vioque E, Dominguez F, Quintana L, Lluís-Ganella C, et al. Genetically Confirmed Familial Hypercholesterolemia in Patients With Acute Coronary Syndrome. J Am Coll Cardiol 2017; 70(14): 1732-40. PMID: 28958330 DOI: 10.1016/j.jacc.2017.08.009
4. Nanchen D, Gencer B, Auer R, Räber L, Stefanini GG, Klingenberg R, et al. Prevalence and management of familial hypercholesterolaemia in patients with acute coronary syndromes. Eur Heart J 2015; 36(36): 2438-45. PMID: 26142466 DOI: 10.1093/eurheartj/ehv289
5. Chan DC, Pang J, Hooper AJ, Bell DA, Bates TR, Burnett JR, et al. A comparative analysis of phenotypic predictors of mutations in familial hypercholesterolemia. J Clin Endocrinol Metab 2018; 103(4): 1704-14. PMID: 29408959 DOI: 10.1210/jc.2017-02622
6. Piepoli, MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. ESC Scientific Document Group. European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Atherosclerosis 2016; 37(252): 207-74. PMID: 27664503 DOI: 10.1016/j.atherosclerosis.2016.05.037
7. Perez L, Alonso R, Mata N, Saltijeral A, Muniz O, Rubio-Marin P, et al, SAFEHEART Investigators. Coronary Heart Disease, Peripheral Arterial Disease, and Stroke in Familial Hypercholesterolemia. Insight from SAFEHEART Registry (Spanish Familial Hypercholesterolemia Cohort Study). Arterioscler Thromb Vasc Biol 2016; Sep;36(9):2004-10. PMID: 27444203 DOI: 10.1161/ATVBAHA.116.307514
8. De Ferranti SD., Rodday AM, Mendelson MM, Wong JB, Leslie LR, Sheldrick RC. Prevalence of Familial Hypercholesterolemia in 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES) Clinical perspective. Circulation 2016; 133(11): 1067-1072. PMID: 26976914 DOI: 10.1161/CIRCULATIONAHA.115.018791
9. De Luca L, Arca M, Temporelli PL, Colivicchi F, Gonzini L, Lucci D, et al, START investigators. Prevalence and pharmacologic management of Familial Hypercholesteremia in unselected contemporary cohort of patients with stablr coronary disease. Clin Cardiol 2018 Aug; 41(8): 1075-83. PMCID: PMC6489755 DOI: 10.1002/clc.23031
10. De Backer G, Besseling J, Chapman J, Hovingh GK, Kastelein K, Ray K, et al, EUROASPIRE Investigators. Prevalence and management of familial hypercholesterolemia in coronary patints; an analysis of EURUASPIRE IV, a study of the European Society of Cardiology. Atherosclerosis 2015; Jul 241(1): 166-75. PMID: 25997074 DOI: 10.1016/j.atherosclerosis.2015.04.809
11. Faggiano P, Pirollo A, Griffo R, Ambrosetti M, Pedretti R, Scorcu G, et al. Prevalence and management of Familial Hypercholesterolemia in patients with coronary artery Disease. The heredity survey. Int J Crdiol 2018; 252: 193-8. PMID: 29249427 DOI: 10.1016/j.ijcard.2017.10.105
12. Cao Y-X, Wu N-Q, Sun D, Liu H-H, Li S, Guo Y-L, et al. Application of expanded genetic analysis in the diagnosis of familial hypercholesterolemia in patients with very early-onset coronary artery disease. J Transl Med 2018 Dec10; 16 (1):345. PMCID: PMC6288904 DOI: 10.1186/s12967-018-1737-7
13. Van der Graaf A, Hutten BA, Kastelein JJ, Vissers MN. Premature cardiovascular disease in young women with heterozygous familial hypercholesterolemia. Expert Rev Cardiovasc Ther 2006; 4(3): 345–35. PMID: 16716095 DOI: 10.1586/14779072.4.3.345
14. Jarauta E, Pérez-Ruiz MR, Pérez-Calahorra S, Mateo-Gallego R, Cenarro A, Cofán M, et al. Lipid phenotype and heritage pattern in families with genetic hypercholesterolemia not related to LDLR, APOB, PCSK9, or APOE. J Clin Lipidol 2016; 10(6): 1397-05. PMID: 27919357 DOI: 10.1016/j.jacl.2016.09.011
15. Durst R, Ibe UK, Shpitzen S, Schurr D, Eliav O, Futema M, et al. Molecular genetics of familial hypercholesterolemia in Israel-revisited. Atherosclerosis 2017; Feb (257): 55-63. PMID: 28104544 DOI: 10.1016/j.atherosclerosis.2016.12.021
16. Isayeva GS, Martynenko AV, Beloded OA, Struk TA, Vovchenko VN, Bondar TN. Effect of age, sex hormones and aldosterone on SCORE in perimenopausal women. Life Sci J 2015; 12: 44-49. DOI: 10.7537/marslsj1201s15.11
17. Slack J. Risks of ischemic heart-disease in familial hyperlipoproteinemic states. Lancet 1969; 2(7635): 1380–82. PMID: 4188273 DOI: 10.1016/s0140-6736(69)90930-1
18. Morita N et al; The Current Conditions and Lifestyles of Obese University Students. ; J Clin Med Res. 2018 Mar; 10(3): 240-246. doi: 10.14740/jocmr3329w.

POPULATION PHARMACOKINETICS OF VANCOMYCIN IN ADULT PATIENTS WITH LONG BONES' FRACTURES

Jasmina Milovanovic[1] Radica Zivkovic Zaric[1]*, Nikola Rosic[2], Dejana Ruzic Zecevic[1], Dragan Milovanovic[1], Marko Folic[1] and Slobodan M. Jankovic[1]
[1]*University of Kragujevac, Faculty of Medical Sciences, Department of Pharmacology and Toxicology, Kragujevac, Serbia*
[2]*Department of Clinical Pharmacology, Clinical Center Kragujevac, Serbia*

POPULACIONA FARMAKOKINETIKA VANKOMICINA KOD ODRASLIH PACIJENATA SA PRELOMIMA DUGIH KOSTIJU

Jasmina Milovanovic[1], Radica Živković Zarić[1]*, Nikola Rosić[2], Dejana Ružić Zečević[1], Dragan Milovanović[1], Marko Folić[1] i Slobodan M. Janković[1]
[1]*Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Katedra za farmakologiju i toksikologiju, Kragujevac, Srbija*
[2] *Služba za klinicku farmakologiju, Klinički centar Kragujevac, Srbija*

Received/Primljen: 05.04.2019. Accepted/Prihvaćen: 31.05.2019.

ABSTRACT

Vancomycin is a tricyclic glycopeptide antibiotic, mostly used in the treatment of severe staphylococcal and enterococcal infections, especially in orthopedic surgery.

The purpose of this analysis was to develop a population pharmacokinetic (PPK) model of vancomycine in hospitalized patients with bone fractures and identify important factors which influence its clearance (CL).

A total of ninety-nine measurements of vancomycin serum concentrations were used in our population modeling. A two-compartment model was applied to describe the pharmacokinetics of vancomycin using subroutines ADVAN3 and TRANS4.

The study population included patients of both sexes, with the mean age of 62.12±14.69 years and body weight of 80.32±12.44kg. Vancomycin was administered as intravenous infusion with average daily dose of 1772.73±521.34mg. Out of twenty different factors evaluated in the study (including demographic, clinical and laboratory data), only daily dose of vancomycin (DD) and co-medication with piperacillin/tazobactam (PT) showed significant effect on clearance of vancomycin. The final model was described by the following equation: CL (l/h) = 0.03 + 0.000468 x DD + 0.675 x PT. Bootstrapping was used for validation of the final model.

In conclusion, the main causes of variability in the clearance of vancomycin among adult patients with bone fractures are daily dose of vancomycin and co-medication with piperacillin/tazobactam.

***Keywords**: vancomycin, population pharmacokinetics, trauma, non-linear mixed effects model (NONMEM).*

SAŽETAK

Vankomicin je triciklicni glikopeptidni antibiotik, koji se koristi u terapiji teških infekcija izazvanih stafilokokom i enterokokom, posebno u ortopedskoj hirurgiji.

Svrha ovog istraživanja bila je da se razvije populacioni farmakokinetski (PPF) model vankomicina kod hospitalizovanih pacijenata sa prelomima dugih kostiju i da se utvrde faktori koji su bitni za klirens (KL) vankomicina.

Devedest devet uzoraka seruma sa izmerenim koncentracijama vankomicina je korišćeno za naš model. Model sa dva prostora je korišćen da opiše farmakokinetiku vankomicina sa potprogramima ADVAN3 i TRANS4.

Populacija je uključivala oba pola, sa prosečnom starošću 62,12±14,69 godina i telesnom težinom 80,32±12,44 kg. Vankomicin je primenjivan u obliku intravenske infuzije sa prosečnom dnevnom dozom 1772,73±521,34 mg. Analizirano je dvadeset faktora, a utvrđeno je da samo dnevna doza vankomicina i primena piperacilin tazobaktama značajno utiču na klirens vankomicina. Završni model je opisan jednačinom: KL (l/h) = 0.03 + 0.000468 x DD + 0.675 x PT. Butstrap analiza je korišćena za validaciju krajnjeg modela.

U zaključku, glavni uzroci varijabilnosti klirensa vankomicina među odraslim pacijentima sa prelomima dugih kostiju jesu dnevna doza vankomicina i komedikacija piperacilin tazobaktamom.

***Ključne reči:** vankomicin, populaciona farmakokinetika, trauma, NONMEM.*

ABBREVIATIONS

acute kidney injury (AKI)
alanine aminotransferase (ALT)
angiotensin-converting enzyme (ACE) inhibitors
aspartate aminotransferase (AST)
clearance (CL)
coefficient of variation (CV)
colistin (COL)
C-reactive protein (CRP)
fibrinogen (FB)
first-order conditional estimation (FOCE)
furosemide (FUR)
heparin (HEP)
minimum objective function (MOF)
non-linear mixed effects model (NONMEM)
nonsteroidal anti-inflammatory drugs (NSAIDs)
piperacillin/tazobactam (PT)
population pharmacokinetics (PPK)
population predicted (PRED)
pro-brain natriuretic peptide (proBNP)
therapeutic drug monitoring (TDM)

sciendo
UDK: 615.33.03
616-089.23-022.3
616.71-001.5-089.23
Ser J Exp Clin Res 2021; 22 (3): 233-240
DOI: 10.2478/sjecr-2019-0025

Corresponding author:
Radica Živković Zarić, MD, PhD
Faculty of Medical Sciences, University of Kragujevac
69 Svetozara Markovica Street
34000 Kragujevac, Serbia
radica_zivkovic@yahoo.com

INTRODUCTION

Vancomycin is a tricyclic glycopeptide antibiotic, first isolated in 1956, mostly used for the treatment of severe staphylococcal and enterococcal infections. The mechanism of action of vancomycin is by inhibiting peptidoglycan fusion within the cell wall by binding alanine (1). Increased incidence of meticillin resistant staphylococcal strains led to more extensive use of vancomycin in various patient populations (2).

Regardless of its hydrophilicity, vancomycin is extensively distributed, as its volume of distribution ranges between 0.4 and 1 l/kg of the total body weight. About 55% of drug in plasma is bound to human serum proteins, mostly to albumin and IgA. Following intravenous administration, vancomycin is minimally metabolized and renal elimination accounts for 80–90% of vancomycin clearance (3-5). Vancomycin pharmacokinetics has been described by one-, two-, or three-compartment models (2-4).The elimination half-life ranges from 3 to 9 hours in patients with normal renal function. Data suggest that maintaining vancomycin trough values above 15 mg/l increases the risk of nephrotoxicity, but low concentrations may result in less effective therapy and an increased bacterial resistance. On the other hand, it was reported that dosing regimens with 4g of vancomycin per day had been related with a high rate of nephrotoxicity or ototoxicity (6, 7). All of these facts created a need to more carefully inspect the factors that influence variability of vancomycin pharmacokinetics (2).

Different patients' conditions such as renal function, type of dialysis or presence of various diseases could influence vancomycin pharmacokinetics (8). Only a few population pharmacokinetic studies of vancomycin were performed in specific subgroups of patients, like neonates, pediatric patients, obese patients and neurosurgical patients among others, and no reports on vancomycin pharmacokinetics in patients with bone fractures were previously published (3, 9-11).

THE AIM OF THE PAPER

The aim of our study was to calculate average values of serum vancomycin concentrations and determine factors that may affect them in adult patients hospitalized due to long bones' fracture.

METHODS

Patient data

Target population consisted of 99 inpatients with long bones' fractures, hospitalized in Clinical Center (Kragujevac, Serbia), where vancomycin was administered as an intravenous infusion. Serum samples were prospectively collected using routine therapeutic drug monitoring (TDM) from January to September 2017. The study protocol was approved by the Ethics Committee of the Clinical Center Kragujevac (N_0 01-1267, approved on February 1st 2016) and informed written consent was obtained from all the participants enrolled. Also, the research was conducted in accordance with the principles of the Helsinki Declaration.

The data were collected from medical documentation and included records related to patient demographic characteristics (body weight, age and sex), value of laboratory tests (creatinine clearance, serum albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), C-reactive protein (CRP), fibrinogen (FB), pro-brain natriuretic peptide (proBNP)) and clinical data (length of hospitalization, presence of sepsis and concomitant medications). All variables are summarized in Table 1. The inclusion criteria were: adult patients (>18 years old) hospitalized due to fracture(s) of long bones and an intravenous administration of vancomycin for at least 3 days without changes in the daily dose. Patients on dialysis, with history of cirrhosis and various types of cancer were excluded. Serum concentrations of vancomycin were measured by immunoassay using Cobas®e 601 analyzer (Roche Diagnostics, Mannheim, Germany), according to the manufacturer's instructions. To ensure that the drug concentrations were at steady-state, all samples were obtained after 72h hours of repeated doses of vancomycin. The trough serum concentrations were the most often recorded (from seventy-eight patients), while only 21 blood samples were taken 1-3h after administration of the drug.

Population pharmacokinetics analysis

Pooled data were available from all patients and analyzed using the NONMEM software version 7.3.0 (Icon Development Solution, MD,) with FOCE (first-order conditional estimation) approach with interaction between parameters included in our population pharmacokinetics (PPK) modeling (12, 13). We evaluated two structural models (one-compartment and two-compartment) in accordance with the literature data related to vancomycin pharmacokinetics. The base model was selected according to the size of the minimum objective function (defined as -2 timed the log-likelihood - MOF) and by the insight into diagnostic plots. Subroutines ADVAN3 and TRANS4 were utilized in a two-compartment model to describe pharmacokinetics of vancomycin and its clearance as the main parameter. Normal distribution of the individual pharmacokinetic parameters was assumed by our model. At this phase of the study, we also investigated various models of error to account for both inter-individual and residual variability. The inter-individual variability was tested using additive and exponential error models, while residual variability was tested using an additive, exponential, constant coefficient of variation (CCV) and combined (additive and CCV) error models.

The following demographic, clinical and laboratory test data were collected for evaluation as potential covariates: total body weight (TBW), age and sex of patients, length of hospitalization, presence of sepsis, total daily dose of vancomycin, creatinine clearance, serum albumin, total bilirubin, AST, ALT, CRP, fibrinogen, proBNP and co-medication with colistin (COL), furosemide (FUR), *piperacillin*/

tazobactam (PT), nonsteroidal anti-inflammatory drugs (NSAIDs), heparin (HEP) and angiotensin-converting enzyme (ACE) inhibitors. All continuous variables examined in the study were not parameterized. The covariate model was built in stepwise manner where each covariate was added one at a time using linear or nonlinear manner. To compare individual covariate models, we used change in the MOF values and the visual inspection of plots in order to estimate better fitting of data relative to the base model. The reduction in the MOF produced by inclusion of a covariate for at least 3.84 ($p<0.05$, d.f.=1) and also the improvements of the fitting data were the main criteria for inclusion of covariate in the full model. The full model was created by insertion of all significant covariates at the same time. This model was further tested by the backward deletion process for each covariate, one at a time, to obtain the final model. An increase in the MOF of at least 6.64 ($p<0.01$, d.f.=1) was used as the main criteria for retaining significant covariate in the final model. During all levels in the building of the final PPK model for vancomycin clearance, we evaluated presence of the reduction in both mentioned variability and also the improvements in diagnostic plot of the observed concentrations versus population predicted concentrations of vancomycin.

In order to validate the derived PPK model and estimate its predictive performance, we applied the bootstrapping analysis. This non-parametric method is a resembling technique that includes large number of data replicates (several hundred or thousand) with replacement from the index set using the individual patients as the sampling unit. Each of the bootstrap data sets was fitted to the final model to obtain the bootstrap estimated values of pharmacokinetic parameters and their variability was tested using NONMEM software. The mean values of estimated PK parameters and 2.5th–97.5th percentile of the bootstrap data set parameters were compared to the final pharmacokinetic parameter estimates.

RESULTS

A total of ninety-nine vancomycin serum concentrations from adult inpatients with long bone fractures were included in our population modeling. A two-compartment model was applied to describe the pharmacokinetics of vancomycin. Our results have shown that an exponential model was the best model that described the inter-individual variability, while the residual error was incorporated as an additive error model. The study population included patients of both sexes with a wide age range from 20 to 86 years. The mean value of body weight was 80.32±12.44 kg, and it ranged from 60 to 110 kg. The drug was usually administered twice a day as intravenous infusion with an average daily dose of 1770 mg (500-3000 mg). Furthermore, our population was very heterogeneous in terms of renal function and included patients with both normal (n=44) and impaired renal function (n=55). The clearance of creatinine varied from 30 to 252 ml/min, with a mean value of 93.22±51.05 ml/min. Patient characteristics are summarized in Table 1. Estimates of vancomycin pharmacokinetic parameters in the target population were 0.922 l/h and 11.1 l for the population value of clearance and the volume of distribution, respectively. The MOF value in this stage was 1103.714 units and both inter-individual and residual variability for clearance of vancomycin were 57.43% and 48.47% expressed as coefficient of variation (CV), respectively.

As a result of the univariate model analyses, a total of seven covariates (daily dose, creatinine clearance, AST, CRP and co-medication with furosemid, piperacillin/tazobactam and NSAIDs) produced significant decreases in MOF values and were detected as influential covariates in the full model. These data are shown in Table 2. Using backward deletion process, only two covariates (daily dose of vancomycin and co-medication with piperacillin/tazobactam) were retained in the final PPK model. Derived population pharmacokinetics model which describes the clearance of vancomycin in the target population is:

$$CL\ (l/h) = 0.03 + 0.000468 \times DD + 0.675 \times PT$$

where 0.03 is a typical population value of clearance, while 0.000468 and 0.675 are magnitudes of effect of vancomycin daily dose and co-medication with *piperacillin*/tazobactam, respectively.

The goodness-of-fit plots indicate a good fit of the data from the final regression model. Population predicted (PRED) values of vancomycin concentrations versus its observed concentrations (DV) in the base model and the final model are shown in Figure 1. Compared to the base model, there is a reduction in coefficients of variation by 19.56% and 16.55% for inter-individual and residual variability, respectively.

Two hundred bootstrap runs were included in the bootstrap analysis. Table 3 shows the summary of parameter estimates and their 95% confidence intervals for the final PPK model obtained by the bootstrap analysis. Furthermore, the mean values of parameter estimates using bootstrap were comparable with the values obtained from original NONMEM analysis, indicating that the estimates of the population PK parameters in the final model were accurate and the model was stable.

Table1. Demographic characteristics of the patients, laboratory and clinical data.

Characteristics	Index set (mean values ± standard deviation)	Range for index set
Number of patients	99	
Number of observations	99	
Gender (male/female)	60/39	
Total body weight (kg)	80.32±12.44	60-110
Age (years)	62.12±14.69	20-86
Vancomycin dose (mg/day)	1772.73±521.34	500-3000
Length of hospitalization (day)	16.06±14.76	1-90
Creatinine clearance (ml/min)	93.23±51.05	30-252
Serum albumin (g/l)	26.71±3.45	13-40
Total bilirubin (µg/l)	12.98±49.12	4.4-493.5
AST concentration (IU/l)	37.76±46.59	9-448
ALT concentration (IU/l)	30.86±52.76	4-436
C-reactive protein (mg/l)	96.57±79.83	1.04-303
Fibrinogen (g/l)	3.49±1.27	1.81-8.17
proBNP (pg/ml)	688.29±2371.07	200-22311
Presence of sepsis (yes/no)	8/91	
Vancomycin + comedication with:		
Colistin	10	
Furosemide	23	
Piperacillin/tazobactam	7	
NSAIDs	23	
Heparin	62	
ACE inhibitors	15	

Table2. Values of minimum objective function for univariate regression models of examined covariates in the process of building a full pharmacokinetic model for vancomycin clearance.

Clearance models	Minimum objective function (MOF)	p-value **
BASE MODEL		
$CL=\theta_1 x\ EXP(ETA(1))$		
REGRESSION MODELS		
$CL=\theta_1 x\ EXP(ETA(1)) + \theta_3 x\ TBW$		>0.05
$CL=\theta_1\ x\ EXP(ETA(1)) + \theta_4\ x\ AGE$	446.478	>0.05
$CL=\theta_1 x\ EXP(ETA(1)) + \theta_5 x\ SEX$	0.005	>0.05
$CL=\theta_1 x\ EXP(ETA(1)) + \theta_6\ x\ DD$	84.698	<0.05
$CL=\theta_1\ x\ EXP(ETA(1)) + \theta_7 x\ CLcr$	34.03	<0.05
$CL=\theta_1 x\ EXP(ETA(1)) + \theta_8 x\ LP$	0.102	>0.05
$CL=\theta_1 x\ EXP(ETA(1)) +\theta_9 x\ ALB$	0.415	>0.05
$CL=\theta_1 x\ EXP(ETA(1)) +\theta_{10} x\ BIL$	0.308	>0.05
$CL=\theta_1\ x\ EXP(ETA(1)) +\theta_{11} x\ AST$	25.186	<0.05

Clearance models	Minimum objective function (MOF)	p-value **
$CL=\theta_1$ x EXP(ETA(1)) $+\theta_{12}$x ALT	0.923	>0.05
$CL=\theta_1$ x EXP(ETA(1)) + θ_{13} x CRP	5.054	<0.05
$CL=\theta_1$ x EXP(ETA(1)) + θ_{14} x FIB	0.740	>0.05
$CL=\theta_1$ x EXP(ETA(1))+θ_{15}x proBNP	0.602	>0.05
$CL=\theta_1$ x EXP(ETA(1)) + θ_{16} x SEP	0.533	>0.05
$CL=\theta_1$ x EXP(ETA(1)) +θ_{17}x COL	3.245	>0.05
$CL=\theta_1$x EXP(ETA(1)) +θ_{18}x FUR	3.95	<0.05
$CL=\theta_1$x EXP(ETA(1)) + θ_{18}x TAZ	23.277	<0.05
$CL=\theta_1$x EXP(ETA(1)) +θ_{19}x NSAIDs	15.628	<0.05
$CL=\theta_1$x EXP(ETA(1)) +θ_{20}x HEP	0.068	>0.05
$CL=\theta_1$x EXP(ETA(1)) +θ_{21}x ACE	0.612	>0.05

CL, clearance (l/h); θ_1,typical value of CL; ETA(1), interindividual variability in CL; [d]θ_3 to θ_{21}, slopes of the covariate effects; TBW, patient´s body weight (kg); SEX, takes the value 1 for male and 0 for female; [g] DD, daily dose of vancomycin (mg/day); CLcr, creatinine clearance (ml/min.); LP, length of hosptalization (day); ALB, serum albumin cholesterol (g/l); BIL, total bilirubin (μg//l); AST, aspartate aminotransferase (IU/l); ALT, alanine aminotransferase (IU/l); CRP, C-reactive protein (mg/l); FIB, fibrinogen (g/l); proBNP, pro-brain natriuretic peptide(pg/ml); COL, FUR, TAZ, NSAIDs, HEP and ACE, co-medication with colistin, furosemid, tazocin, nonsteroidal anti-inflammatory drugs, heparin and angiotensin-converting-enzyme inhibitortakes the value 1 if the patient received co-medication and 0 otherwise

**p-value for the MOF difference between the base and tested models

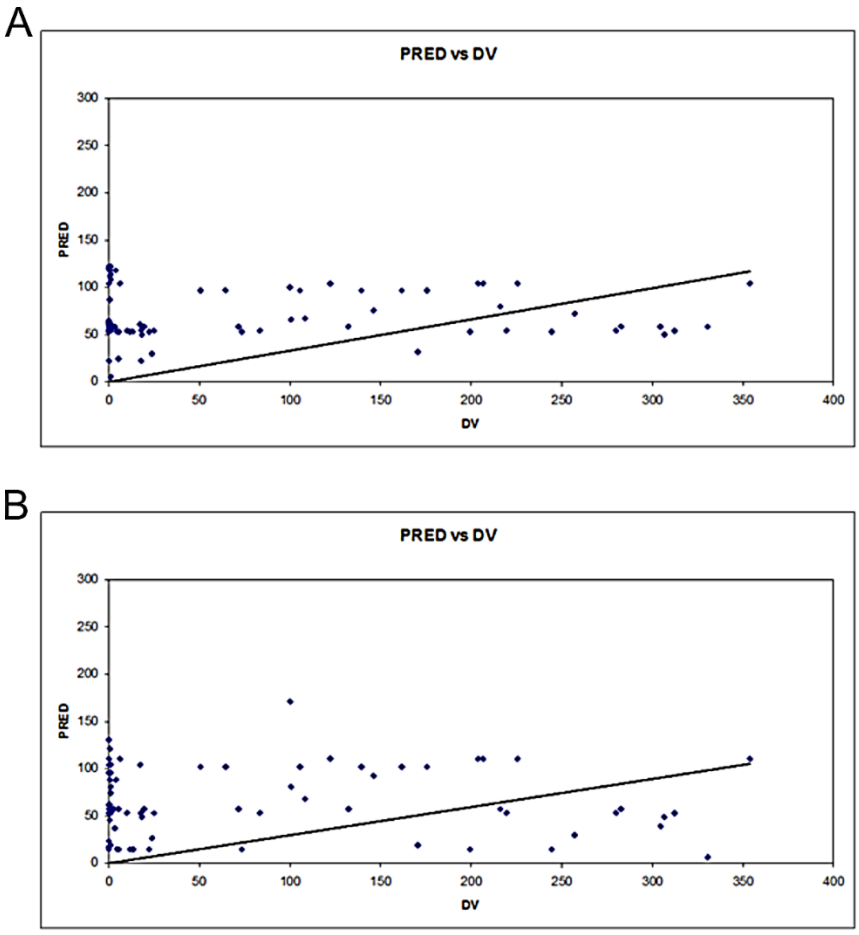
Table 3. The final model parameter estimates

Parameter	NONMEM		Bootstrap analysis	
	Estimate	95% CI*	Estimate	95% CI**
Clearance of vancomycin - CL (l/h)	0.03	0.023-0.035	0.029	0.025-0.032
Central volume of distribution -	13.2	9.84-16.56	13.22	9.09-17.35
Intercompartment clearance Q(l/h)	0.0001	0.00008-0.0001	0.0001	0.00009-0.00011
Daily dose (mg/day)	0.000468	0.000365-0.000571	0.000464	0.000322-0.000507
Tazacin	0.675	0.5076-0.8424	0.676	0.592-0.861
Interindividual variance of clearance - ω^2_{CL}	0.134	0.0817-0.1863	0.133	0.0801-0.1860
Residual variance - σ^2	0.097	0.0527-0.1413	0.096	0.0510-0.1410

* (Estimate)±1.96*(standard error of the estimate)

** 2.5th and 97.5th percentile of the ranked bootstrap parameter estimates

Figure 1. Predicted vancomycin concentrations versus measured concentrations in the base model (a) and the final model (b), respectively.



DISCUSSION

Current study used a population approach to establish the pharmacokinetic parameters of vancomycin in Serbian patients with long bones' fractures, accounting for its large pharmacokinetic variability. Using two-compartment model, typical values of clearance and volume of distribution were calculated, and daily dose of vancomycin and co-medication with piperacillin/tazobactam confirmed as factors with significant influence on clearance of vancomycin.

Higher doses of vancomycin were associated with larger clearance of vancomycin and lower trough serum concentration of vancomycin in our study. Such result is not the first one reported, as Bakke et al. presented similar results, with 70-80 percent of the patients not achieving minimum threshold value of ≥ 15 mg/l (14). Campassi et al. demonstrated that patients with augmented renal clearance had lower serum concentrations of vancomycin during the first days of therapy despite higher doses, and none of the patients reached therapeutic levels on the first day of the therapy (15). Some authors have proposed that increased loading doses and higher dose frequencies or continuous infusions are necessary in order to achieve higher success rates (16). On the other hand, vancomycin serum concentrations during the first days of therapy also depend on creatinine clearance and low creatinine clearance levels can result in supratherapeutic vancomycin concentrations (17). Hutshala et al. also suggested that more severe impact on renal function might be due to potentially high vancomycin peak concentrations during intermittent infusion. In contrast, constant lower concentrations of vancomycin seem to cause much less renal damage (18). One of the possible explanations of relation between higher doses of vancomycin and its larger clearance could be reduced reabsorption of vancomycin from ultra-filtrate due to tubular toxicity of this drug. Indeed, necrosis of tubular cells was confirmed in histological studies of kidney biopsies taken from the patients who experienced vancomycin-induced renal toxicity, and vancomycin is both secreted and reabsorbed by renal tubular cells (19, 20).

The only medication which significantly affected vancomycin CL in our patients was piperacillin/tazobactam (PT). Piperacillin/tazobactam, similar to the most beta-lactams, was rarely associated with acute kidney injury and incidence of piperacillin/tazobactam's nephrotoxicity reported in the literature was less than 1% (21). However, recent meta-analysis that included 14 studies reported that co-administration of vancomycin and piperacillin/tazobactam compared to vancomycin and "any β-lactam" resulted in the adjusted odds ratio for acute kidney injury in adults of 3.15 (95% confidence interval [CI], =1.72-5.76) (22). The mechanism by which piperacillin/tazobactam had influence on vancomycin clearance in not well known. It has been thought that vancomycin may cause direct proximal tubular toxicity. The concomitant use of vancomycin and PT has been hypothesized to potentiate acute kidney injury (AKI) via acute interstitial nephritis or decreased secretion of creatinine and vancomycin, but further investigation was considered necessary to confirm those facts (23). By increasing toxic effect of vancomycin on renal tubules, piperacillin may further decrease its reabsorption, leading to increase in vancomycin clearance (24).

Relation between creatinine and vancomycin clearance has been described in various studies (3, 8, 23, 24). We did not observe such relation in our patients. Furthermore, there are studies that supported our observation (27, 28). The existence of a nonrenal mechanism for vancomycin elimination may explain the relatively high values of vancomycin clearances observed in patients with compromised renal function. Hepatic conjugation of vancomycin would seem the most possible nonrenal route of excretion. The vancomycin particle has molecular weight of 1,450 and has essential chemical groups for conjugation with other compounds (27). Some authors reported measurable vancomycin concentrations in the bile after intravenous administration of vancomycin, which is also supporting the idea of extrarenal way of vancomycin elimination (28).

In some earlier pharmacokinetic studies, it was suggested that patients with malignancy had increased clearance of vancomycin (29). Conversely, other authors reported that patients with acute myeloid leukemia had lower clearance of vancomycin (1). It was also noticed that body weight may affect clearance of vancomycin, as increase in weight was related to higher values of both clearance and volume of distribution (3, 30). Finally, some authors showed that furosemide may influence vancomycin clearance, while the others concluded that concomitant drugs had no influence on clearance (9.25).

CONCLUSION

In conclusion, clearance of vancomycin positively correlated with administered daily dose of that drug and significantly increased by co-medication with piperacillin/tazobactam. This should be taken into account when dosing vancomycin in critically ill patients with fractures of long bones who frequently require high doses of the drug and combination of antibiotic therapy.

ACKNOWLEDGEMENTS

This study was partially financially supported by Grant No 175007 by the Serbian Ministry of Education, Science and Technological Development. The authors declare that they have no conflict of interest.

REFERENCE

1. Jarkowski A, Forrest A, Sweeney RP et al. Characterization of vancomycin pharmacokinetics in the adult acute myeloid leukemia population. J Oncol Pharm Pract. 2012;18(1):91-6.
2. Marsot A, Boulamery A, Bruguerolle B et al. Vancomycin: A Review of Population Pharmacokinetic Analyses. Clin Pharmacokinet. 2012;51(1):1-13.
3. Adane ED, Herald M, Koura F. Pharmacokinetics of Vancomycin in Extremely Obese Patients with Suspected or Confirmed Staphylococcus aureus Infections. Pharmacotherapy. 2015;35(2):127-39.
4. Rodvold KA, Blum RA, Fischer JH et al. Vancomycin pharmacokinetics in patients with various degrees of renal function. Antimicrob Agents Chemother. 1988;6:848-52.
5. Darko W, Medicis JJ, Smith A et al. Mississippi Mud No More: Cost-Effectiveness of Pharmacokinetic Dosage Adjustment of Vancomycin to Prevent Nephrotoxicity. Pharmacotherapy. 2003;23(5):643-50.
6. Lodise TP, Patel N, Lomaestro BM et al. Relationship between Initial Vancomycin Concentration-Time Profile and Nephrotoxicity among Hospitalized Patients. Clin Infect Dis. 2009;49(4):507-14.
7. De Hoog M, Mouton JW, Van den Anker JN. New dosing strategies for antibacterial agents in the neonate. Semin Fetal Neonatal Med. 2005;10:185-94.
8. Purwonugroho TA, Chulavatnatol S, Preechagoon Y et al. Population Pharmacokinetics of Vancomycin in Thai Patients. Scientific World Journal. 2012;2012:762649.
9. Lin WW, Wu W, Jiao Z et al. Population pharmacokinetics of vancomycin in adult Chinese patients with post-craniotomy meningitis and its application in individualised dosage regimens. Eur J Clin Pharmacol. 2016;72(1):29-37.
10. Stockmann C, Hersh AL, Roberts JK et al. Predictive Performance of a Vancomycin Population Pharmacokinetic Model in Neonates. Infect Dis Ther. 2015;4(2):187-98.

11. Hahn A, Frenck RW Jr, Zou Y et al. Validation of a pediatric population pharmacokinetic model for vancomycin. Ther Drug Monit. 2015;37(3):413-6.
12. Beal SL, Boeckmann AJ, Sheiner LB. NONMEM users guide. Parts I–VIII ICON Development Solutions.
13. Jamsen KM, McLeay SC, Barras MA, et al. Reporting a population pharmacokinetic-pharmacodynamic study: a journal's perspective. Clin Pharmacokinet. 2014;53(2):111-2.
14. Bakke V, Sporsem H, Von der Lippe E et al. Vancomycin levels are frequently subtherapeutic in critically ill patients: a prospective observational study.Acta Anaesthesiol Scand. 2017;61(6): 627-35.
15. Campassi ML, Gonzalez MC, Masevicius FD et al. Augmented renal clearance in critically ill patients: incidence, associated factors and effects on vancomycin treatment. Rev Bras Ter Intensiva. 2014; 26:13-20.
16. Rybak MJ, Lomaestro BM, Rotschafer JC et al. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the infectious diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis. 2009;49: 325–7.
17. Saugel B, Gramm C, Wagner JY et al. Evaluation of a dosing regimen for continuous vancomycin infusion in critically ill patients: an observational study in intensive care unit patients. J Crit Care. 2014; 29:351-5.
18. Hutschala D, Kinstner C, Skhirdladze K et al. Influence of Vancomycin on Renal Function in Critically Ill Patients after Cardiac Surgery: Continuous versus Intermittent Infusion. Anesthesiology. 2009;111(2): 356-65.
19. Bamgbola O. Review of vancomycin-induced renal toxicity: an update. Ther Adv Endocrinol Metab. 2016;7(3):136-47.
20. Nakamura T, Hashimoto Y, Kokuryo T et al. Effects of fosfomycin and imipenem/cilastatin on nephrotoxicity and renal excretion of vancomycin in rats. Pharmaceutical research.1998;15(5):734-8.
21. Philadelphia, PA: Pfizer; 2012. Zosyn (piperacillin - tazobactam) package insert. https://www.pfizer medicalinformation.com/en-us/zosyn/storage-handling.
22. Hammond DA, Smith MN, Li C, et al. Systematic Review and Meta-Analysis of Acute Kidney Injury Associated with Concomitant Vancomycin and Piperacillin/tazobactam. Clin Infect Dis. 2017;64 (5):666-74.
23. Blevins AM, Lashinsky JN, McCammon C et al. Incidence of Acute Kidney Injury in Critically Ill Patients Receiving Vancomycin with Concomitant Piperacillin/Tazobactam, Cefepime, or Merope nem. Antimicrob Agents Chemother. 2019. pii:AAC.02658-18.
24. Kim T, Kandiah S, Patel M et al. Risk factors for kidney injury during vancomycin and piperacillin/ tazobactam administration, including increased odds of injury with combination therapy. BMC research notes. 2015;8(1):579.
25. Medellín-Garibay SE, Ortiz-Martín B, Rueda-Naharro A et al. Pharmacokinetics of vancomycin and dosing recommendations for trauma patients. J Antimicrob Chemother. 2016;71(2):471-9.
26. Sanchez JL, Dominguez AR, Lane JR et al. Population pharmacokinetics of vancomycin in adult and geriatric patients: Comparison of eleven approaches. Int J Clin Pharmacol Ther. 2010;48: 525–33.
27. Garaud JJ, Regnier B, Ingleber F et al. Vancomycin pharmacokinetics in critically ill patients. J Antimicrob Chemother. 1984;14, Suppl. D, 53-5.
28. Rotschafer JC, Crossley K, Zaske DE et al. Pharmacokinetics of Vancomycin: Observations in 28 Patients and Dosage Recommendations. Antimicrob Agents Chemother. 1982;22(3):391-4.
29. Al-Kofide H, Zaghloul I, Al-Naim L Pharmacokinetics of vancomycin in adult cancer patients. J Oncol Pharm Pract. 2010;16(4):245-50.
30. Moore JN, Healy JR, Thoma BN et al. A Population Pharmacokinetic Model for Vancomycin in Adult Patients Receiving Extracorporeal Membrane. CPT Pharmacometrics Syst Pharmacol. 2016;5(9): 495-502.

THE EFFECTS OF *SATUREJA HORTENSIS L.* EXTRACT ON CISPLATIN-INDUCED BEHAVIORAL ALTERATIONS IN THE TAIL SUSPENSION TEST

Igor Kumburovic[1*], Davor Kumburovic[1*], Sanja Vujovic[2], Zlata Rajkovic[2] and Stefan Velickovic[2]
[1]*University of Kragujevac, Faculty of Medical Sciences, Department of Physiology, Kragujevac, Serbia*
[2]*University of Kragujevac, Faculty of Medical Sciences, Department of Dentistry, Kragujevac, Serbia*

**Authors Igor Kumburovic and Davor Kumburovic contributed equally to this study as the first author*

EFEKTI PRIMENE EKSTRAKTA BILJKE *SATUREJA HORTENSIS L.* NA BIHEVIORALNE MANIFESTACIJE NEUROTOKSIČNOSTI IZAZVANE CISPLATINOM KOD PACOVA

Igor Kumburović[1*], Davor Kumburović[1*], Sanja Vujović[2], Zlata Rajković[2] i Stefan Veličković[2]
[1]*Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Katedra za fiziologiju, Kragujevac, Srbija*
[2]*Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Katedra za stomatologiju, Kragujevac, Srbija*

Received/Primljen: 04.06.2019. Accepted/Prihvaćen: 08.06.2019.

ABSTRACT

In order to evaluate the effects of Satureja hortensis L. extract on cisplatin-induced behavioral alterations in the tail suspension test (TST), we included 35 male Wistar albino rats in this study, divided into 7 equal groups. Cisplatin was administered (single dose of 7.5 mg/kg, i.p., on the fifth day) alone, and in groups with orally administered (for 10 days) Satureja hortensis L. extract (50, 100, and 200 mg/kg), and silymarin (100 mg/kg) in individual groups. The behavioral testing was performed in TST, and the following parameters were obtained: the latency to the first immobility, the number of immobility episodes, and the total duration of immobility. Cisplatin application increased the latency to the first immobility, but decreased the number of immobility episodes and the total duration of immobility. Oral administration of Satureja hortensis L. extract in a dose of 100 mg/kg attenuated cisplatin-induced alterations, and those effects were similar to silymarin group. The extract in a dose of 200 mg/kg diminished cisplatin-induced effect only for the total duration of immobility, while in a dose of 50 mg/kg, the extract had no impact on cisplatin effects. Although common use of this methodology would lead to a conclusion that cisplatin produced antidepressant effect, comparison with certain literature data allows the conclusion that this action of cisplatin may be attributed to its anxiogenic action that was attenuated by antioxidant supplementation (Satureja hortensis L.) in an adequate dose (100 mg/kg).

***Keywords**: cisplatin, Satureja hortensis L., anxiety, depression, tail suspension test, rats.*

SAŽETAK

U cilju ispitivanja efekata ekstrakta Satureje hortensis L. na promene ponašanja izazvane cisplatinom u testu kačenja za rep (TKR), u studiju je uključeno 35 muških Wistar albino pacova, podeljenih u 7 jednakih grupa. Cisplatina je primenjivana (pojedinacna doza od 7.5 mg/kg, i.p., petog dana) samostalno, i u grupama sa oralnom primenom (tokom 10 dana) ekstrakta Satureje hortensis L. (50, 100 i 200 mg/kg), i silimarina (100 mg/kg) u pojedinačnim grupama. Bihejvioralno testiranje je sprovedeno u TKR, uz određivanje sledećih parametara: vreme do prve imobilnosti, broj epizoda imobilnosti i ukupno trajanje imobilnosti. Primena cisplatine je povećavala vreme do prve imobilnosti, dok je skraćivala broj epizoda imobilnosti i ukupno trajanje imobilnosti. Oralna primena ekstrakta Satureje hortensis L. u dozi od 100 mg/kg je smanjivala promene izazvane cisplatinom, što je bilo slično efektima u grupi sa silimarinom. Ekstrakt je u dozi od 200 mg/kg umanjio efekat cisplatine samo za ukupno trajanje imobilnosti, dok u dozi od 50 mg/kg ekstrakt nije imao uticaja na efekte cisplatine. Iako bi uobičajena primena ove metodologije dovela do zaključka da cisplatina izaziva antidepresantni efekat, poređenje sa odgovarajućim podacima iz literature omogućava zaključak da se uticaj cipslatine može pripisati njenoj anksiogenoj ulozi, što je bilo umanjeno antioksidantnom suplementacijom (Satureja hortensis L.) u odgovarajućoj dozi (100 mg/kg).

***Ključne reči:** cisplatina, Satureja hortensis L., anksioznost, depresivnost, test kačenja za rep, pacovi*

sciendo
UDK: 615.322:582.943
Ser J Exp Clin Res 2021; 22 (3): 241-247
DOI: 10.2478/sjecr-2019-0029

Corresponding author:
Stefan Velickovic
velickovicstefan91@gmail.com

INTRODUCTION

Cisplatin is one of the most widely used anticancer drugs worldwide. Alone or along with other cytostatic agents, cisplatin has been considered a first-line therapy in the treatment of various malignancies for decades, especiallysolid tumors such as ovarian, testicular, head, neck and small cell lung cancers (1).

Despite its well confirmed efficacy in the treatment of a numerous types of cancers, clinical use of cisplatin is often limited because of the dose- and duration-dependent cell resistance. Although, up to date, more than 40 specific types of cisplatin adverse effects have been recognized, according to their incidence and severity, cisplatin side effects have been categorized into seven main groups: nephrotoxicity, ototoxicity, cardiotoxicity, hematological toxicity, hepatotoxicity, gastrointestinal toxicity and neurotoxicity (2). Regardless of the reports that pointed out poor penetration through the blood-brain barrier for the majority of platinum-based compounds (3), it was observed that platinum agents accumulate in the central nervous system (CNS) (4), reaching the highest concentration in specific brain regions such as hippocampus in mice (5). Those findings may be the explanation for the variety of clinical manifestations following cisplatin treatment. Therefore, the following CNS disorders in cisplatin treated patients have been reported: acute blindness and seizures, encephalopathy and stroke-like episodes (6). Also, cisplatin therapy was accompanied with cognitive impairment and emotional dysfunction (7). The cognitive impairment, with the decreased locomotor and exploratory activity, was also observed in cisplatin treated animals (8, 9).

Although all kinds of cisplatin-induced toxicities are connected to specific clinical features, the spectrum of underlying pathophysiological mechanisms can be specified in a few principle categories. The most frequently described processes that could be connected to cisplatin-induced toxicities are: the apoptosis (10), DNA damage (11) and inflammation (12). Also, some investigations confirmed that oxidative stress is the key mechanism that disturbs homeostasis following cisplatin treatment and may be the base of its toxicities (13). The prooxidative action of cisplatin comes as a result of combined effects of increased production of reactive oxygen species, such as hydroxyl radical (14), hydrogen peroxide (15), superoxide anion radical (16), and nitrites (17, 18), and simultaneous decline in cellular antioxidant capacity, manifested as a decrease in antioxidant enzymes (superoxide dismutase and catalase) activity (19, 20), as well as glutathione (21).

The confirmed strong connection between the chemotherapeutics-induced oxidative damage and the clinical manifestations of toxicities in the specific tissues has targeted an antioxidant supplementation as a potentially useful therapeutic approach in the treatment of numerous anticancer drugs adverse effects. In the last decade, the medicinal plants have been widely confirmed as an important source of dietary antioxidants that showed protective effect when applied along with anticancer drugs, by means of diminished oxidative damage, which resulted in attenuation of cytostatic-induced toxicities (22, 23, 24). Recent study confirmed that *Satureja hortensis* L., the plant with the high content of antioxidants, such as phenolic compounds, and especially high concentration of rosmarinic acid, showed beneficial antioxidant properties in the treatment of cisplatin-induced nephro- and hepatotoxicity (25).

The aim of this study was to evaluate the behavioral manifestations of cisplatin administration in the TSTin rats. Furthermore, we estimated the potential alterations in behavioral outcome following antioxidant supplementation with *Satureja hortensis* L. extract in different doses.

MATERIAL AND METHOD

Animals and treatment

Animals were housed in seven cages (5 per cage), under standard environmental conditions (temperature 23±1°C, humidity 55±5%, 12/12h light/dark cycle). The animals had access to food and water ad libitum. The rats were randomly divided into 7 experimental groups as follows:

- control group, that received tap water for 10 days and a single dose of 500 μL saline on the day 5;

- cisplatin group that received tap water for 10 days and a single dose of cisplatin (7.5 mg/kg b. w.) on the day 5;

- CIS+E50 group that received S. hortensis L. extract (50 mg/kg b. w.) orally for 10 days and a single dose of cisplatin (7.5 mg/kg b. w.) on the day 5;

- CIS+E100 group that received S. hortensis L. extract (100 mg/kg b. w.) orally for 10 days and a single dose of cisplatin (7.5 mg/kg b. w.) on the day 5;

- CIS+E200 group that received S. hortensis L. extract (200 mg/kg b. w.) orally for 10 days and a single dose of cisplatin (7.5 mg/kg b. w.) on the day 5;

- CIS+SILYMARIN group that received silymarin (100 mg/kg b. w.) orally for 10 days and a single dose of cisplatin (7.5 mg/kg b. w.) on the day 5;

- E200 group that received S. hortensis L. extract (200 mg/kg b. w.) orally for 10 days.

Cisplatin and saline were administered intraperitoneally, while the extracts were dissolved in tap water. Phytochemical characterization of methanolic extract of S. hortensis L. was previously described in the study by Boroja et al (25).

After completing the described protocols, the animals were placed in the testing room, at approximately 8 a.m., in order to accommodate for behavioral testing that usually

started at 10 a.m. The testing room was acoustically and visually isolated.

Tail suspension test (TST)

In order to evaluate the behavioral alterations, we performed TST. This test, usually obtained for the estimation of depressive state level, is based on the assumption that the rodents under specific circumstances are expected to put an effort in order to avoid evidently aversive (stressful) stimulus (26). The original apparatus for TST is constructed of metal frame (0.6 x 0.6 m) and circular barrier (25 cm in diameter) with the central hole (the opening of 15 mm in diameter) where the tails were slipped through.

Rats were suspended by the tail attached to the adhesive tape (with the barrier 1 cm below the position of the adhesive tape on the tail, in order to prevent tail climbing), so that they could freely dangle facing downward.

The key point of TST was the quantification of immobility. The immobility was considered as a state with no visible voluntary movement (<1 cm) of head, body or limbs for at least 5 seconds. Expected involuntary swinging was declared as the state of immobility. The test lasted for six minutes, without any experimenter intervention during the testing. The complete testing was recorded by a video camera. The following parameters were analyzed from the recordings: the latency to the first immobility, the number of immobility episodes and the total duration of immobility.

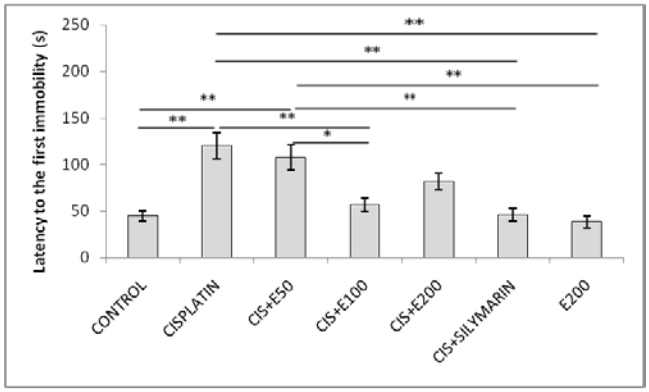
Statistical Analysis

The data were presented as means ± S.E.M. After completing the tests for homogeneity (Levene's) and normality (Shapiro-Wilk), comparisons between the groups were performed using One-way ANOVA, followed by Bonferroni post hoc analysis. Significance was determined at $p<0.05$. Statistical analysis was performed with SPSS version 20.0 statistical package (IBM SPSS Statistics 20).

RESULTS

The applied protocols significantly altered the latency to the first immobility ($F=11.539$, $df=6$). As shown in Figure 1, the administration of cisplatin in a single dose significantly increased the latency to the first immobility compared to the control group ($p<0.01$). *S. hortensis* L. extract, when applied alone, had no effect on this parameter when compared to the control. However, when applied along with cisplatin, *S. hortensis* L. extract in a dose of 100 mg/kg significantly reduced cisplatin-induced augmentation of the latency to the first immobility when compared to the cisplatin group ($p<0.01$), and the values remained similar compared to the control. On the other hand, both lower (50 mg/kg) and higher (200 mg/kg) dose of *S. hortensis* L. extract failed to significantly attenuate the cisplatin-induced increase in the latency to the first immobility, and this parameter was still significantly higher compared to the control in CIS+E50 group ($p<0.01$). Even more, the values of this parameter achieved with the lower dose were statistically below the values observed in the CIS+E100 group ($p<0.05$). The impact of simultaneous administration of cisplatin and silymarin was very much alike the observed effect in the CIS+E100 group – significant decline of cisplatin-induced increase in the latency to the first immobility, while preserving the values almost equal with the control group.

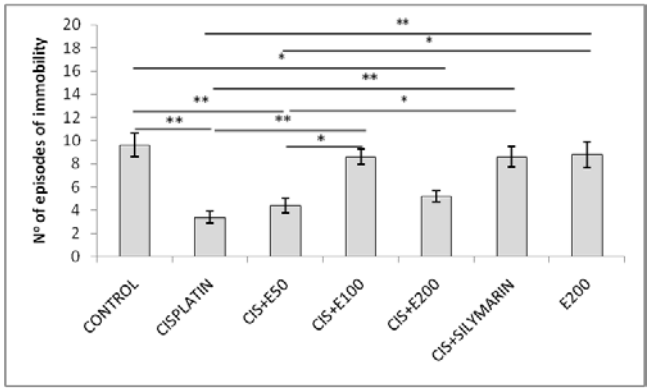
Figure 1. The latency to the first immobility in the tail suspension test.



Values are mean ± standard error of the mean (SEM), n=5 per group,
*denotes a significant difference $p<0.05$, **denotes a significant difference $p<0.01$.

Like for the latency to the first immobility, the number of immobility episodes in TST was also significantly affected by the applied protocols (F=10.137). Cisplatin application resulted in a significant decrease in the number of immobility episodes compared to the control values ($p<0.01$). As shown in Figure 2, the decline in this parameter was compensated ($p<0.01$) with neither the middle dose of S. hortensis L. extract (100 mg/kg), nor with the higher (200 mg/kg) or the lower (50 mg/kg) dose of S. hortensis L. extract. It should be noticed that the increase in the number of immobility episodes observed following simultaneous administration of cisplatin and S. hortensis L. extract in a dose of 100 mg/kg was even statistically significant when compared to the CIS+E50 group ($p<0.05$). Again, the effect obtained with the middle dose of S. hortensis L. extract was very similar to the one achieved with the same concentration of silymarin when applied along with cisplatin. Also, the number of immobility episodes was not significantly affected by S. hortensis L. extract in a dose of 200 mg/kg, when applied alone, compared to the control group.

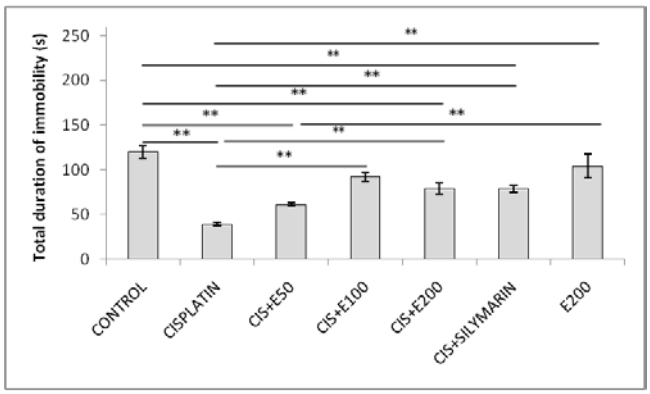
Figure 2. The number of episodes of immobility in the tail suspension test.



Values are mean ± standard error of the mean (SEM), n=5 per group,
*denotes a significant difference $p<0.05$, **denotes a significant difference $p<0.01$.

Finally, as shown in Figure 3, all the applied protocols also had significant impact on the total duration of immobility (F=16.271). Administration of cisplatin in a single dose (7.5 mg/kg) resulted in a significant decline in the immobility duration compared to the control ($p<0.01$). Although the individual administration of S. hortensis L. extract did not result in a significant change in the total duration of immobility, the administration of S. hortensis L. extract in the doses of 100 and 200 mg/kg significantly augmented the cisplatin-induced decrease in the total immobility ($p<0.01$). Only the values achieved in the CIS+E200 group remained significantly below the control values ($p<0.01$). The lowest dose of extract (50 mg/kg) failed to reduce the cisplatin-induced reduction in the total duration of immobility. The impact of simultaneous administration of cisplatin and silymarin on the duration of immobility in TST resembled the effects observed with the middle and the highest dose of S. hortensis L. extract. However, the total duration of immobility achieved in the CIS+SILYMARIN group, unlike the CIS+E100 group, remained statistically below the control values ($p<0.01$).

Figure 3. The total duration of immobility in the tail suspension test.



Values are mean ± standard error of the mean (SEM), n=5 per group,
**denotes a significant difference $p<0.01$.

DISCUSSION

Beside its unquestionable anticancer properties, cisplatin-based chemotherapy is usually limited by numerous side effects (27), including clinical manifestations of neurotoxicity (28). Many cisplatin-induced toxicities are accompanied with an evident mitochondrial dysfunction and oxidative damage in various tissues (29). Therefore, any of therapeutic approaches that may prevent the cisplatin-induced increase in oxidative stress, as a trigger factor for tissue damage, may be potentially useful as a supplementary treatment along with cisplatin therapy.

One of the most recently reported manifestations of adverse effect of cisplatin on CNS has clinical form with characteristics of increased depressive state level (30). The prodepressant action of cisplatin, by means of behavioral tests results, in that study (performed on rats) was accompanied with prooxidant alterations in both cortex and hippocampus. Also, neuronal degeneration in hippocampus paralleled the decline in BDNF and GABA content, as well as the increase in hippocampal glutamate (30).

However, the results obtained in our study may lead to a conclusion that cisplatin administration had the antidepressant effect by means of behavioral patterns observed in TST. On the other hand, the literature data offer a recently established possibility that the estimation of depressive state level can be substantially mimicked with significant alterations in anxiety levels. Namely, the specific mood disorders that are dominantly characterized with strong anxiogenic features may overcome the prodepressant action resulting in inadequately pronounced antidepressant effect (31). The offered explanation is that increased motor activity observed in the tests for depressive level estimation (such as TST) may rather be considered as the behavioral outcome of anxiety-induced overreacting than antidepressant action. When comparing the results for prodepressant action of cisplatin (30) and increased locomotor response in TST observed in this study, we must take into consideration two important information. Firstly, those two studies were performed with the significantly different protocols: the prodepressant effect was reported in the study with the chronic exposure to cisplatin (10 weeks), while the opposite effect on depressive level was obtained in the study with a single dose of cisplatin. Secondly, the recent study of Kumburovic et al. (32) confirmed the extremely strong anxiogenic response to a single dose of cisplatin, as the earliest behavioral manifestation of cisplatin administration. Therefore, we can conclude that the results of those two studies are not the opposite or even contradictory. It seems that the cisplatin impact in certain brain regions involved in mood regulation that includes numerous biochemical and morphological alterations is very complex. It seems that the cisplatin action in the CNS, by means of behavioral changes, starts with predominantly anxiogenic response followed by prodepressant action if the cisplatin treatment lasts long enough. Therefore, the behavioral outcome of cisplatin-induced neurotoxicity has strong time dependent characteristics. In addition, it is not surprising that beneficial effects of antioxidant supplementation following cisplatin therapy also strongly depend on the principle behavioral outcome. Namely, the benefits obtained with *S. hortensis* L. extract in this study were manifested not by prodepressant action, but as the clear anxiolytic-like response to antioxidant supplementation. Our results are in line with previously reported beneficial action of various antioxidant sources on cisplatin-induced neurotoxicity with clinical manifestations that involve increased anxiety levels (8, 9).

CONCLUSION

In summary, the neurotoxic manifestations of cisplatin treatment as observed in this study, manifested by anxiogenic response in TST, can be significantly attenuated by S. hortensis L. extract supplementation. So, according to the results of our study, it seems that antioxidant supplementation may be useful in diminishing cisplatin-induced neurotoxicity.

ACKNOWLEDGMENTS

This paper was supported by the Faculty of Medical Sciences (JP 06/18, 01/19), University of Kragujevac.

CONFLICT OF INTERESTS

None of the authors of the present study have any actual or potential conflicts of interest to disclose, including financial, personal, or other relationships with specific persons or organisations.

REFERENCE

1. Rosic G, Joksimovic J, Selakovic D, Jakovljevic V, Zivkovic V, Srejovic I, Djuric M, Djuric D. (2018). The Beneficial Effects of Sulfur-containing Amino Acids on Cisplatin induced Cardiotoxicity and Neurotoxicity in Rodents. Curr Med Chem, 25(3), 391-403.
2. Oun R, Moussa YE, Wheate NJ. (2018). The side effects of platinum-based chemotherapy drugs: a review for chemists. Dalton Trans, 47(19), 6645-53. Erratum in: Dalton Trans, 47(23), 7848.
3. McKeage MJ, Hsu T, Screnci D, Haddad G, Baguley BC. (2001). Nucleolar damage correlates with neurotoxicity induced by different platinum drugs. Br J Cancer, 85(8), 1219-25.
4. Nakagawa H, Fujita T, Kubo S, Tokiyoshi K, Yamada M, Kanayama T, Hagiwara Y, Nakanomyo H, Hiraoka M. (1996). Difference in CDDP penetration into CSF between elective intraarterial chemotherapy in patients with malignant glioma and intravenous or intracarotid administration in patients with metastatic brain tumor. Cancer Chemother Pharmacol, 37(4), 317-26.
5. Koppen C, Reifschneider O, Castanheira I, Sperling M, Karst U, Ciarimboli G. (2015). Quantitative imaging of platinum based on laser ablation-inductively coupled plasmamass spectrometry to investigate toxic side effects of cisplatin. Metallomics, 7(12), 1595-603.
6. Gulec M, Oral E, Dursun OB, Yucel A, Hacimuftuoglu A, Akcay F, Suleyman H. (2013). Mirtazapine protects against cisplatin-induced oxidative stress and DNA damage in the rat brain. Psychiatry Clin Neurosci, 67(1):50-8.
7. Filley CM. (1999). Toxic leukoencephalopathy. Clin Neuropharmacol, 22(5), 249-60.
8. Shabani M, Nazeri M, Parsania S, Razavinasab M, Zangiabadi N, Esmaeilpour K, Abareghi F. (2012). Walnut consumption protects rats against cisplatin-induced neurotoxicity. Neurotoxicology, 33(5), 1314-21.
9. Golchin L, Shabani M, Harandi S, Razavinasab M. (2015). Pistachio supplementation attenuates motor and cognition impairments induced by cisplatin or vincristine in rats. Adv Biomed Res, 4, 92.
10. Kong D, Zhuo L, Gao C, Shi S, Wang N, Huang Z, Li W, Hao L. (2013). Erythropoietin protects against cisplatin-induced nephrotoxicity by attenuating endoplasmic reticulum stress-induced apoptosis. J Nephrol, 26(1), 219-27.
11. Li XB, Schluesener HJ. (2006). Therapeutic effects of cisplatin on rat experimental autoimmune encephalomyelitis. Arch Immunol Ther Exp (Warsz), 54(1), 51-3.
12. Kang KP, Kim DH, Jung YJ, Lee AS, Lee S, Lee SY, Jang KY, Sung MJ, Park SK, Kim W. (2009). Alpha-lipoic acid attenuates cisplatin-induced acute kidney injury in mice by suppressing renal inflammation. Nephrol Dial Transplant, 24(10), 3012-20.
13. Karasawa T, Steyger PS. (2015). An integrated view of cisplatin-induced nephrotoxicity and ototoxicity. Toxicol Lett, 237(3), 219-27.
14. Shino Y, Itoh Y, Kubota T, Yano T, Sendo T, Oishi R. (2003). Role of poly (ADP-ribose) polymerase in cisplatin induced injury in LLC-PK1 cells. Free Radic Biol Med, 35, 966–77.
15. Kadikoylu G, Bolaman Z, Demir S, Balkaya M, Akalin N, Enli Y. (2004). The Effects of desferrioxamine on cisplatin induced lipid peroxidation and the activities of antioxidant enzymes in rat kidneys. Hum Exp Toxicol, 23(1), 29-34.
16. Davis CA, Nick HS, Agarwal A. (2001). Manganese superoxide dismutase attenuates Cisplatin-induced renal injury: importance of superoxide. J Am Soc Nephrol, 12(12), 2683-90.
17. Rosic G, Srejovic I, Zivkovic V, Selakovic D, Joksimovic J, Jakovljevic V. (2015). The effects of N-acetylcysteine on cisplatin-induced cardiotoxicity on isolated rat hearts after short-term global ischemia. Tox Rep, 2, 996–1006.
18. Rosic G, Selakovic D, Joksimovic J, Srejovic I, Zivkovic V, Tatalovic N, Orescanin-Dusic Z, Mitrovic S, Ilic M, Jakovljevic V. (2016). The effects of N-acetylcysteine on cisplatin-induced changes of cardiodynamic parameters within coronary autoregulation range in isolated rat hearts. Toxicol Lett, 242, 34-46.
19. Almaghrabi OA. (2015). Molecular and biochemical investigations on the effect of quercetin on oxidative stress induced by cisplatin in rat kidney. Saudi J Biol Sci, 22(2), 227–31.
20. Yuce A, Atessahin A, Ceribasi AO, Aksakal M. (2007). Ellagic acid prevents cisplatin-induced oxidative stress in liver and heart tissue of rats. Basic Clin Pharmacol Toxicol, 101(5), 345-9.
21. Noori S, Mahboob T. (2010). Antioxidant effect of carnosine pretreatment on cisplatin-induced renal oxidative stress in rats. Indian Clin Biochem, 25(1), 86-91.
22. Moon JH, Shin JS, Kim JB, Baek NI, Cho YW, Lee YS, Kay HY, Kim SD, Lee KT. (2013). Protective effects of 6-hydroxy-1-methylindole-3-acetonitrile on cisplatin-induced oxidative nephrotoxicity via Nrf2 inactivation. Food Chem Toxicol, 62, 159-66.
23. Singh TD, Meitei HT, Sharma AL, Robinson A, Singh LS, Singh TR. (2015). Anticancer properties and enhancement of therapeutic potential of cisplatin by leaf extract of Zanthoxylum armatum DC. Biol Res, 48, 46.
24. Yadav YC. (2015). Hepatoprotective effect of Ficus religiosa latex on cisplatin induced liver injury in Wistar rats. Rev Bras Farmacogn 25, 278–83.
25. Boroja T, Katanić J, Rosić G, Selaković D, Joksimović J, Mišić D, Stanković V, Jovičić N, Mihailović V. (2018). Summer savory (Satureja hortensis L.) extract: Phytochemical profile and modulation of cisplatin-induced liver, renal and testicular toxicity. Food Chem Toxicol, 118, 252-63.
26. Chermat R, Thierry B, Mico JA, Steru L, Simon P. (1986). Adaptation of the tail suspension test to the rat. J Pharmacol, 17(3), 348-50.

27. Astolfi L, Ghiselli S, Guaran V, Chicca M, Simoni E, Olivetto E, Lelli G, Martini A. (2013). Correlation of adverse effects of cisplatin administration in patients affected by solid tumours: a retrospective evaluation. Oncol Rep, 29(4), 1285-92.
28. Kanat O, Ertas H, Caner B. (2017). Platinum-induced neurotoxicity: A review of possible mechanisms. World J Clin Oncol, 8(4), 329-35.
29. Bobylev I, Joshi AR, Barham M, Neiss WF, Lehmann HC. (2018). Depletion of Mitofusin-2 Causes Mitochondrial Damage in Cisplatin-Induced Neuropathy. Mol Neurobiol, 55(2), 1227-35.
30. Abdelkader NF, Saad MA, Abdelsalam RM. (2017). Neuroprotective effect of nebivolol against cisplatin-associated depressive-like behavior in rats. J Neurochem, 141(3), 449-60.
31. Rosic G, Joksimovic J, Selakovic D, Milovanovic D, Jakovljevic V. (2014). Anxiogenic effects of chronic exposure to nandrolone decanoate (ND) at supraphysiological dose in rats: a brief report. Neuro Endocrinol Lett, 35(8), 703-10.
32. Kumburovic I, Selakovic D, Juric T, Jovicic N, Mihailovic V, Stankovic JK, Sreckovic N, Kumburovic D, Jakovljevic V, Rosic G. (2019) Antioxidant Effects of Satureja hortensis L. Attenuate the Anxiogenic Effect of Cisplatin in Rats. Oxid Med Cell Longev. 2019:8307196.

CHALLENGES IN THE SURGICAL CORRECTION OF HIATAL HERNIAS AND WAYS TO OVERCOME THEM

Oleg Vladimirovich Galimov, Vladislav Olegovich Khanov and Dmitry Olegovich Galimov
Department of Surgery and Innovative Technologies in Surgery, Bashkir State Medical University, Ufa, Russia Federation

IZAZOVI U HIRURŠKOJ KOREKCIJI HIJATALNIH KILA I NAČINI NJIHOVOG PREVAZILAŽENJA

Oleg Vladimirovich Galimov, Vladislav Olegovich Khanov i Dmitry Olegovich Galimov
Odeljenje za hirurgiju i inovativne tehnologije u hirurgiji, Baškirski državni medicinski univerzitet, Ufa, Rusija

Received/Primljen: 05.06.2020. Accepted/Prihvaćen: 16.08.2020.

ABSTRACT

More than a thousand laparoscopic fundoplication operations for hiatal hernia (HH) have been performed at the Clinic of the Bashkir State Medical University over the period between 2000 and 2019 and the results of surgical treatment of 502 patients were analyzed. Our research results indicate that routine instrumental methods used in hiatal hernia diagnosis provide valuable information, however only their combined application allows us to establish the correct diagnosis in all patients. Authors propose a new original X-ray balloon method that allows to improve the quality of diagnosis of hiatal hernia significantly. Balloon X-ray allows us to establish the true dimensions of the hiatus and select the most appropriate treatment accordingly. Isolated fundoplication without plastic of esophageal opening was performed in 180 patients. Surgical correction of the hiatus was performed on 322 patients. Diaphragmcrouroraphy was carried out in 199 cases, in 123 cases mesh implants were used to support the crus of the diaphragm. In 215 cases, simultaneous surgical procedures were performed to treat multiple abdominal pathology. We studied the changes in quality of life of 100 patients with hiatal hernia before and after laparoscopic esophagofundoplication by comparing the results of the survey (questionnaires) and medical examination of the cardiac sphincter of the esophagus function. The vast majority of patients demonstrated a significant improvement in the cardiac closure function, a decrease in the frequency and severity of gastroesophageal reflux, and reduced signs of reflux esophagitis.

Keywords: *hiatal hernia, surgical correction, fundoplication.*

SAŽETAK

Više od hiljadu laparoskopskih operacija fundoplikacije za hijatalnu kilu (HH) izvedeno je na Klinici Baškirskog državnog medicinskog univerziteta u periodu između 2000. i 2019. godine i analizirani su rezultati hirurškog lečenja 502 pacijenta. Rezultati našeg istraživanja ukazuju na to da rutinske instrumentalne metode koje se koriste u dijagnostici hijatalne kile daju vredne informacije, međutim samo njihova kombinovana primena omogućuje nam da postavimo ispravnu dijagnozu kod svih pacijenata. Autori predlažu novu originalnu metodu rendgenskog balona koja omogućava značajno poboljšanje kvaliteta dijagnoze hijatalne kile. Rendgenski snimak balona omogućava nam da utvrdimo prave dimenzije pauze i prema tome odaberemo najprikladniji tretman. Izolovana fundoplikacija bez plastifikacije otvora jednjaka izvedena je kod 180 pacijenata. Hirurška korekcija pauze izvedena je na 322 pacijenta. Krourorafija dijafragme izvedena je u 199 slučajeva, u 123 slučaja su korišteni mrežasti implantati za podršku prignječenju dijafragme. U 215 slučajeva istovremeno su izvedeni hirurški zahvati za lečenje multiple abdominalne patologije. Proučavali smo promene u kvalitetu života 100 pacijenata sa hijatalnom kilom pre i posle laparoskopske ezofagofundoplikacije upoređujući rezultate ankete (upitnika) i lekarskog pregleda srčanog sfinktera funkcije jednjaka. Velika većina pacijenata pokazala je značajno poboljšanje funkcije zatvaranja srca, smanjenje učestalosti i težine gastroezofagealnog refluksa i smanjene znakove refluksnog ezofagitisa.

Ključne reči: *hijatalna kila, hirurška korekcija, fundoplikacija.*

sciendo
UDK: 616.33-007.43-089
Ser J Exp Clin Res 2021; 22 (3): 249-255
DOI: 10.2478/sjecr-2020-0066

Corresponding author:
Prof. Oleg Vladimirovich Galimov.
Adress Chernishevskogo Street 104-119,
Ufa 450077, Russia,
Tel: +7(917)342 58 92,
E-mail: galimovov@mail.ru

INTRODUCTION

Numerous statistical studies indicate that hiatal hernias, including recurrent, complicated and acute cases, are prevalent worldwide, which makes the problem of treatment of this condition extremely relevant. Recent advances in medical technology contributed to the development of new diagnostic methods, while new medication and innovative surgical instruments significantly improved the results of treatment of patients with hiatal hernia (1,2,3). At the same time, many researchers agree that, despite the wide range of available methods for correcting hiatal hernia, a single commonly accepted strategy in surgical treatment of this pathology has not yet been developed. This is primarily due to unsatisfactory results both in the immediate and long-term postoperative period [4,6,8]. When discussing modern methods of surgical correction of hiatal hernia, restoring the functional state of the esophageal-gastric junction and creating an anti-reflux barrier become a priority. The introduction of video-endoscopic technologies has made it possible to increase the effectiveness of anti-reflux surgical procedures (5,7,9).

With the increase in the number of laparoscopic surgeries to treat hiatal hernia performed at hospitals and clinics of the city of Ufa (Russia), in recent years, doctors have often faced the problem of rising rates of unsatisfactory results associated with relapse of hiatal hernia and/or the development of pathological postoperative symptom complexes. According to our observations, many complications following the operations to correct hiatal hernia are associated with insufficient or excessive narrowing of the esophagus [5]. In order to address this issue, authors propose a new original X-ray balloon method that allows to improve the quality of diagnosis of hiatal hernia significantly and the results are presented in this paper.

MATERIALS AND METHODS

More than a thousand laparoscopic fundoplication operations have been performed at the Clinic of the Bashkir State Medical University over the period between 2000 and 2019 and the results were thoroughly monitored and analyzed.

A total of 520 patients with hiatal hernia were treated in our Clinic. There were 284 (54,6%) men among them and 236 (45,4%) women. The average age of patients was 49,5±5,62 years.

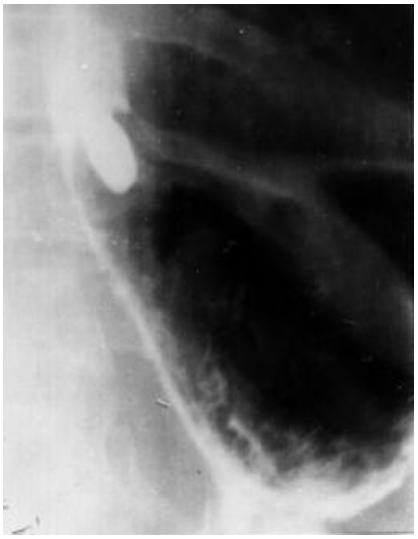
The following criteria for inclusion in the study were used: patient must be over 18 years old; diagnosed with hiatal hernia; anesthetic risk assessment score (ASA) of 1-3. The criterion for exclusion from the study was the patient's signed refusal to take part in the research and/or to undergo examination. All medical procedures and examination methods, including the original methods developed by the authors, used in this study were approved by the BSMU Clinic Ethics Committee.

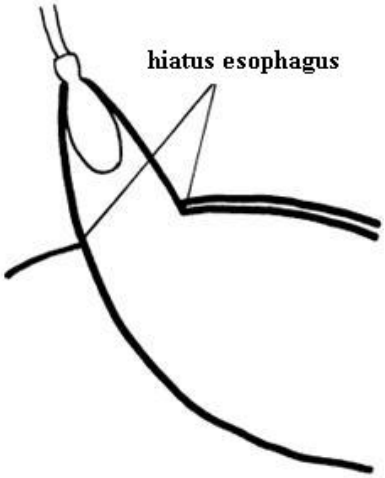
All patients were submitted to endoscopy and targeted biopsy, manometry, intraesophageal pH-monitoring and Barium contrast X-ray.

The “Balloon X-ray” Method (aka traction X-ray balloonography method) developed by authors (Copyright certificate for the invention N 1463233) was used to evaluate the valve function of the cardia and, to establish the true dimensions of the hiatus esophagus (5). The detailed description of the original method can be found below.

The examination is performed on an empty stomach in the X-ray laboratory. The general X-ray examination of thorax and belly cavity organs in vertical position is performed. Then the patient is offered to drink approximately 100 ml of barium. As the barium suspension passes through, the patency of the esophagus, its peristalsis, the precise shape of the His angle, rugae and the folds of the gastric mucosa are studied. An X-ray examination of the stomach at this point is focused on the key properties and functioning of the esophagus, particularly, the shape, size, stomach contents and its evacuation. Then, when hiatal hernia is suspected, a gastric probe with a radiopaque olive-shaped head and an inflatable balloon attached is inserted into the stomach. As soon as the head of the probe is actually in the stomach, 50 ml of liquid substance is syringed in, that allows to distinguish the contours of the balloon from the gas bubble in the stomach. The inflated balloon is then pulled out with gradually increasing pressure up to 1 kg, controlled by the dynamometer. The healthy hiatus esophagus with the size ranging within 2-3 cm resists the pressure applied and stops the inflated balloon from being pulled out however, the hiatus esophagus with hernia easily allows approximately 50 ml of the balloon to pass through into the thorax followed by the stomach bottom (Fig. 1). After the X-ray examination is completed, the balloon is deflated and safely removed. Then the standard procedure of further examination is resumed.

Fig. 1. The image of the Y-patient’s hiatus esophagus obtained using the Balloon X-Ray Method





In all cases, the intraoperative size of the hiatus was measured by a special endoscopic instrument that was developed by the authors (Fig 2). The instrument has one active moving jaw with adjustable metric scale (from 0 to 9cm), that can change its angle between 0 and 90◦. Figure 3 shows measurements of hiatus taken intraoperative.

Fig.2. Special endoscopic instrument for intraoperative measurement of the esophageal opening

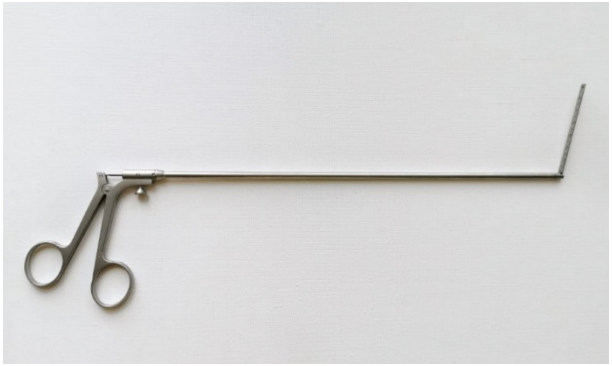
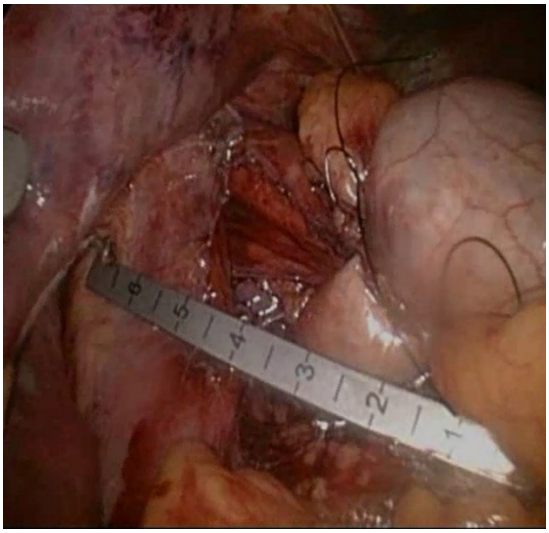


Fig.3. Intraoperative size measurement of the hiatus



Usually, patients after laparoscopic fundoplication stayed at the clinic for 2 to 5 days and the immediate results (typically 90-95% good and very good) were observed. In addition, our study included long-term observation. Gastroesophageal Reflux Disease-Health Related Quality of Life (GERD-HRQL) Questionnaire and General Health Survey (SF-36 questionnaire) were used to obtain data on the quality of life of patients with hiatal hernia after anti-reflux surgical treatment. All operated patients were asked to fill in the two questionnaires in order to obtain data on their the physical (Physical Component Summary) and psychological (Mental Component Summary) well-being in addition to the instrumental methods for studying the cardiac closure function (14).

A selective study of two-year postoperative treatment results was performed in 100 (19,9%) patients with hiatal hernia in the period following 1 to 5 years after surgery, including 68 women and 32 men. The average age of the patients was 44,3±8,47 years. The sample included 80 patients who were treated with total (360°) fundoplication (Nissen), 20 patients partial (180-270 °) fundoplication (Dor, Toupet). Correction of the esophageal opening was performed by diaphragmocrurography in 32 cases, and in 17 cases with mesh implants. The surgeons that performed operations were different. Simultaneous operations were performed in 16 cases (cholecystectomy-13, hernia-2). The long-term results were studied using the questionnaire method. 14 patients were subject to control instrumental examination. Patients were offered to assess their general well-being on a 4-point scale.

The performance and effectiveness of the methods used to diagnose hiatal hernia was evaluated based on Sensitivity and Specificity. Sensitivity, in this case, is the ability of the particular diagnostic method to detect the disease in people who actually have the disease (the probability of a positive result in people with the disease), that is, the proportion of truly positive cases. Specificity refers to the ability of a diagnostic method to distinguish patients who have not been diagnosed with the disease, from people who do not really have the disease (the probability of a negative result in people without the disease), that is, the proportion of truly negative cases that were correctly identified by the particular method. Diagnostic effectiveness or Accuracy is the average between diagnostic sensitivity and diagnostic specificity. Positive predictive value refers to the likelihood of patient actually having a hiatal hernia, when positively diagnosed by a particular method. Negative predictive value is the likelihood of the absence of HH when medical examination (with a particular method) produces a negative result.

The performance was calculated according to the following formulae:

Sensitivity = TP/(TP+FN),

Specificity = TN/(TN+FP),

Diagnostic effectiveness (accuracy) = (sensitivity+specificity)/2,

Positive predictive value = TP/(TP+FP),

Negative predictive value = FN/(FN+TN), where TP were True Positive cases, patients correctly diagnosed with HH;

TN - True Negative cases, healthy patients correctly identified as healthy;

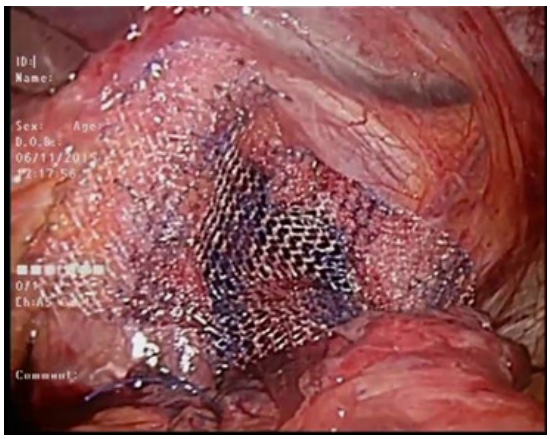
FN - False Negative cases, patients suffering from HH, incorrectly identified as healthyl;

FP - False Positive cases, healthy patients misdiagnosed with HH.

RESULTS

We performed and analyzed the results of surgical treatment in 502 patients with hiatal hernia. 18 patients declined surgery in favor of conservative therapy. Laparoscopic Nissen fundoplication method was the preferred procedure at the Clinic, as the most adequate procedure that can prevent the reflux of gastric contents into the esophagus. Isolated fundoplication without esophageal opening plastic was performed in 180 patients. The expansion of the esophageal opening by more than 3.5 cm was considered an indication to surgery correction of hiatus. In total, additional procedures for correction of the hiatus were performed on 322 patients. Diaphragmcrouroraphy was carried out in 199 cases. In 123 cases, when crura of diaphragm were unable to sustain stiches and when the expansion of the esophageal opening was more than 5 cm, mesh implants were used to support the crura (Fig. 4).

Fig.4. Surgical correction of hiatal hernia with a mesh implant



When the main pathology was combined with other abdominal diseases, requiring surgical correction, in 215 cases, simultaneous surgical procedures were performed.

The data on concomitant medical conditions and hiatal hernia-related clinical manifestations are presented in Table 1.

Table 1. Summary of symptoms, Surgical procedures and Sample Composition

	Number (Percentage)
Total number of patients:	520
-men	284 (54,6%)
-women	236 (45,4%)
Age (years)	49,5±5,62
Concomitant diseases (number of cases, percentage):	
- duodenal ulcer	162 (31,2%)
- cholelithiasis, chronic cholecystitis	131 (25,2%)
- chronic pancreatitis	76 (14,6%)
- chronic violation of duodenal patency	62 (11,9%)
- biliary dyskinesia	28 (5,4%)
- Casten syndrome	21 (4,0%)
- Saint's triad	15 (2,9%)

	Number (Percentage)
Clinical manifestations (esophageal)	
- pain:	
• in the upper abdomen area	500 (96,2%)
• behind the sternum	424 (81,5%)
• in the right hypochondrium area	220 (42,3%)
• in the left hypochondrium area	212 (40,8%)
• in the area of the heart	192 (36,9%)
- heartburn	420 (80,8%)
- dysphagia	212 (40,8%)
- belching	188 (36,2%)
- nausea	168 (32,2%)
- vomiting	164 (31,5%)
- regurgitation	160 (30,8%)
Clinical manifestations (non-esophageal)	
- anemia and bleeding	130 (25%)
- aspiration bronchopulmonary complications	114 (21,9%)
- neurological disorders	52 (10%)
- asymptomatic course	14 (2,7%)
Performed surgical procedures	
- complete (360°) Nissen fundoplication	436 (86,8%)
- partial (180°- 270°) Toupet fundoplication	62 (12,4%)
- partial (180°) Dor fundoplication	4 (0,8%)
Procedures performed simultaneously	
- cholecystectomy	157 (31,3%)
- benign ovarian tumors removal	29 (5,8%)
- dissection of the ligament of Treitz	16 (3,2%)
- viscerolysis	11 (2,2%)
- hernioplasty (hernia repair)	2 (0,4%)
Total	520 (100%)

The most frequently combined procedures included cholecystectomy (157 cases), removal of benign ovarian tumors (29 cases), dissection of the Treitz ligament (16 cases), viscerolysis (11 cases), hernia corrections (2 cases). Intraoperative complications were diagnosed in 9 (1,8%) patients. Early postoperative disfunction directly related to anti-reflux procedures were diagnosed in 73 (14,5%) patients, the most common was transient dysphagia 39 (7,7%) cases. Reactive serous pleurisy occurred in 8 (1,6%) cases. These complications were transient in nature and were corrected by conservative therapy.

The preoperative Balloon X-ray examination results always matched the intraoperative measurements. The procedure proved to be convenient and effective, no complications ever occurred during and/or after the Balloon X-ray examination. In addition, the technique does not require any expensive equipment.

The results show that the reliability of the sliding hiatal hernias diagnosis increased to 95,5 % particularly for hiatal hernias where the esophageal opening of the diaphragm increased to between 3.5 and 7.5 cm. Thus, the Balloon X-ray method developed at the Clinic was proven effective in our clinical practice and today is mandatory before performing surgery for hiatal hernia.

Our results presented in Table 2 demonstrate that routine instrumental methods used in hiatal hernia diagnosis provide valuable information, however only their combined application allows us to establish the correct diagnosis in all patients.

Table 2. Comparison of methods of hiatal hernia diagnosis.

	Sensitivity	Specificity	Accuracy	Positive predictive value	Negative predictive value
X-ray	78,9%	25%	51,96%	83,4%	80,01%
Esophagogastroduodenoscopy	92,6%	83,3%	87,95%	98,8%	58,3%
pH-monitoring, Esophagomanometry	89,5%	25%	57,25%	85%	66,6%
Balloon X-ray	94,7%	71,4%	83,05%	97,8%	50%

As for two-year postoperative patient well-being results, the complete survey data was obtained from 84 patients of 100 who took part in the research. Patients were offered to assess their general well-being on a 4-point scale. 7 (8,3%) patients reported it as Excellent, 45 (53,6%) as Good, 24 (28,5%) Satisfactory and 8 (9,5%) noted unsatisfactory results.

When patients self-assessed their state of health according to the GERD-HRQL questionnaire, a statistically significant restoration of the cardiac closure function according to manometric data and the DeMeester indicator was noted. At the same time, in some patients with excellent and good results, gastroesophageal reflux and reflux esophagitis in the lower third of the esophagus was observed according to the daily intra-esophageal pH-meter and esophagogastroduodenoscopy (23,81 ± 4,65%). Self-reported quality of life of patients, according to the SF-36 questionnaire, increased during the 1st and 2nd year after surgery compared with preoperative values. To the question of whether preoperative complaints disappeared, 48 patients (57,1%) answered affirmatively, whereas 36 (42,9%) patients noted slight presence of pathological symptoms, which are often observed after various types of esophagus cardiac sphincter correction.

When asked if patients were generally satisfied with the results of surgical treatment, 52 (61,9%) patients answered "Yes" while 32 (38,1%) of patients answered "No". Moreover, all patients who underwent combined surgical procedures were in the group satisfied with the results of surgery. Of 14 patients submitted for control instrumental examination, the majority (78,7%) showed no deviations from the normal, only 2(14,2%) patients were diagnosed with esophagitis, and 1 (7,1%) patient, earlier treated with partial Toupet fundoplication, upon X-ray examination showed early signs of a relapse of hiatal hernia.

DISCUSSION

Modern X-ray technology in a traditional medical examination does not always allow one to identify reflux esophagitis and sliding hiatus hernias, as well as to differentiate them from an ampoule or diverticulum of the esophagus. Thus, X-ray does not provide sufficient evidence to form an informed medical opinion as to the severity of the pathological process, in particular, assess the size of the hernia defect (10,11).

The "Balloon X-ray" Method (aka traction X-ray balloonography method) developed by authors increases the HH diagnostics effectiveness; which allows us to evaluate the valve function of the cardia and, most importantly, to establish the true dimensions of the hiatus esophagus (5).

Moreover, precise information on the hernia defect size is very valuable as it helps in selection of the hiatal hernia treatment and the most appropriate technique for the operation if needed. Knowing the exact dimensions of the defect, implants can be prepared, if necessary, according to the specified size.

As many authors point out (12, 13), every instrumental method used in hiatal hernia diagnosis provides valuable information. Esophagogastroduodenoscopy is one of the most reliable methods for the diagnosis of esophagitis, which allows to visually examine the condition of the mucous membrane of the esophagus and stomach, as well as to obtain biopsy samples for further histological examination. Manometry and intraesophageal pH-monitoring enable assessment of the cardiac sphincter tone and help to identify the diseases of the esophageal-gastric transition in the functional phase; help to reliably assess the disease dynamics and the effectiveness of the treatment. None of these procedures should be treated as rival diagnostic methods but only as complementing each other.

CONCLUSION

Our research results show that routine instrumental methods used in hiatal hernia diagnosis provide valuable information, however only their combined application allows us to establish the correct diagnosis in all patients. We propose a new original X-ray balloon method that allows to improve the quality of diagnosis of hiatal hernia significantly. Balloon X-ray allows us to establish the true dimensions of the hiatus and select the most appropriate surgical treatment accordingly. The long-term results studied by us did not reveal any significant difference in the postoperative subjective sensations of patients between surgical procedures (total or partial fundoplication). It is suggested that the results of operations in patients with hiatal hernia depend largely on a thorough selection of patients for intervention. Indications to surgery should be based on sufficient data obtained from preoperative clinical and instrumental examination, including potential concomitant pathologies.

LITERATURE

1. Cáterin Arévalo MD., Rubén D., Luna MD., Carlos A. et all. Literature review: a surgeon's view of recurrent hiatal hernia. Rev. Col. Gastroenterol. 2015; 30(4); 443 - 451.
2. Dellemagne B, Perretta S. Twenty years of laparoscopic fundoplication for GERD. World J Surg. 2011;35(7):1428-35. doi: 10.1007/s00268-011-1050-6.
3. Yu HX, Han CS, Xue JR, Han ZF, Xin H. Esophageal hiatal hernia: risk, diagnosis and management. //Expert Rev Gastroenterol Hepatol. 2018 Apr;12(4):319-329. doi: 10.1080/17474124.2018.1441711.
4. 4.Fuchs KH, Babic B, Breithaupt W, Dallemagne B et al. EAES recommendations for the management of gastroesophageal reflux disease. Surg Endosc. 2014;28(6):1753-73. doi: 10.1007/s00464-014-3431-z.
5. Galimov OV, Khanov VO et al. Creative surgery for hiatal hernia. Khirurgiya. Zhurnal imeni N.I. Pirogova 2017; 7; 30-32.
6. Le Page PA, Furtado R, Hayward M, Law S et al. Durability of giant hiatus hernia repair in 455 patients over 20 years Ann R Coll Surg Engl. 2015; 97(3):188-93. doi: 10.1308/003588414X14055925060839
7. Tam V, Winger DG, Nason KS A systematic review and meta-analysis of mesh versus suture cruroplasty in laparoscopic large hiatal hernia repair Am J Surg.2016; 211(1):226-38. doi: 10.1016/j.amjsurg.2015.07.007.
8. Mayor MA, Fernando HC. Endoluminal approaches to gastroesophageal reflux disease. Thorac Surg Clin. 2018;28(4):527-532. https://doi.org/10.1016/j.thorsurg.2018.07.008
9. Watson DI, Thompson SK, Devitt PG et al. Laparoscopic repair of very large hiatus hernia with sutures versus absorbable mesh versus nonabsorbable mesh. A randomized controlled trial Ann Surg. 2015;261(2):282-9. doi: 10.1097/SLA.0000000000000842.
10. Weyhe D, Uslar V, Kühne J, Kluge A. Hiatus hernia: Standards and controversies in diagnostics and treatment. //Chirurg. 2019 Apr;90(4):331-348. doi: 10.1007/s00104-019-0932-2.
11. Siegal SR, Dolan JP, Hunter JG. Modern diagnosis and treatment of hiatal hernias.//Langenbecks Arch Surg. 2017 Dec;402(8):1145-1151. doi: 10.1007/s00423-017-1606-5.
12. Seif Amir Hosseini A, Uhlig J, Streit U, Uhlig A, Sprenger T, Wedi E, Ellenrieder V, Ghadimi M, Uecker M, Voit D, Frahm J, Lotz J, Biggemann L. Hiatal hernias in patients with GERD-like symptoms: evaluation of dynamic real-time MRI vs endoscopy. //Eur Radiol. 2019 Dec;29(12):6653-6661. doi: 10.1007/s00330-019-06284-8.
13. 13.Tatum JM, Samakar K, Bowdish ME, Mack WJ, Bildzukewicz N, Lipham JC. Videoesophagography versus Endoscopy for Prediction of Intraoperative hiatal hernia size. //Am Surg. 2018 Mar 1;84(3):387-391.
14. V.I. Oskretkov, V.A. Gankov, A.R. Andreasyan, M.A. Ovsepyan The comparison of a questionnaire survey and special methods of examination in patients with gastroesophageal reflux disease Endosurgery.2018;6:29-32.

sciendo

EFFICIENCY OF LEG EXOSKELETON USE IN REHABILITATION OF CEREBRAL STROKE PATIENTS

Sergey V. Kotov[1], Alexander I. Romanov[2], Ekaterina V. Silina[3], Victor A. Stupin[4], Elena V. Isakova[1], Viktorija Yu. Lijdvoy[1], Kira A. Petrushanskaya[1], Alexey S. Kotov[1], Liana Kh. Kodzokova[1], Nikolaj A. Filatov[1] and Elena V. Pismennaya[5]
[1]*Moscow Regional Research and Clinical Institute named after M.F. Vladimirskiy ("MONIKI"), Moscow, Russia*
[2]*Russian Academy of Sciences (RAS); Association of Clinical Rehabilitologists, Moscow Region, Russia*
[3]*I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia*
[4]*Pirogov Russian National Research Medical University (RNRMU), Moscow, Russia*
[5] *Institute of mechanics of Lomonosov Moscow State University, Moscow, Russia*

EFIKASNOST UPOTREBE EGZOSKELETA NOGE U REHABILITACIJI PACIJENATA KOJI SU PRETRPELI MOŽDANI UDAR

Sergey V. Kotov[1], Alexander I. Romanov[2], Ekaterina V. Silina[3], Victor A. Stupin[4], Elena V. Isakova[1], Viktorija Yu. Lijdvoy[1], Kira A. Petrushanskaya[1], Alexey S. Kotov[1], Liana Kh. Kodzokova[1], Nikolaj A. Filatov[1] i Elena V. Pismennaya[5]
[1]*Moskovski regionalni istrazivački i klinički institut nazvan po M.F. Vladimirskiy ("MONIKI"), Moskva , Rusija*
[2]*Ruska akademija nauka (RAN), Udruženje kliničkih rehabilitologa, Moskovski region, Rusija*
[3]*I.M. Sečenov Prvi moskovski državni medicinski univerzitet (Univerzitet Sečenov), Moskva, Rusija*
[4]*Ruski nacionalni istraživački medicinski univerzitet Pirogov, Moskva Rusija*
[5] *Institut za mehaniku, Moskovski državni univerzitet Lomonosov , Moskva, Rusija*

Received/Primljen: 06.07.2021. Accepted/Prihvaćen: 14.08.2021.

ABSTRACT

The study aimed to *evaluate the effectiveness of functional and motor activity restoration, including the walking function, in patients after an ischemic stroke using the ExoAtlet lower limb exoskeleton.* ***Patients and methods.*** *A clinical study was carried out on 42 patients who had undergone a cerebral infarction in the mid cerebral artery system with a post-stroke paresis of the leg, and who had undergone a rehabilitation course in a round-the-clock hospital during the early recovery period. Patients were randomized into two equal groups comparable in terms of the stroke severity: the patients in group 1 were receiving a standard rehabilitation program (control group), the patients in group 2 were additionally receiving a course of gait rehabilitation using the ExoAtlet exoskeleton - 10 sessions, 5 sessions per week for 14 days.* ***Results.*** *The study demonstrated the effectiveness of the ExoAtlet exoskeleton used in the rehabilitation of stroke patients over the standard course of rehabilitation. The advantages include a decrease in the hemiparesis degree, an increase in the muscle strength of the paretic limb, an improvement in balance, an improvement and acceleration of the walking process. The obtained results of the instrumental study confirmed the benefits of physical training on the Exoskeleton, which was demonstrated through an increase in stability and balance, as well as through a decrease in the energy consumption index for maintaining the stable verticalization.* ***Conclusion.*** *The usage of the ExoAtlet exoskeleton increases the effectiveness of rehabilitation measures and improves motor and functional activities of patients who have suffered a cerebral stroke.*

Keywords: *stroke, rehabilitation, exoskeleton, ExoAtlet, walking, stabilometry.*

SAŽETAK

Ova studija je imala za cilj da proceni efikasnost ponovnog vraćanja finkcionalne i motorne aktivnosti, uključujući funkciju hodanja kod pacijenata koji su pretrpeli ishemijski moždani udar korišćenjem ExoAtlet egzoskeleta za donje udove. ***Pacijenti i metode.*** *Klinička studija je sprovedena na 42 pacijenta koji su pretrpeli ishemijski moždani udar u sistemu srednje cerebralne arterije sa parezom noge nakon moždanog udara i koji su prošli kroz tok rehabilitacije uz neprekidnu negu u bolnici tokom početnog perioda oporavka. Pacijenti su nasumično raspoređeni u dve jednake grupe koje su mogle da se porede u smislu jačine moždanog udara: pacijenti u prvoj grupi su dobijali standardni rehabilitacioni program (kontrolna grupa), pacijenti u drugoj grupi su dobijali dodatno i rehabilitaciju za hod uz korisćenje ExoAtlet egzoskeleta – 10 sesija, 5 sesija nedeljno 14 dana.* ***Rezultati.*** *Studija je pokazala efikasnost ExoAtlet egzoskeleta koji se koristi u rehabilitaciji pacijenata koji su pretrpeli mozdani udar u odnosu na standardni tok rehabilitacije. Prednosti uključuju smanjenje u stepenu hemipareze, povećanje u mišićnoj snazi paretičnog uda, poboljsanje u ravnoteži, poboljsanje i ubrzavanje procesa hodanja. Dobijeni rezultati instrumentalne studije potvrđuju koristi fizičkog treniranja na egzoskeletu što je pokazano kroz povećanje u stabilnosti i ravnoteži kao i kroz smanjenje indeksa potrošnje energije za održavanje stabilne vertikalizacije.* ***Zaključak.*** *Upotrebom ExoAtlet egzoskeleta povećava se efikasnost mera rehabilitacije i povećavaju se motorne i funkcionalne aktivnosti pacijenata koji su pretrpeli moždani udar.*

Ključne reči: *moždani udar, rehabilitacija, egzoskelet, ExoAtlet, hodanje, stabilometrija.*

sciendo
UDK: 616.718-089.28
616.831-005.1:615.8
Ser J Exp Clin Res 2021; 22 (3): 257-264
DOI: 10.2478/sjecr-2021-0045

Corresponding author:
Prof. Ekaterina Vladimirovna Silina,
Department of Human Pathology,
I.M. Sechenov First Moscow State Medical University
(Sechenov University), Trubetskaya Str, 8, Moscow,
119991, Russia
E-mail: silinaekaterina@mail.ru

INTRODUCTION

In recent decades, a stroke has become an acute medical and social problem all over the world. The figures for stroke cases are growing primarily in economically developed countries and this may be explained not only as an increase in life expectancy (1, 2). An increase in social interactions, constant stress, and brain overload has raised the number of strokes in young patients, most often engaged in mental work (3-5). Any successful introduction of new pharmacological, surgical, and X-ray endovascular methods of the stroke treatment, has been leading to a new problem - a significant increase in the number of patients with disabilities (6-8). Therefore, in recent years, some acute questions have been raised regarding the effectiveness of rehabilitation measures and reintegration of people with disabilities into society (9, 10).

The main disabling factor after the stroke is an impaired motor function, particularly, the walking function (10-12). As a result of the stroke unilateral muscle weakness, imbalance in the movement coordination due to uneven distribution of the body weight, sensory disturbances, post-stroke spasticity, aggravating fear of falling have been observed (13-14). Muscle weakness, combined with spasticity and violation of the correct reciprocal innervation, makes it impossible to implement an automated walking pattern and reduce imbalance, which significantly disrupts the physical activity of patients, restricts their social and daily activity (14-16). That is why the walking function rehabilitation is an important component for resocialization and improvement of life quality for patients. Despite the foundation of new rehabilitation centers and the emergence of new modern methods to restore lost motor functions, more than a third of patients cannot restore the ability to walk independently after the rehabilitation. Therefore, our search for new technologies of the motor function rehabilitation continues.

One of the prospective research areas that has emerged at the intersection of technology and medicine is the creation of exoskeletons - devices with the built-in electronic systems that may allow partial replacement of lost motor functions as a result of illness. The technical implementation of these devices is done in different ways: both simple mechanical devices and complex ones have been created using the brain-computer neuro-interfaces (17-20). However, at present, a sufficient amount of clinical data has not been collected yet, which prevents us from the objective calculation of the effectiveness of different types of such devices and determination of certain clinical groups in which the usage of exoskeletons will be most effective.

The aim of the study was to evaluate the effectiveness of restoring the functional and motor activity, including the walking function, in patients after the ischemic stroke in the middle cerebral artery basin using the ExoAtlet lower limb exoskeleton during the early recovery period after the stroke compared with the traditional methods of rehabilitation.

PATIENTS AND METHODS

The study was designed as a clinical prospective study. The research included 42 patients aged between 45 and 75 years (the mean age 61.2 ± 9.3 years, median - 63 years) who had suffered the cerebral infarction, who had undergone a course of rehabilitation in a 24-hour working hospital in the early recovery period of the stroke. The study was approved by the Independent Ethics Committee at the State Budgetary Institution of Healthcare in the Moscow Region "Moscow Regional Research Clinical Institute named after M.F. Vladimirsky" (the protocol No. 6 of 15.06.2017).

The mandatory inclusion procedure involves signing of patients' voluntary informed consent, the ischemic stroke in the middle cerebral artery system confirmed by neuroimaging (CT/MRI of the brain) without signs of the hemorrhagic transformation, the presence of spastic hemiparesis or leg monoparesis, muscle strength - 3-4 points according to the Medical Research Council Scale (MRCS), the degree of functional activity/disability - 2-3 points on the modified Renkin scale and 70-95 points on the Bartel index (mild to moderate disability), as well as preserved cognitive functions (25-30 points on the Mini-Mental State Examination). Besides that, the study included the patients who, according to the Hauser Ambulation Index, were ranging from 3 points (the patient can walk without assistance, in the meantime, he could walk 8 meters in 11-20 seconds) to 6 points (the patient needed double-sided support and more than 20 seconds to walk 8 meters).

The study did not include patients outside the inclusion criteria, and who were not able to walk 10 meters even with bilateral assistance, who had a severe comorbid status, the obesity rate ≥ II, who had the presence of critical stenosis of great vessels of the head (≥ 70% of lumen diameter), dementia, depression, low level of motivation to participate in the rehabilitation training.

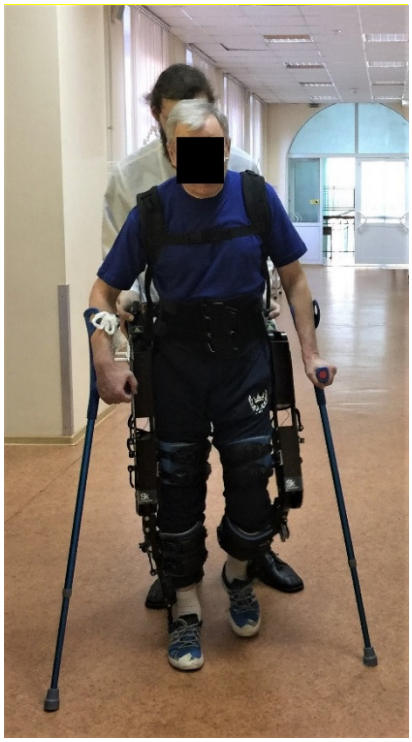
The patients were simply randomized into two identical groups.

The patients of the 1st group, the Comparison group (n = 21) received the standard rehabilitation program, which included the physical therapy, exercise therapy, massage, sessions with a speech therapist and a medical psychologist, as well as the cognitive training and secondary prevention of the ischemic stroke by drugs. The walking training on a flat surface was carried out 5 days a week for 2 weeks, the duration of each lesson varied within 20-40 minutes, depending on the patient's functional capabilities.

The patients of the 2nd group, the main group (n = 21), received the course of gait restoration using the ExoAtlet exoskeleton (ExoAtlet Company, Russia) - the complex robotic mechanotherapy (Fig. 1) in addition to the standard rehabilitation scheme. The sessions varied within 10-30 minutes, were focused on the somatic and functional state of each

patient, and were increased in the duration of each subsequent session. The total number of sessions was 10 and spread over 2 weeks (5 per week). The physical activity was being increased daily, depending on the condition and endurance of the patient.

Figure 1. A patient walking with the ExoAtlet exoskeleton during the rehabilitation session.



Under the study protocol, two control points were identified: (1) - before the start of the study (the inclusion of the patient in the study, randomization), (2) - day 14, after the end of the rehabilitation course. The study duration was 14 days for all patients.

At the control points of the study, muscle strength in the lower extremities was assessed using the Medical Research Council Scale (MRCS) (21); the functional assessment was done according to the Rankin scale (22) and the Bartel index of daily activity (23); the safety of the walking function was measured according to the Hauser Ambulation Index (HAI) (24), the study of stability and balance was performed using the Berg Balance Scale (BBS) (25). In addition to the clinical examination and assessments on various scales, the dynamics of motor function restoration were recorded using a stabiloplatform, and the dynamics of walking speed (10-meter walking test, 10MWT) were also obtained using a stopwatch (26). Using an instrumental study of stabilometry (stabiloplatform "ST-150", Mera-TSP, Russia), the state of vertical stability was studied, evaluating such indicators as the length of the statokinesiogram (L, mm) - the length sum of the segments that connect all projection points of a patient's pressure center on the surface of the stabiloplatform in the coordinate system during the functional test; the surface area of the statokinesiogram (S, mm2) which accounts for 90-95% of all positions of the pressure center during the study, is determined by calculating the area of the ellipse; the energy consumption index (Ei, J) - an indicator of energy consumption for the movement of the general pressure center during the study, calculated as the sum of increments of kinetic energies of the subject's body, was counted for each elementary movement of the general center of pressure. These indicators were obtained via two functional tests - a simple uncomplicated Romberg test, 2 consecutive 51-second phases of calm vertical standing with open and closed eyes, in the "European" feet placement (27, 28).

At the time of inclusion into the study, both patient groups were indistinguishable in terms of functional and motor capabilities (Table 1), which made it possible to conduct an objective comparative statistical analysis.

Table 1. The patient groups` characteristics according to the assessments via different scales and tests at the time of inclusion into the study.

Indicator		Statistical characteristic	Group1 Comparison (n=21)	Group 2 Exoskeleton (n=21)	p
Muscle strength, The Medical Research Council Scale, score		Me (Q1 : Q3)	4 (3 : 4)	4 (3 : 4)	0,750
The Bartel index, score		Me (Q1 : Q3)	80 (75:85)	80 (70:85)	0,746
The Berg Balance Scale, score		Me (Q1 : Q3)	41 (41 : 45)	41 (41 : 46)	0,939
The Rankin Scale, score	2 3	n (%)	3 (14,3%) 18 (85,7%)	4 (19,0%) 17 (81,0%)	0,682

Indicator		Statistical characteristic	Group1 Comparison (n=21)	Group 2 Exoskeleton (n=21)	p
The Hauser Ambulation Index, score	3 4 5 6	n (%)	4 (19,0%) 11 (52,4%) 6 (28,6%) 0	4 (19,0%) 9 (42,9%) 7 (33,3%) 1 (4,8%)	0,544
10-meter walking test, sec		Me (Q1 : Q3)	23 (18 : 23)	22 (18 : 23)	0,406

The baseline stabilometry indicators which were recorded in patients at the moment of the inclusion into the study, were also statistically indistinguishable in both groups ($p > 0.05$), with the exception in the index of energy expenditure with eyes closed, which was 1.5 times higher in the Comparison group (Table 2). In this regard, the analysis of the stabilometry indicators was carried out by both the absolute values of L, S, and Ei, determined on the 14th day, and by the percentage change dynamics in the observed parameters concerning the initial data.

Table 2. The baseline stabilometry indicators before the rehabilitation program in both groups.

Indicator	Statistical characteristic	Group 1 Comparison (n=21)	Group 2 Exoskeleton (n=21)	p
The length with eyes open, mm	Me (Q1 : Q3)	549 (538 : 564)	507 (503 : 513)	0,059
The length with eyes closed, mm	Me (Q1 : Q3)	730 (567 : 899)	598 (515 : 615)	0.071
The area with eyes open, mm^2	Me (Q1 : Q3)	339 (270 : 470)	319 (235 : 509)	0.658
The area with eyes closed, mm^2	Me (Q1 : Q3)	399 (273 : 498)	258 (242 : 471)	0.075
Energy consumption to keep balance with eyes open, J	Me (Q1 : Q3)	8.7 (5.7 : 12.1)	7.1 (6.3 : 16.0)	0.791
Energy consumption to keep balance with eyes closed, J	Me (Q1 : Q3)	19.9 (16.0 : 22.0)	13.8 (11.1 : 16.5)	0.005

Statistical processing of the research results was carried out using the SPSS 23.0 software. The differences were considered to be significant at $p < 0.05$. The descriptive statistics of the continuous quantitative data are presented as the mean (M) and standard deviation (± SD) with the normal distribution, as well as the median (Me), values of the lower (25%, Q1) to the upper (75%, Q3) quartiles with the abnormal distribution. To compare the quantitative indicators of two independent samples, the Mann-Whitney test was used, to compare the indicators of two related ones - the Wilcoxon test. The qualitative variables were analyzed in absolute and relative (by percent) units and compared using the $\chi 2$ test (the analysis of the contingency tables).

RESULTS

During the study, a significant positive effect of the Exoskeleton physical activity training was recorded in the dynamics of muscle strength, assessed by the Medical Research Council Scale (MRCS) (Table 3). An improvement in the MRCS score during 14 days was achieved by the majority (71.4%) of patients of the Exoskeleton group, whilst the improvement was recorded only in 28.6% of the Comparison group cases, and mostly, patients didn`t demonstrate changes in the limb paresis dynamics. ($p < 0.05$).

The full recovery of muscle strength in the limbs on the 14th day of the study was noted in 7 (33.3%) patients of the Exoskeleton group and only in 1 case (4.8%) in the Comparison group ($p < 0.05$).

Table 3. The assessment of muscle strength in the lower extremities using the Medical Research Council Scale on the 14th day of the study (n,%).

		Comparison	Exoskeleton	p
The MRCS score	3 4 5	3 (14,3%) 17 (81,0%) 1 (4,8%)	0 14 (66,7%) 7 (33,3%)	0,006
Dynamics	No changes Improvement	15 (71,4%) 6 (28,6%)	6 (28,6%) 15 (71,4%)	0,011

The study paid a particular attention to the assessment of the gait function. Conducting a 2-week rehabilitation course with the additional inclusion of 10 ExoAtlet sessions into the program led to a significant improvement in the patients' physical activity. The improvement in walking measured according to the Hauser index scale was observed in 15 (71.4%) cases in the Exoskeleton group, which is 3.8 times more than in the Comparison group where the improvement was recorded in 4 (19.0%) cases. ($p < 0.05$). Only in the Exoskeleton group, there were some patients (14.3%) who, by the end of the rehabilitation course, could walk 8 meters in less than 10 seconds, and gait disturbances were insignificant and almost imperceptible.

The walking speed test at a distance of 10 meters also confirmed the effectiveness of rehabilitation on the ExoAtlet Exoskeleton. On average, in the Exoskeleton group, the 10-meter distance was covered 18% faster (4 seconds), decreasing from 22 seconds on the day 0 to 18 seconds on the day 14 ($p < 0.001$). The patients walking speed in the Comparison group was also improved, but this improvement was 2 times less than in the Exoskeleton group ($p < 0.05$) (Table 4).

Table 4. The assessment of walking according to the Hauser Ambulation Index and 10-meter walking test on the 14th day of the study.

			Comparison	Exoskeleton	p
The Hauser Ambulation index,n (%)	Score	2 3 4 5 6	0 4 (19,0%) 15 (71,4%) 2 (9,5%) -	3 (14,3%) 11 (52,4%) 3 (14,3%) 4 (19,0%) -	0,039
	Score dynamics	No changes 1 score 2 scores	17 (81,0%) 4 (19,0%) 0	6 (28,6%) 12 (57,1%) 3 (14,3%)	0,001
10-meter walking test, sec Me (Q1 : Q3) 95CL		Speed on day 14	21 (14 : 21) 11-25	18 (13 : 21) 13-24	0,045
		Dynamics, -sec	2 (2:3) 0-5	4 (2:5) 2-7	0,007*

The Berg balance scale indices did not reveal any significant intergroup differences, the average score on the 14th day was 46 (46: 50) in the Comparison group and 47 (45: 56) in the Exoskeleton group ($p > 0.05$). However, after analyzing the indicator dynamics, a difference was recorded and expressed as an improvement in the balance dynamics by 7 points averagely in the Exoskeleton group and by 5 points in the Comparison group. The 2 points difference was statistically significant ($p < 0.05$).

As a result, a decrease in the disability degree and an improvement in the social adaptation were found in both groups, but the decrease was better expressed in the Exoskeleton group. Thus, the average score on the Bartel index in the Comparison group was 85 (80:95) points, in the Exoskeleton group - 90 (75: 100) points. Although the 5 points difference did not showany statistical significance, the frequency assessment of adaptation`s complete recovery revealed the significance. 100 points according to the Bartel index in the Comparison group were observed in 3 (14.3%) patients, in the Exoskeleton group - in 10 (47.6%) patients, which is 3.3 times more ($p < 0.05$). The analysis of the disability level according to the modified Rankin scale on the day 14 also showed a significant effect of the Exoskeleton rehabilitation course on the disability degree of the stroke patients. The improvement in the functional activity according to Rankin was found in 3 (14.3%) cases in the Comparison group and in 9 (42.9%) cases in the Exoskeleton group, which is significantly 3 times higher ($p < 0.05$) (Table 5).

Table 5. The assessment of the functional activity efficiency according to the modified Rankin scale on the 14th day of the study (n, %).

	Comparison	Exoskeleton	p
Me (Q1 : Q3)	3 (2:3)	2 (2:3)	0,028
Score 1 2 3	0 6 (28,6%) 15 (714%)	1 (4,8%) 12 (57,1%) 8 (38,1%)	0,025
No changes Improvement	18 (85,7%) 3 (14,3%)	12 (57,1%) 9 (42,9%)	0,043

Throughout the instrumental study of the stabilometric indicators (length, area of statokinesiogram, index of energy consumption), significant intergroup differences were recorded in the functional tests, which the patients hadperformed with both open and closed eyes. The recorded differences showed a positive effect of exercises on the Exo-Atlet exoskeleton, the greatest differences were registered with eyes open (Table 6).

Table 6. The stabilometry indicators on the 14th day of the study.

		Comparison	Exoskeleton	p
Length (L) with eyes open	Day 14, mm	492 (475: 537)	376 (343 : 393)	**<0,0001**
	Dynamics by day 14, %	-12.5 (-15.8: -1.5)	-26.7 (-39.1: -24.9)	**<0,0001**
	- decrease - increase	17 (81,0%) 4 (19,0%)	21 (100%) 0	0.053
Length (L) with eyes closed	Day 14, mm	663 (398: 780)	423 (348 : 553)	**0,021**
	Dynamics by day 14, %	-18,6 (-26,9: -11,3)	-28,9 (-31,4: -22,4)	**0.045**
	- decrease - increase	20 (95.2%) 1 (4.8%)	19 (90.5%) 2 (9.5%)	0.500
Surface area (S) with eyes open	Day 14, mm2	315 (210: 346)	154 (123 : 231)	**<0,0001**
	Dynamics by day 14, %	-22,2 (-32,9: -13,3)	-54,6 (-61,4: -48,9)	**<0,0001**
	- decrease - increase	16 (76.2%) 5 (23.8%)	19 (90.5%) 2 (9.5%)	0.205
Surface area (S) with eyes closed	Day 14, mm2	352 (200 : 374)	232 (110 : 242)	**0,001**
	Dynamics by day 14, %	-26,7 (-29,6: 1,4)	-46,2 (-54,5: -6,2)	0.071
	- decrease - increase	13 (61.9%) 8 (38.1%)	17 (81.0%) 4 (19.0%)	0.153
Energy consumption index (Ei) with eyes open	Joule	7.5 (6.0: 10.8)	4.1 (3.5 : 5.0)	**<0,0001**
	Dynamics in %	-13,8 (-17,4: -1,8)	-61,1 (-68,7: -29,6)	**<0,0001**
	- decrease - increase	16 (76.2%) 5 (23.8%)	21 (100%) 0	**0.024**
Energy consumption index (Ei) with eyes closed	Joule	11.0 (9.7 : 16.5)	7.2 (3.1 : 12.2)	**<0,0001**
	Dynamics in %	-34,0 (-39,4: -25,7)	-51,2 (-71,3: -37,7)	**0.007**
	- decrease - increase	17 (81,0%) 4 (19,0%)	18 (85.7%) 3 (14.3%)	0.500

DISCUSSION

The figures for the statokinesiogram length on the 14th day of the study in the Comparison group were 1.31 times larger on average with eyes open ($p < 0.05$), and 1.57 times larger with eyes closed ($p < 0.05$) than in the Exoskeleton group. Meanwhile, within the Comparison group, the statokinesiogram length with eyes open decreased by 12.5% on average, within the Exoskeleton group - by 26.7% concerning the initial values that had been recorded before the start of the rehabilitation course, the 2.14 times difference is statistically significant and indicates the positive impact of the Exoskeleton training. With eyes closed, the statokinesiogram length dynamics were more significant: the reduction in length in the Comparison group was 18.6%, in the Exoskeleton group - 28.9% (1.55 times higher, $p < 0.05$). It is also important to note that the statokinesiogram length indicator with eyes open became worse by the day14 in 19% of the cases in the Comparison group, but there were no such cases recorded in the Exoskeleton group.

The statokinesiogram area on the 14th day was averagely higher for the Comparison group, 2.05 times more with eyes open ($p < 0.05$) and 1.52 times more with eyes closed ($p < 0.05$). In the Comparison group, the statokinesiogram area with eyes open decreased by 22.2% on average, in the Exoskeleton group - by 54.6% compared to the initial values, the 2.46 times difference is statistically significant ($p < 0.05$). With eyes closed, the area decreased by 26.7% in the Comparison, and by 46.2% in the Exoskeleton groups, respectively. It is interesting to note the tendency of a 2-2.5-fold reduction in the number of patients whose statokinesiogram area worsened by the day 14 (with eyes open, there were 23.8% of such cases in the Comparison group, and 9.5% of cases in the Exoskeleton group; with eyes closed - 38, 1% and 19.0% of cases, respectively, $p > 0.05$). The findings confirm the improved resilience of patients receiving the Exoskeleton training.

The energy consumption index for maintaining the stable verticalization on the 14th day of the study also became significantly better in the functional tests for both eyes closed and open ($p < 0.05$) in the Exoskeleton group. On average, the patients in the Comparison group were spending 1.83 times more energy with eyes open, and 1.53 times with eyes closed ($p < 0.05$). Simultaneously, in the Comparison group, the energy consumption index with eyes open averagely decreased by 13.8%, in the Exoskeleton group - it dropped by 61.1% compared to 1 day, which is 4.42 times higher ($p < 0.05$). The same indicator for eyes closed demonstrated the improvement in the Comparison group by 34.0% on average, in the Exoskeleton group it was 1.51 times more, 51.2% compared with the initial figures ($p < 0.05$). We would like to emphasize that with eyes open, the energy consumption index diminished in 23.8% of cases of the Comparison group, no such cases were recorded in the Exoskeleton group ($p < 0.05$).

Our clinical prospective pilot comparative study demonstrated the effectiveness of the ExoAtlet exoskeleton in the rehabilitation of patients after the middle cerebral artery system stroke. The advantages over the standard rehabilitation course include the decrease in the hemiparesis degree, the increase in the paretic limb muscle strength, the improvement in balance, the improvement and acceleration of walking, which ultimately made it possible to increase the degree of social adaptation and reduce the degree of disability. The obtained results of the instrumental study confirmed the benefits of the Exoskeleton physical training, which were expressed by the increase in stability and balance (a more pronounced reduction in the statokinesiogram length and area) by 1.3-2.0 times, as well as in the decrease in the energy consumption for maintaining the stable verticalization by 1.5-1.8 times with eyes open and closed. The degree of the established intergroup differences allows us to conclude that 10 additional sessions on the ExoAtlet for 2 weeks of rehabilitation during the early recovery period of the stroke for patients with mild and moderate disadaptation, increase the effectiveness of the physical activity rehabilitation till 15-20%. This could increase the number of patients with full functional and motor recovery.

CONCLUSION

The use of the ExoAtlet exoskeleton increases the effectiveness of rehabilitation measures and improves the motor and functional activity of patients who have suffered the cerebral stroke. Therefore, it can probably be recommended for permanent inclusion in the rehabilitation program for patients after the stroke. However, for the final decision of both the inclusion itself and the modes of use of the ExoAtlet exoskeleton, it is necessary to conduct a more in-depth study on protocols that meet the requirements of the principles of evidence-based medicine. In particular, it is advisable to conduct a control-spawning study of several groups of patients undergoing the rehabilitation using other robotic technologies, as well as technologies used in exoskeletons.

LITERATURE

1. Venketasubramanian N, Yoon BW, Pandian J, Navarro JC. Stroke Epidemiology in South, East, and South-East Asia: A Review. J. Stroke. 2017;19(3):286-294.
2. Donkor E.S. Stroke in the 21st century: A snapshot of the burden, epidemiology, and quality of life. Stroke Res Treat. 2018:3238165.
3. Kalashnikova LA, Dobrynina LA. Ishemicheskiĭ insul't v molodom vozraste Ischemic stroke in young adults. Zh Nevrol Psikhiatr Im S S Korsakova. 2017;117(8-2):3-12.
4. Béjot Y, Bailly H, Durier J, Giroud M. Epidemiology of stroke in Europe and trends for the 21st century. Presse Med. 2016;45(12,Pt2):391-398.
5. Hathidara MY, Saini V, Malik AM. Stroke in the young: a Global update. Curr. Neurol. Neurosci. Rep. 2019;19(11):91.
6. Rumyantseva SA, Silina EV, Svischeva SP, Komarov AN. (Medical and organizational issues of pre- and post-

stroke disablement). Zh Nevrol Psikhiatr Im S S Korsakova. 2013;113(9-2):43-49.
7. Feigin VL, Norrving B, Mensah GA. Global Burden of Stroke. Circ Res. 2017;120(3):439-448.
8. Rajsic S, Gothe H, Borba HH, Sroczynski G, Vujicic J, Toell T, Siebert U. Economic burden of stroke: a systematic review on post-stroke care. Eur J Health Econ. 2019;20(1):107-134.
9. Coleman ER, Moudgal R, Lang K, Hyacinth HI, Awosika OO, Kissela BM, Feng W. Early Rehabilitation After Stroke: a Narrative Review. Curr Atheroscler Rep. 2017;19(12):59.
10. Stinear CM, Lang CE, Zeiler S, Byblow WD. Advances and challenges in stroke rehabilitation. Lancet Neurol. 2020;19(4):348-360..
11. Suri R, Rodriguez-Porcel F, Donohue K, Jesse E, Lovera L, Dwivedi AK, Espay AJ. Post-stroke Movement Disorders: The Clinical, Neuroanatomic, and Demographic Portrait of 284 Published Cases. J Stroke Cerebrovasc Dis. 2018;27(9):2388-2397. Caproni S, Colosimo C. Movement disorders and cerebrovascular diseases: from pathophysiology to treatment. Expert Rev Neurother. 2017;17(5):509-519.
12. Barer D, Watkins C. Could upright posture be harmful in the early stages of stroke? Lancet. 2015;386(10005):1734.
13. Kal E, Prosée R, Winters M, van der Kamp J. Does implicit motor learning lead to greater automatization of motor skills compared to explicit motor learning? A systematic review. PloS one. 2018;13(9):e0203591.
14. Tanaka H, Nankaku M, Nishikawa T, Hosoe T, Yonezawa H, Mori H, Kikuchi T, Nishi H, Takagi Y, Miyamoto S, Ikeguchi R, Matsuda S. Spatiotemporal gait characteristic changes with gait training using the hybrid assistive limb for chronic stroke patients. Gait & posture. 2019;71:205–210.
15. Park J, Kim TH. The effects of balance and gait function on quality of life of stroke patients. NeuroRehabilitation. 2019; 44 (1): 37–41.
16. Klamroth-Marganska V. Stroke Rehabilitation: Therapy Robots and Assistive Devices. Adv Exp Med Biol. 2018;1065:579-587.
17. Shusharina NN, Bogdanov EA, Botman SA, Silina EV, Stupin VA, Patrushev MV. Development of the Brain-computer Interface Based on the Biometric Control Channels and Multi-modal Feedback to Provide A Human with Neuro-electronic Systems and Exoskeleton Structures to Compensate the Motor Functions. Biosciences Biotechnology Research Asia. 2016;13(3):1523–1536.
18. Molteni F, Gasperini G, Cannaviello G, Guanziroli E. Exoskeleton and End-Effector Robots for Upper and Lower Limbs Rehabilitation: Narrative Review. PMR. 2018;10(9 Suppl 2):S174-S188.
19. Pismennaya EV, Petrushanskaya KA, Kotov SV, Avedikov GE, Mitrofanov IE, Tolstov KM, Efarov VA. Clinical and biomechanical foundation of application of the exoskeleton Exoatlet at walking of patients with poststroke disturbances. Russian Journal of Biomechanics. 2019;23(2):204-230.
20. Paternostro-Sluga T, Grim-Stieger M, Posch M, Schuhfried O, Vacariu G, Mittermaier C, Bittner C, Fialka-Moser V. Reliability and validity of the Medical Research Council (MRC) scale and a modified scale for testing muscle strength in patients with radial palsy. J Rehabil Med. 2008;40(8):665-671.
21. Broderick JP, Adeoye O, Elm J. Evolution of the Modified Rankin Scale and Its Use in Future Stroke Trials. Stroke. 2017;48(7):2007–2012.
22. Wade DT, Collin C. The Barthel ADL Index: a standard measure of physical disability? Int Disabil Stud. 1988;10(2):64-67.
23. Hauser SL, Dawson DM, Lehrich JR, Beal MF, Kevy SV, Propper RD, Mills JA, Weiner HL. Intensive immunosuppression in progressive multiple sclerosis. A randomized, three-arm study of high-dose intravenous cyclophosphamide, plasma exchange, and ACTH. N Engl J Med. 1983;308(4):173-80.
24. Blum L, Korner-Bitensky N. Usefulness of the Berg Balance Scale in stroke rehabilitation: a systematic review. Phys Ther. 2008; 88 (5): 559-566.
25. Peters DM, Fritz SL, Krotish DE. Assessing the reliability and validity of a shorter walk test compared with the 10-Meter Walk Test for measurements of gait speed in healthy, older adults. J Geriatr Phys Ther. 2013; 36 (1): 24-30.
26. Kubriak OV, Isakova EV, Kotov SV, Romanova MV, Grokhovskiĭ SS. Increase in patient vertical stability in acute period of ischemic stroke. Zhurnal Nevrologii i Psikhiatrii Im. S.S. Korsakova. 2014;114(12-2): 61-65.
27. Wang Z, Molenaar PC, Newell KM. The effects of foot position and orientation on inter- and intra-foot coordination in standing postures: a frequency domain PCA analysis. Exp Brain Res. 2013;230(1):15-27.

PLEURAL EMPYEMA MENAGEMENT: A BRIEF REVIEW OF LITTERATURE

Milos Arsenijevic [1,2], Slobodan Milisavljevic [1,2], Stanko Mrvic[1] and Dragan Stojkovic[1]
[1] Departement of Thoracic Surgery, Clinical Centre Kragujevac, Kragujevac, Serbia
[2] University of Kragujevac, Faculty of Medical Sciences, Department of Surgery, Kragujevac, Serbia

LEČENJE EMPIJEMA PLEURE: PREGLED LITERATURE

Milos Arsenijević [1,2], Slobodan Milisavljević [1,2], Stanko Mrvić[1] i Dragan Stojković[1]
[1] Klinika za grudnu hirurgiju, Klinički centar Kragujevac, Kragujevac, Srbija
[2] Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Katedra za hirurgiju, Kragujevac, Srbija

Received / Primljen: 01. 10. 2017. Accepted / Prihvaćen: 24. 10. 2017.

ABSTRACT

Pleural empyema, defined as the presence of purulent material within the pleural space, is the consequence of a suppurative process involving the serous pleural layers. Thoracic empyema is a dynamic process, inflammatory in origin and taking place within a preformed space bordered by both the visceral and parietal pleura. It is a complex clinical entity, neither a sole clinical, laboratory, nor a radiological diagnosis. The primary therapeutic aim: 'ubi pus evacua' — if you find pus remove it—has not changed since the age of Celsus. Therefore, treatment of the acute empyema of the pleura is directed to early and complete evacuation of empirical fluid and content, achieving full re-expansion of the lungs and eradication of the infection using appropriate surgical procedures, antibiotics and other supportive procedures. The optimum method of treating empyema should be adjusted to the condition of the patient and the stage of the disease in which the patient is located. The method of treatment depends on the etiology (pneumonic or traumatic), the general condition of the patient and the stage of disease development. By reviewing the available literature, it can be concluded that treating the pleural empyemas is a demanding procedure, in which it is necessary for the treating physician to apply all of his knowledge, and that there is good cooperation with the patient.

Keywords: *Empyema, treatment, pleura*

SAŽETAK

Empijem pleure, koji se definiše kao prisustvo gnojnog sadržaja unutar pleuralnog prostora, predstavlja posledicu gnojnog zapaljenja seroznih opni unutar grudne duplje. To je inflamatorni dinamičan procs koji se odvija unutar grudne duplje, sa nekad nedovoljno jasnim kliničkim, radiografskim i laboratorijskim manifestacijama. Osnovni terapeutski princip „ubi pus evacua" se nije promenio od vremena Celzusa. Stoga, evakuacija gnojne nakupine unutar pleuralnog prostorauz kompletnu eradikaciju infektivnog agensa i obliteracije pleuralnog kavuma, tokom rane faze razvoja bolesti, predstavlja primarni cilj lečenja. Optimalni metod lečenja empijema pleure bi trebalo da bude prilagodjen fazi razvoja bolesti, kao i opštem stanju pacijenta.

Pregledom dostupne literature, dolazimo do zaključka da lečenje pleuralnog empijema zahteva punu kooperaciju pacijenta, uz upotrebu svog medicinskog znanja i iskustva lekara, a u cilju postizanja izlečenja, što predstavlja izazov za lekara.

Ključne reči: *Empijem, tretman, pleura*

sciendo
UDK: 616.25-002.3
Ser J Exp Clin Res 2021; 22 (3): 265-269
DOI: 10.1515/sjecr-2017-0056

Corresponding author:
Milos Arsenijevic, MD, PhD
University of Kragujevac, Serbia, Faculty of Medical Sciences,
Department of Surgery
Email – milos.arsenijevic83@gmail.com

INTRODUCTION

Pleural empyema, defined as the presence of purulent material within the pleural space, is the consequence of a suppurative process involving the serous pleural layers (1). The first case of empyema was described by Hippocrates about 2,400 years ago (2). Nowadays, the increased incidence of nosocomial infections, acquired immunodeficiencies and antibiotic-resistant germs reflects in a dramatic increase of pleural empyema cases resulting in a challenging management and therapeutic approach.

Considering that in 47-56% of cases no direct infectious agent of the empyema is known, and because of the need to treat it as soon as possible and in the best possible way, it is most effective to keep Light and Muers criteria for the diagnostics of contents from the pleural space (3, 4).

The most common microorganisms that lead to the formation of the empyema of pleura are: pneumococcus, streptococcus, staphylococcus and tuberculosis bacillus. Infections with coliform bacilli, Proteus vulgaris, various fungi and mixed microorganisms is a rare occurrence. The pathophysiological invasion of the pleural space can occur in several ways: the direct spread of the infection from the pneumonic focus (parapneumonic empire) (4), rupture of a pyogenic or tuberculous lung abscessus, a contamination resulting from an operation or trauma (5, 6), the direct spread of an infection that is primarily subdiaphragmatic and hematogenous dissemination within a generalized infection (sepsis) (7). Empyema pleura to the clinical course can be: acute and chronic.

Thoracic empyema is a dynamic process, inflammatory in origin and taking place within a preformed space bordered by both the visceral and parietal pleura. It is a complex clinical entity, neither a sole clinical, laboratory, nor a radiological diagnosis (8).

The diagnosis of empyema pleura is not difficult to set because clinical presentation is often obvious. Local symptoms of empyema include thoracic pain, cough, weakness, fever and leukocytosis. Acute empyema with a high amount of purulent effusion are manifested clinically by dyspnoea and signs of intoxication. A physical finding is characteristic of pleural effusion, and chest radiography and MSCT scan are considered "gold standards" in imaging diagnostics of pleural empyema. Positron emission tomography (18F-FDG-PET/CT) does not appear to be a diagnostic tool in evaluating patients with pleural effusion due to its low specificity and subsequent difficulty in differentiating between inflammatory and neoplastic disease (9-11).

In 1962, the American Thoracic Surgery (ATS) defined three different stages according to clinical evolution of pleural effusions: (I) essudative phase (Stage I), characterized by an increase in the permeability of serous layers with exudate production. Despite of fibroblasts and angioblastic cells proliferation with fibrin deposition, no thickenings or pleural remodeling can be identified; (II) fibrinopurulent phase (Stage II), characterized by a massive deposition of fibrin predominantly on the parietal pleura. The purulent exudate exhibits a high concentration of polymorphonucleated lymphocytes. Septa begin to form in a reversible condition; (III) organized Phase (Stage III), with massive fibroblastic proliferation and consensual formation of diffuse septa on both the serous membranes and leading to lung incarceration with an impaired re-expansion (12, 13).

Taking into account the clinical findings, the criteria for diagnosing the pleura empires are as follows:

1. Obtained pure pus with pleural puncture and / or directly / indirectly confirmed presence of bacteria in the punctate (Gram stain, microbiological analysis)
2. The pH of the content is less than 7, 2, the glucose concentration is less than 400 mg / l, values of LDH punctate over 1000 IU / ml, protein level above 3 g / ml and WBC over 15 000 cells / mm3
3. Clinical and radiographic findings that point to the existence of an inflammatory process in the lungs(3).

Muers criteria includes also glucose level in pleural effusio, as well as its relation with serum glucose (3).

Chronic empyuemas represent a long-term phase of the development of acute pleura empires. When the empyema becomes chronic, the visceral pleura thickens and is firmly glued to the encapsulated collection. Empyema becomes chronic for several reasons, some of which are late diagnosis, or inadequate treatment of acute empyema, the existence of a bronchopleural fistula, tuberculosis or actinomycosis infection, the presence of a foreign body in the pleural area, osteomyelitis of the rib, a lung disease that prevents and prevents re-expansion and possibility of malignant disease. Chronic empyemas today are rarely meet in clinical practice. Its treatment is long lasting and complicated, and is aimed at the sterilization of the pleural cavity and eventualy surgical treatment, that is, the decortication of the lungs and the possible resection of the devastated part of the lungs (due to abscess, bronchiectasis, bronchopleural fistulae, etc.).

DISSCUSION

The primary therapeutic aim: 'ubi pus evacua' — if you find pus remove it—has not changed since the age of Celsus. Therefore, treatment of the acute empyema of the pleura is directed to early and complete evacuation of empirical fluid and content, achieving full re-expansion of the lungs and eradication of the infection using appropriate surgical procedures, antibiotics and other supportive procedures (8, 12-18).

The 2017 pleural effusion management guidelines of American Association for Thoracic Surgery (AATS) suggest management schemes based on the "risk-benefit" relationships and, according to the increase in this ratio, three classes have been identified; Class III has a poorly-rated treatment given the high risk factors compared to benefits; Class II has likely better rated treatment given risk factors over the benefits, but not enough trial data; Class I has highly rated benefits than risk factors (17).

The success of treatment depends on the stage in which the development of the empyema is initiated. When therapy begins at an early stage of the disease, parapneumonic

effusions and/or early stage empyema can be successfully cured using thoracic drainage and antibiotics.

Therapeutic drainage, video-assisted thoracoscopic surgery (VATS), fibrinolytic (enzymatic) decortication, open decortication of pleura, thoracoplasty and open thoracotomy are used in treating empyema pleuralis.

I. Thoracic chest tube placement

Thoracentesis is a useful tool in the management of uncomplicated pleural effusion and a recommended step in the diagnosis of complicated effusion (12, 13). However, in the setting of known pleural infection, ongoing pleural drainage is regarded as a requirement for adequate treatment and thoracentesis alone, without pleural drain placement, is not recommended (17).

Drainage of infected material from the pleural space is a fundamental part of empyema treatment. Traditionally tube thoracostomy has been performed with large bore catheters, but no consensus exists regarding ideal drain size (11, 12, 13, 14, 17).

Expert opinion holds that small-bore catheters are ineffective in draining thick pus or extensively septated effusions; however, absent any randomized trials, the role of empyema stage in the success or failure of image-guided drain placement is unclear. Existing data are mixed. In an unblinded trial, the presence of sonographic septations was predictive of more aggressive treatment, but did not specifically address the success or failure of tube drainage in this population (19).

II. Fibrinolytic (enzymatic) decortication

The removal of fibrin septes that occur during the second phase of empyema development is one of the key factors that Tilet and associates first dealt with in 1951. (20) Studies comparing the effect of drainage in the treatment of the empyema and the effect of drainage with the use of fibrinolytic, argue in favor of the use of fibrinolytic in the treatment of empyemas during the second phase of the disease with a success rate of 87.7% (21).

By developing more modern fibrinolytics, the fibrinolysis efficiency can be extended to a later period in the development of the empyema (21-23).

A thorough meta-analysis on the utility of intrapleural fibrinolytic therapy published in 2012 concluded that fibrinolytic therapy is potentially beneficial in the management of parapneumonic effusions and empyemas in adults but that there is insufficient vidence to support the routine use of this therapy for all patents with parapneumonic effusions/empyemas (23).

III. Use of video - assisted thoracoscopic surgery (VATS) in the treatment of empires

Since the mid-1990s, the thoracoscopic evacuation of the empirical bag has gained great popularity as a treatment method (24).

Subsequent studies supported the original conclusions and made certain remarks on the limitations of this procedure in the treatment of empires (25). The effectiveness of the treatment of empyema by this method varies between 68 - 93%, but very often correlates with the patient group examined. Namely, the longer the disease lasts, the failure is more frequent. In patients with a disease lasting up to 4 weeks, the effectiveness of the VATS method is higher (26).

Also, in the early stages of the posttraumatic empiric emission, VATS is for now the sovereign method of success (27).

The choice of open *vs.* thoracoscopic strategies must be made by considering a complete evacuation of potentially infected fluid and a complete lung re-expansion. Moreover, with either approach, the main technical considerations include safe access into the chest, drainage of pleural space and maneuvers to allow full expansion of lung. Potential contraindications and drawbacks of VATS include the inability to tolerate single lung ventilation, severe coagulopathy and operative time with increased costs (28).

IV. Decortication of pleura

Decortication of pleura is a method of choice in cases where it is not possible to achieve complete lung reexpansion ("captured lungs") due to already formed thick fibrin deposits on the visceral pleura, and the patient is in a sufficiently good general condition for great intervention in general anesthesia. The procedure was originally used for the treatment of tuberculous and posttraumatic empyema (29), and relies on the elasticity of the lung parenchyma that needs to fill the pleural space, leading to obliteration of the pleural space. In the event that the illness itself lasts for more than 6 weeks, which is equivalent to Phase III of the disease, recommendations are to apply decortication if the patient is capable of carrying out the operation (30).

In patients with long-standing post-tuberculous collapse of the lungs with minimal lung perfusion, decortication can be attempted, but the outcome is uncertain (29). In patients subjected to VATS for the treatment of empyema, conversion to open procedure (decortication) can occur in 3, 8 - 40% (30, 31).

V. Toracoplasty

Thoracoplasty ("collapse therapy") represents a partial resection of the chest wall in order to control the underlying inflammatory process, was among the first effective chest surgical interventions (32). Nowadays, the aim of this method is to fill the pleural cavity with connective tissue and / or fill the empirical cavity with tissue (omentum, muscle transposition). This procedure can be performed alone or in combination with other treatment methods. Despite the development of modern technology, there are no available reports on non-

biological materials that can be used to obliterate the pleural space (33).

In cases where there is no improvement within less aggressive treatment procedures, toracomyoplasty may be the only option (34, 35). This method may be a sovereign for the treatment of empires following pneumonectomy caused by bronchopular and / or esophagus - complicated fistula after pneumonectomy (36).

VI . Open thoracic window

In advanced stages of the disease, in patients in severe general condition, operative thoracostomy (fenestration of the pleural space) is the first, and often the only method of treating empyema (36, 37).

The advantage of this method is the establishment of a wide opening through which the infectious substance is dried, but the quality of life of such patients is very bad. This method is most commonly applied to the empyema of pleura produced by the existence of a bronchopleural fistula after pneumonectomy, when all other options for controlling the infection are exhausted. In itself, the method of open thoracostomy can be the ultimate solution in treating the empyema of the pleura, but often represents the first phase of treatment, which "buys the time" until the conditions for closing the torakostom and reconstructing the chest wall are achieved (37, 38).

CONCLUSIONS

The optimum method of treating empyema should be adjusted to the condition of the patient and the stage of the disease in which the patient is located. The method of treatement depends on the etiology (pneumonic or traumatic), the general condition of the patient and the stage of disease development. By reviewing the available literature, it can be concluded that treating the pleural empyemas is a demanding procedure, in which it is necessary for the treating physician to apply all of his knowledge, and that there is good cooperation with the patient.

Regardless of the stage of the disease and the applied methods, the goals of the treatment must always be the same:

1. Complete removal of infectious contents from the pleural cavity
2. Achieve complete obliteration of the pleural space
3. Infection control
4. Applying good physical rehabilitation at the very beginning of the therapy

The way of achieving these goals, as can be seen in the reviewed literature, is not rigid and narrowly limited, but is based on the experience of doctors as well as on active monitoring of the development of the disease, where the doctor must provide himself with a working width, with the best intention for the patient.

REFERENCES

1. Redden MD, Chin TY, van Driel ML. Surgical versus non-surgical management for pleural empyema. Cochrane Database Syst Rev 2017;3:CD010651. [PubMed].
2. Tsoucalas G, Sgantzos M. Hippocrates (ca 460-375 bc), introducing thoracotomy combined with a tracheal intubation for the parapneumonic pleural effusions and empyema thoracis. Surg Innov 2016;23:642-3. [Crossref] [PubMed]
3. Muers MF. Streptokinase for empyema. Lancet 1997;349:1491-2. [Crossref] [PubMed].
4. Mandal AK, Thadepalli H, Mandal AK, Chettipalli U. Posttraumatic empyema thoracis: a 24-year experience at a major trauma center. J Trauma 1997;43:764—77.
5. V. Cvijanovic et al. Surgical treatment of war posttraumatic pleural empyemas, Vojnosanитetski pregled. Military - medical and pharmaceutical review 64(12):813-8 · January 2008
6. Petrakis IE, Kogerakis NE, Drositis IE, Lasithiotakis KG, Bourous D, Chalkiadakis GE. Video-assisted thoracoscopic surgery for thoracic empyema: primarily, or after fibrinolytic therapy failure? Am J Surg 2004;187:471—4.
7. Mutsaers SE, Prele CM, Brody AR, Idell S. Pathogenesis of pleural fibrosis. Respirology 2004;9:428—40.
8. Thomas F. Molnar; Current surgical treatment of thoracic empyema in adults, European Journal of Cardio-Thoracic Surgery, Volume 32, Issue 3, 1 September 2007, Pages 422–430, https://doi.org/10.1016/j.ejcts.2007.05.028
9. Porcel JM, Hernández P, Martínez-Alonso M, et al. Accuracy of fluorodeoxyglucose-PET imaging for differentiating benign from malignant pleural effusions: a meta-analysis. Chest 2015;147:502-12.
10. Toaff JS, Metser U, Gottfried M, et al. Differentiation between malignant and benign pleural effusion in patients with extra-pleural primary malignancies: assessment with positron emission tomography-computed tomography. Invest Radiol 2005;40:204-9.
11. Divisi D, Gabriele F, Barone M, Zaccagna G, Di Francescantonio W, Crisci R. Clinical history and surgical management of parapneumonic empyema what is the role of video-assisted thoracoscopic surgery (VATS)? Video-assist Thorac Surg 2017;2:65.,
12. Andrews NC, Parker EF, Shaw RR, Wilson NJ, Webb WR. Management of nontuberculous empyema: a statement of the subcommittee on surgery. Am Rev Respir Dis 1962;85:935.
13. Storm HKR, Krasnik M, Bang K, Frimodt Moller N. Treatment of pleural empyema secondary to pneumonia: thoracocentesis regimen versus tube drainage. Thorax 1992;47:821—4.
14. Thourani VH, Brady KM, Mansour KA, Miller JI, Lee RB. Evaluation of treatment modalities for thoracic empyema: a cost - effectiveness analysis. Ann Thorac Surg 1998;66:1121—27.

15. Molnar TF, Hasse J, Jeyasingham K, Rendeki S. Changing dogmas: history of treatment for traumatic hemothorax, pneumothorax and empyema thoracis. Ann Thorac Surg 2004;77:372—8.;
16. Mandal AK, Thadepalli H, Mandal AK, Chetipally U. Outcome of primary empyema thoracis: therapeutic and microbiologic aspects. Ann Thorac Surg 1998;66:1782—6.
17. The American Association for Thoracic Surgery consensus guidelines for the management of empyemaShen, K. Robert et al.The Journal of Thoracic and Cardiovascular Surgery , Volume 153 , Issue 6 , e129 - e146
18. Hajjar WM, Ahmed I, Al-Nassar SA, et al. Video-assisted thoracoscopic decortication for the management of late stage pleural empyema, is it feasible? Annals of Thoracic Medicine. 2016;11(1):71-78. doi:10.4103/1817-1737.165293
19. Chen KY, Liaw YS, Wang HC, Luh KT, Yang PC. Sonographic septation: a useful prognostic indicator of acute thoracic empyema. J Ultrasound Med. 2000 Dec;19(12) :837-43
20. Tillet SA, Sherry S, Read CT. The use of streptokinase - streptodornase in the treatment of postpneumonic empyema. J Thorac Surg 1951;21: 275—97.
21. Misthos P, Sepsas E, Konstantnou M, Athanassiadi K, Skottis I, Lioulias A. Early use of ıntrapleural fibrinolytics in the management of postpneumonic empyema. A prospectıve study. Eur J Cardıothorac Surg 2005; 28:599—603.
22. Thommi, G., Nair, C. K., Aronow, W. S. et al, Efficacy and safety of intrapleural instillation of alteplase in the management of complicated pleural effusion or empyema. Am J Ther. 2007 Jul–Aug;14:341–345.
23. Janda, S. and J. Swiston (2012). "Intrapleural fibrinolytic therapy for treatment of adult parapneumonic effusions and empyemas: a systematic review and meta-analysis." Chest 142(2): 401-411.
24. Lawrence DR, Ohri KS, Moxon RE, Townsend ER, Fountain SW. Thoracosocopic debridement of empyema thoracis. Ann Thorac Surg 1997;64:1448—50.
25. Kim BY, Oh BS, Jang WC, Min YI, Park YK, Park YC. Video - assisted thoracoscopic decortıcation for management of postpneumonic pleural empyema. Am J Surg 2004;188(3):321—4.
26. Oguzkaya F, Akcali Y, Bilgin M. Videothoracoscopy versus intrapleural streptokinase for management of post - traumatic retained haemothorax: a retrospective study of 65 cases. Injury 2005;36:526—9.
27. Samson PC, Buford TH. Total pulmonary decortications. Its evaluation and present concepts of indication and operative technique. J Thorac Surg 1947;16:153—7.
28. Chambers A, Routledge T, Dunning J, et al. Is video assisted thoracoscopic surgical decortication superior to open surgery in the management of adults with primary empyema? Interact Cardiovasc Thorac Surg 2010;11:171-7..
29. Olgac G, Yilmaz MA, Ortakoulu MG, Kutlu CA. Decision making for lung resection in patients with empyema and collapsed lung due to tuberculosis. Thorac Cardiovasc Surg 2005;130:131—5 [Discussion: 2005;130(6): 1732]
30. Luh SP, Choy MC, Wang LS, Chen JY, Tsai TP. Video - assisted thoracoscopic surgery in the treatment of complicated parapneymonic effusions or empyemas. Chest 2005;127:1427—32.,
31. Lardinois D, Gock M, Pezzeta E, Bychli C, Roysson V, Fyrrer M, Ris HB. Delayed referral and gram negative organisms increase the conversion thoracotomy rate in patients undergoing vıdeo - assisted thoracoscopic surgery for empyema. Ann Thorac Surg 2005;79(6):1851—6.
32. Peppas G, Molnar TF, Jeuasingham K, Kirk A. Thoracoplasty in the context of current surgical practice. Ann Thorac Surg 1993;56:903—9.
33. Tezel CS, Goldstraw P. Plombage thoracoplasty with lucite balls. Ann Thorac Syrg 2005;79:1063.
34. Icard P, LeRochais JP, Rabut B, Cazaban S, Martel B, Evrard C. Andrews thoracoplasty as a treatment of post - pneumonectomy empyema: experience in 23 cases. Ann Thorac Surg 1999;68:1159—63.
35. Trigui W, Le Pimpec - Barthes F, Shaker W, Lang - Lazdunski L, Riquet M. Simultaneous bronchopleural and esophagopleural fistulas after pneumonectomy. Ann Thorac Surg 2002;74:923—4.
36. Deslauriers J, Jacques LF, Gregoire J. Role of Eloesser flap and thoracoplasty in the third millennium. Chest Surg Clin N Am 2002;12:605—23.
37. Regnard JF, Alifano M, Puyo P, Fares E, Magdeleinat P, Levasseyr P. Open window thoracostomy followed by intrathoracic flap transposition in the treatment of empyema complicating pulmonary resection. J Thorac Cardiovasc Surg 2000;120:270—5.,
38. Rand RP, Maser B, Dry G, Vallieres E. Reconstruction of irradiated postpneumonectomy empyema cavity with chain - link coupled microsurgical omental and TRAM flaps. Plast Reconstr Surg 2000;105:183—6.

sciendo

WANDERING SPLEEN - A POSSIBLE CAUSE OF ADRENAL ”MASS“ - CASE REPORT

Slavica Markovic[1,2], Milan Paunovic[2,3], Biljana Vuletic[1,2], Zorica Raskovic[1,2] , Gordana Kostic[1,2], Zoran Igrutinovic[1,2], Nevena Folic[1,2], Dragana Savic[1,2] and Rasa Medovic[1]

[1]*Pediatric Clinic, Clinical Centre Kragujevac, Kragujevac, Serbia*

[2]*University of Kragujevac, Faculty of Medical Sciences, Department of Pediatrics, Kragujevac, Serbia*

[3]*Clinic of Pediatric Surgery, Clinical Centre Kragujevac, Kragujevac, Serbia*

LUTAJUĆA SLEZINA KAO MOGUĆI UZROK ADRENALNE „MASE“ - PRIKAZ SLUČAJA

Slavica Marković[1,2], Milan Paunović [2,3], Biljana Vuletić[1,2], Zorica Rašković[1,2], Gordana Kostić[1,2], Zoran Igrutinović[1,2], Nevena Folić[1,2], Dragana Savić[1,2] i Raša Medović[1]

[1]*Pedijatrijska klinika, Klinički centar Kragujevac, Kragujevac, Srbija*

[2]*Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Katedra za pedijatriju, Kragujevac, Srbija*

[3]*Klinika za dečju hirurgiju, Klinički centar Kragujevac, Kragujevac, Srbija*

Received/Primljen: 28.08.2018. Accepted/Prihvaćen: 11.02.2019.

ABSTRACT

Wandering spleen is a very rare clinical condition characterized by spleen absence in the normal anatomical location in the upper left quadrant of the abdomen and its presence at another location in the abdomen or pelvis. The ectopic spleen is extremely rare in children, where its increased mobility is the result of a congenital disturbance of the fixation for the anterior wall due to the absence or weakness of the supporting ligaments. Wandering spleen is usually asymptomatic, but its torsion is possible, as well as infarction or rupture which demand an urgent diagnosis and surgical treatment. The diagnosis of wandering spleen can easily be overlooked due to low incidence and insufficient clinical experience, which multiplies patient's risk from life-threatening conditions. We present a case of wandering spleen in an 11-year-old girl with acute abdominal pain, which after ultrasound examination raised suspicion on the right adrenal gland tumor. Additional diagnostics verified an ectopic spleen in the right adrenal box, after which the recommended preventive splenopexy was seriously considered. Due to the fixation of the vital spleen in the new position, but also the negative attitude of the parents towards the surgical intervention, clinical monitoring was selected, with exclusion of intense physical activity that carries the risk of traumatization of the spleen. As the girl has been in good health for over 3 years and without symptoms, we consider that the selection of conservative access although difficult, was correct. We hope that our experience in treating wandering spleen in girls will increase the number of valid facts about this rare condition.

Keywords: *spleen, splenic diseases, splenic torsion, wandering spleen*

SAŽETAK

Lutajuća slezina je vrlo retko kliničko stanje koje odlikuje odsustvo slezine u normalnom anatomskom položaju u gornjem levom kvadrantu abdomena i prisustvo na drugom mestu u abdomenu ili karlici. Ektopična slezina je izuzetno retka kod dece, gde je njena povećana mobilnost posledica kongenitalnog poremećaja fiksacije za prednji trbušni zid usled odsustva ili slabosti potpornih ligamenta. Obično je asimptomatska, ali je moguća njena torzija, infarkt ili ruptura, kada je neophodna urgentna dijagnostika i splenektomija. Dijagnoza lutajuće slezine ne može se lako prevideti zbog niske učestalosti i nedovoljnog kliničkog iskustva, što višestruko povećava rizik pacijenta od stanja opasnih po život. U radu se prikazuje slučaj lutajuće slezine 11-godišnje devojčice sa akutnim abdominalnim bolom, kod koje je nakon ultrazvučnog pregleda posumnjano na tumor desne nadbubrežne žlezde. Dodatnom dijagnostikom je verifikovana ektopična slezina u desnoj nadbubrežnoj loži, nakon čega je pažljivo razmatrana preporučena preventivna splenopeksija. S obzirom na fiksiranost vitalne slezine u novom položaju, ali i negativan stav roditelja prema hirurškoj intervenciji, izabrano je kliničko praćenje, sa poštedom od intenzivne fizičke aktivnosti koja nosi rizik od traumatizacije slezine. Kako je devojčica tokom skoro 3 godine od dijagnoze dobrog zdravstvenog stanja i bez simptoma, smatramo da je izbor konzervativnog pristupa iako težak, bio ispravan. Nadamo se da će naše iskustvo kao i pozitivni ishod u tretmanu lutajuće slezine kod devojčice doprineti povećanju broja važnih činjenica o ovom retkom stanju.

Ključne reči: *slezina, bolesti slezine, torzija slezine, lutajuća slezina*

sciendo
UDK: 616.411-007.41
Ser J Exp Clin Res 2021; 22 (3): 271-275
DOI: 10.2478/sjecr-2019-0004

Corresponding author:
Slavica Markovic
Pediatric Clinic, Clinical Centre Kragujevac, Kragujevac, Serbia
Department of Pediatrics, Faculty of Medical Sciences, University of Kragujevac
Phone: +38134505170: +381641460444
Fax: +38134370213
E-mail: slavica.markovicr@gmail.com

INTRODUCTION

"Wandering spleen" is a very rare clinical condition characterized by the absence of spleen outside the normal anatomical position in the upper left quadrant of the abdomen (1, 2) and the presence at another place in the abdomen or small pelvis (3, 4). The etiology is multifactorial and potentially very serious, sometimes even life-threatening. (5-7). This condition is extremely rare in children, where, with the developmental disorder, weakness and disturbance of the fixation of spleen supporting ligaments to the front abdominal wall (4, 7, 8), there may be hypoplasia of the anterior abdominal wall muscle with the appearance of dry plums ("belly syndrome") event/congenital hernia of the diaphragm, volvulus of the stomach, an ectopic kidney, obstructive anomalies of the urinary tract and/or retention of the testis (8, 9).

In adults, wandering spleen is in a state where the force of gravity, trauma, enlargement of the spleen in various illnesses, or hormonal changes in pregnancy can cause increased mobility of the spleen (10, 11). Wandering spleen most often appears as asymptomatic or with non-specific gastrointestinal symptoms, dysuria or dysmenorrhea in women (10-12). Sometimes, there are episodes of acute or recurrent abdominal pain with/without melanoma and hematemesis caused by torsion and spontaneous deterioration of ligaments and/or blood vessels of the spleen and other organs (13-15). Symptoms can be alleviated by stretching and occupying the most suitable position in which the ligaments swell and the spleen returns to normal.

After such episodes, fibrosis and abscess of the spleen, as well as hypersplenism, can develop (5-16). In the most severe cases, there is a clinical picture of the acute abdomen condition (2-15) due to arising ischemia, bleeding, necrosis and acute splenomegaly, which can fatally affect patients and requires rapid diagnosis and immediate surgical treatment in the form of splenectomy (17, 18). In the cases of recurrent serious symptomatology, preventive splenopexy is increasingly being proposed, which permanently reduces symptomatology.

CASE REPORT

We present the case of an 11-year-old girl who was diagnosed with a tumor in the right adrenal gland during an abdominal pain episode, but after the diagnosis, the condition of wandering spleen was verified. After a slight improvement and recurrent episodes of abdominal pain, clinical trials were verified at the age of 4: Situs solitus, Displasio v.mitralis cum regurgitatio trivialis, Reflux oesophagitis, urease negative Gastritis antralis. After H2 blocker therapy, a significant reduction in symptoms was experienced, which were repeated at the age of 7. Then, the echosonographic examination of the abdomen was neat, and the introduced therapy with a proton pump blocker continued to reduce symptoms for more than 3 years.

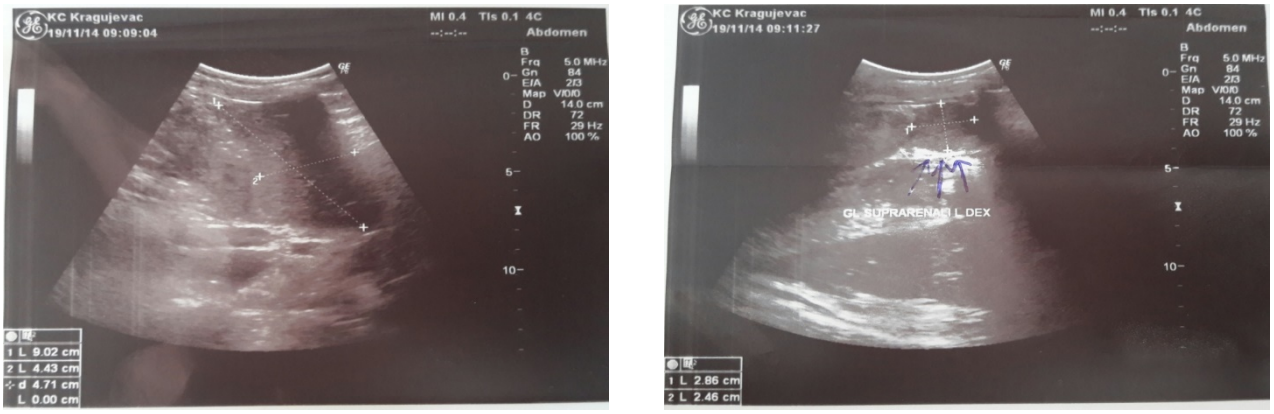
At the age of 11, the girl was hospitalized at the Clinic of Pediatric Surgery, Clinical Centre Kragujevac, for vomiting and severe pain in the right lumbar bed. After the ultrasound examination of the abdomen, a tumor in the right adrenal lodge was suspected. An additional examination at the Pediatric Clinic established that the girl had regular vital functions, growth, development and nutrition: TV + 0.25SD, BMI 16, 43kg/m2 (p50) and initial pubertal signs (B2, PH2). The analysis performed - blood count, biochemical analysis and hormonal status were in reference values.

The ultrasound examination described an elliptical 90x44mm diameter change in the left upper quadrant of the abdomen that could correspond to the tissue of the spleen, left lobe of the liver, and tumor formation in the right adrenal lodge (Figure 1: a, b). In the absence of clinical and biochemical indicators of the right ankle tumor, a contrast-abdominal NMR was performed (Figure 2: a, b) which showed that the left lobe of the liver was present in the left hypochondriac, which did not contain the spleen tissue. As the right retroperitoneal, behind the liver and above the right ankle, two changes of the correct crown shape, diameter 35mm and 33mm, dominantly benign, were seen as an anomalous position of the spleen. A selective spleen scintigraphy (99mTc-denaturated erythrocytes) at a given location showed a spleen of the correct shape that intensely and relatively evenly connected the radionuclide (Figure 3). Thus, the diagnosis of the isolated fixed ectopic spleen of the preserved vitality was established.

After that, the best therapeutic options for the girl were considered - primarily, preventive splenopexy was recommended. Given the occasional symptomatology, the preserved function and the apparently permanently fixed position of the spleen in a new position, as well as the negative attitude of the parents towards a surgical intervention, a more conservative approach was selected, with the restriction of more intense physical activity, which increases the risk of traumatization of the spleen.

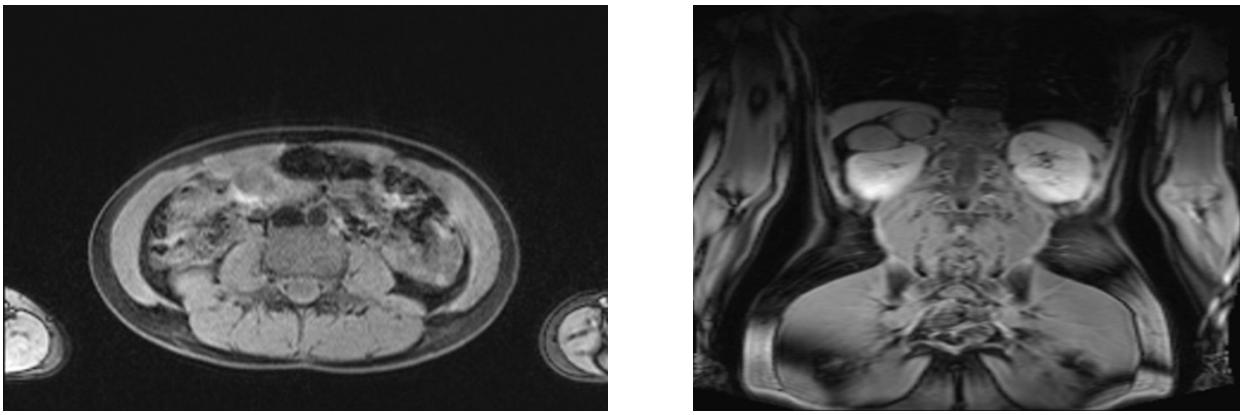
For more than 3 years of monitoring the girl was healthy, without abdominal or hematologic symptomatology.

Figure 1 (a, b): Abdominal ultrasound recordings show that spleen tissue does not clearly differentiate into the left hypochondriac, where normal liver signal is seen (a) while two ovoid formations are visualized in the region of the right adrenal gland (b)



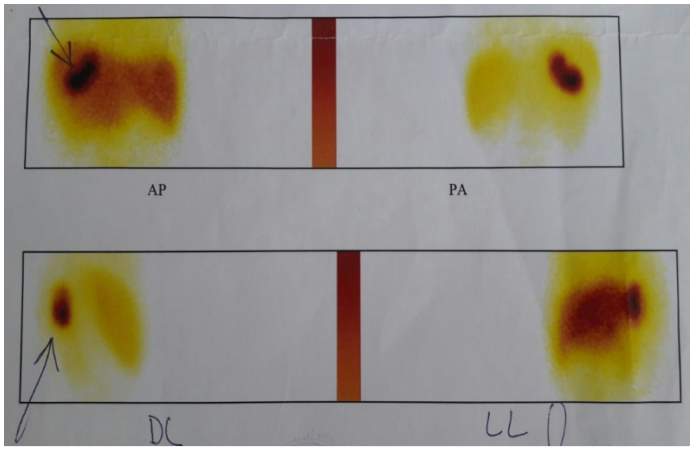
a) b)

Figure 2 (a, b): Transverse and sagittal MR section of the abdomen showing a blank left hypochondriac, partly filled with the left lobe of the liver (a) and retroperitoneal and below the diaphragm, above the upper pole of the right adrenal gland two circular changes diameter 33mm and 35mm, which correspond to ectopic spleen (b)



a) b)

Figure 3. Selective spleen scintigraphy (99mTc-denatured erythrocytes) shows a spleen of regular shape, with intense and relatively evenly bound radionuclide, located in the right hypochondriac, behind the right lobe of the liver and above the right adrenal gland.



DISCUSSION

Wandering spleen in children is a condition that is rarely displayed in the professional literature, (1, 2) where it is most often talked about its congenital origin (4, 13, 20). Given the early onset of symptoms, as is the case in our patient, asymptomatic flow with occasional abdominal symptomatology can be attributed to occasional torsion/detachment of ligaments and/or vascular spleen or spontaneous gastrointestinal obstruction (19, 21, 22). An echosonographic examination revealed the ectopic position of the spleen only after its permanent fixation in the new position (12, 23). Diagnostic procedures have met the criteria for diagnosing an isolated wandering spleen (6, 9), since the situs inversus was excluded in differential diagnosis (5, 9). Analyzing recommendations for the treatment of wandering spleen in children who depend on the severity of symptoms, detailed estimates of its location, size, and functional status (18-20), we did not consider splenectomy as it is recommended in acute cases or in cases of hypersplenism (13-18). Considering the important hematological and immunological functions of the spleen at that age, further treatment after splenectomy must be very careful (4, 6).

Due to the high risk of developing a life-threatening infection with encapsulated strains of bacteria, immunization against these causes (13-15) is mandatory, but also the use of antibiotics at the first signs of infection (4, 17). Leading to a maximally conservative approach, we seriously considered preventive splenopexy (21-23). By this indication, the first classical splenopexy was performed in 1990, and laparoscopic splenopexy in 1998, continues to be technically advanced (21-25). Relying on occasional symptomatology, preserved vitality and apparently permanently fixed new position of the spleen, and looking at the negative attitude of parents towards surgical therapy, we chose a more conservative approach. The fact that the girl has been in good health for almost 3 years after diagnostics, without symptomatology, suggests that our therapeutic choice, although difficult, was correct, so we hope that our experience will contribute to an increase in the number of valid facts about this rare condition.

CONFLICT OF INTERESTS

Not declared.

REFERENCES

1. Magowska A.: Wandering spleen: a medical enigma, its natural history and rationalization. World Journal of Surgery. March 2013,Volume 37, Issue 3, 545–550 Published online 2012 Dec 13. DOI: 10.1007/s00268-012-1880-x , PMCID: 23238797. PMC3566390
2. McHeik JN, Richer JP, Levard G. Torsion of the spleen in children.Arch Pediatr. 2005 Oct;12(10):1496-9. Epub 2005 Aug 15. PMID:16102952 DOI:10.1016/j.arcped.2005.06.021
3. Impellizzeri P[1], Montalto AS, Borruto FA, Antonuccio P, Scalfari G, Arena F, Romeo C. Accessory spleen torsion: rare cause of acute abdomen in children and review of literature. J Pediatr Surg. 2009 Sep;44(9):e15-8. PMID: 19735802 DOI:10.1016/j.jpedsurg.2009.06.029
4. Corcione F, Caiazzo P, Cuccurullo D, Miranda L, Settembre A, Pirozzi F, Bruzzese G. Laparoscopic splenectomy for the treatment of wandering spleen.Surg Endosc. 2004 Mar;18(3):554-556 PMID: 15115016 DOI:10.1007/s00464-003-4254-5
5. Steinberg R, Karmazyn B, Dlugy E, Gelber E, Enrique Freud E, Gadi Horev G, Zer M: Clinical presentation of wandering spleen. Journal of Pediatric Surgery 2002 Oct; 37(10):E30 PMID: 12378476 A DOI:10.1053/jpsu.2002.35443
6. Brown CV, Virgilio GR, Vazquez WD. Wandering spleen and its complications in children: a case series and review of the literature. Journal of Pediatric Surgery November 2003 Volume 38, Issue 11, Pages 1676–1679 PMID:14614725 DOI:10.1016/s0022-3468(03)00582-7
7. Raissaki M, Prassopoulos P, Daskalogiannaki M, Magkanas E, Gourtsoyiannis N. Acute abdomen due to torsion of wandering spleen: CT diagnosis. European Radiology September 1998, Volume 8, Issue 8, pp 1409–1412 PMID: 9853224 DOI: 10.1007/s0033000 50562
8. Di Crosta I, Inserra A, Gil CP, Pisani M, Ponticelli A: Abdominal pain and wandering spleen in young children: the importance of an early diagnosis. Journal of Pediatric Surgery. July 2009 Volume 44, Issue 7, 1446–1449 PMID:19573677 DOI:10.1016/j.jpedsurg.2009.02.062
9. Samarasinghe RN, Protyniak B, Bethel CAI: Wandering spleen and splenic torsion associated with upper respiratory tract infection. Journal of Pediatric Surgery Case Reports Vol 1, Issue 6, 2013, 129–131 DOI:http://dx.doi.org/10.1016/j.epsc.2013.05.006
10. Ben Ely A, Seguier E, Lotan G, Strauss S, Gayer G. Familial wandering spleen: a first instance. Journal of Pediatric Surgery May 2008 Volume 43, Issue 5, Pages e23–e25 PMID:18485931 DOI: 10.1016/j.jpedsurg.2007.12.077
11. G Gayer, R Zissin, S Apter, E Atar, O Portnoy, Y Itzchak "CT findings in congenital anomalies of the spleen" September 2001 British Journal of Radiology Volume

74, Issue 884 2001 767–77274 (884):767-72 PMID 11511 506. DOI: 10.1259/bjr.74.884.740767
12. Wallace S, Herer E, Kiraly J, Valikangas E, Rahmani R.: A wandering spleen: unusual cause of a pelvic mass. Obstetrics & Gynecology. August 2008 112(2):478-480, PMID:18669771 DOI:10.1097/AOG.0b013e3181809671
13. Chen S, Kao Y, Sun H, Lin W: Splenogonadal Fusion. Journal of the Formosan Medical Association (2008). 107 (11):892–895.ISSN 0929-6646. PMID 18971159 DOI:10.1016/S0929-6646(08)60206-5.
14. Hamada T, Isaji S, Mizuno S, Tabata M, Yamagiwa K, Yokoi H, Uemoto S.: Laparoscopic spleen-preserving pancreatic tail resection for an intrapancreatic accessory spleen mimicking a nonfunctioning endocrine tumor: report of a case. Surgery Today. 2004; 34(10):878-881. PMID:15449162 DOI: 10.1007/s0059 5-004-2839-9
15. Tucker ON, Smith J, Fenlon HM, McEntee GP. Recurrent torsion of a wandering spleen. American Journal of Surgery. July 2004 Volume 188, Issue 1, Pages 96–97 PMID:15219495 DOI:10.1016/j.amjsurg. 2003.11.042
16. Singla ShL, Rattan KN, Sharma S, Bansal S Torsion in a paediatric wandering spleen: Case report and review of literature. Journal of Indian Association of Pediatric Surgeons 2007 Volume 12, Issue 1, 30-31 DOI:10.4103/ 0971-9261.31087
17. Misawa T,.Yoshida K,.Shiba H.,.Kobayashi S .Yanaga K . Wandering spleen with chronic torsion. The Ame rican Journal of Surgery April 2008 Volume 195, Issue 4, Pages 504–505 PMID:18070724 DOI: 10.1016/ j.amjsurg.2006.08.083
18. Moran JC[1], Shah U, Singer JA. Spontaneous rupture of a wandering spleen: case report and literature review. Curr Surg 2003;60:310-2. DOI: 10.1016/S0149-7944(02)00737-7 PMID:14972263 DOI: 10.1016/S014 9-7944(02)00737-7
19. Soleimani M, Mehrabi A, Kashfi A, Fonouni H, Büchler MW, Kraus TW: Surgical treatment of patients with wandering spleen: report of six cases with a review of the literature. Surg Today. 2007;37(3):261-9. Epub 2007 Mar 9. PMID:17342372 DOI:10.1007/s00595-006-3389-0
20. Lemke J, Scheele J, Juchems M, Henne-Bruns D, and Brockschmidt C: Laparoscopic splenectomy of a wandering spleen with coincidental enormous splenomegaly GMS Interdiscip Plast Reconstr Surg DGPW. 2012; 1: Doc14. PMID: 26504696 PMCID: PMC4582471 DOI: 10.3205/iprs000014
21. Upadhyaya P, St Peter SD, Holcomb GW 3rd: Laparoscopic splenopexy and cystectomy for an enlarged wandering spleen and splenic cyst .Journal of Pediatric Surgery (2007) 42, E23–E27 PMID: 17502172 DOI: 10.1016/j.jpedsurg.2007.03.001
22. Seashore JH, McIntosh S. Elective splenopexy for wandering spleen. Journal of Pediatric Surgery 1990 Feb;25(2):270-2. DOI: 10.1016/0022-3468(90)90438-f PMID: 2303996
23. K. Schaarschmidt, M. Lempe, A. Kolberg-Schwerdt, F. Schlesinger, I.Hayek U. Jaeschke The technique of laparoscopic retroperitoneal splenopexy for symptomatic wandering spleen in childhood. Journal of Pediatric Surgery March 2005 Volume 40, Issue 3, Pages 575–577. DOI:10.1016/j.jpedsurg.2004.11.020 PMID: 15793739
24. Kleiner, N Newman, Z Cohen: Pediatric wandering spleen successfully treated by laparoscopic splenopexy .Journal of Laparoendoscopic & Advanced Surgical TechniquesVol. 16, No. 3 Pediatric Endosurgery & Innovative Techniques.2006 Jun;16(3):328-30. PMID: 16796453 DOI: 10.1089/lap.2006.16.328
25. M Piccoli, GM De Luca, Pasculli A, Angelini, et all: Laparoscopic Transperitoneal Left Adrenalectomy and Wandering Spleen Risk JSLS. 2014 Jul-Sep; 18(3): e2014.00278. DOI:10.4293/JSLS.2014.00278 PMCID: PMC4154420
26. Martínez-Ferro M, Elmo G, Laje P Laparoscopic pocket splenopexy for wandering spleen: a case report. J Pediatr Surg 2005;40:882- 4 May 2005 Volume 40, Issue 5, Pages 882–884 PMID:15937839 DOI: 10.1016/ j.jpedsurg.2005.02.009
27. Fukuzawa H, Urushihara N, Ogura K, Miyazaki E, Matsuoka T, Fukumoto K, Kimura S, Mitsunaga M, Hasegawa S : Laparoscopic splenopexy for wandering spleen: extraperitoneal pocket splenopexy Pediatr Surg Int (2006) 22: 931.PMID:16944182 DOI:10.1007/ s00383-006-1760-2

sciendo

SPONTANEOUS RESOLUTION OF A RHEGMATOGENOUS RETINAL DETACHMENT

Biljana Vukadinovic-Pajovic[1], Miroslav Stamenkovic[1], Dusan Todorovic[2], Suncica Sreckovic[3] and Vladimir Jakovljevic[4]
[1] *Clinical Center Zvezdara, Clinic of Ophthalmology " PhD Ivan Stankovic", Belgrade, Serbia*
[2] *University of Kragujevac, the Faculty of Medical Sciences, Department of Ophthalmology, Kragujevac, Serbia*
[3] *Clinical Center Kragujevac, Clinic of Ophthalmology, Kragujevac, Serbia*
[4] *University of Kragujevac, the Faculty of Medical Sciences, Department of Physiolology, Kragujevac, Serbia*

SPONTANO NALEGANJE RETINE POSLE REGMATOGENE ABLACIJE RETINE

Biljana Vukadinović-Pajović[1], Miroslav Stamenković[1], Dušan Todorović[2], Sunčica Srećković[3] i Vladimir Jakovljević[4]
[1] *Klinika za očne bolesti "Prof. dr Ivan Stanković", KBC Zvezdara, Beograd, Srbija*
[2] *Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Katedra za oftalmologiju, Kragujevac, Srbija*
[3] *Klinički centar Kragujevac, Klinika za oftalmologiju, Kragujevac, Srbija*
[4] *Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Katedra za fiziologiju, Kragujevac, Srbija*

Received/Primljen: 21.01.2019. Accepted/Prihvaćen: 08.03.2019.

ABSTRACT

A retinal detachment is the term used to describe detachment of the neurosensory retina from the underlying membrane, the retinal pigment epithelium (RPE). Rhegmatogenous detachments are caused by a break in the retina through which fluid passes from the vitreous cavity into the subretinal space. The incidence of rhegmatogenous retinal detachment in the general population in Europe is 1 in 10 000 persons per year. Danger is the greatest in the age range from 55 to 70 years. Without treatment, blindness in the affected eye may occur. Individual risks depend on the presence or absence of specific factors including myopia, positive family anamnesis, retina rupture, trauma, ablation in the other eye, ablation in a vitreous body, retina high-risk peripheral degenerations and vitreoretinal degenerations. Majority of the untreated rhegmatogenous retina ablations progress to the subtotal or total retinal detachment and blindness. This paper describes a very rare case of the spontaneous complete reattachment of the sensory retina to the retinal pigment epithelium in a patient with the total rhegmatogenous retinal ablation in the right eye. The female patient, who was 52 years old, was examined by an Ophthalmologist after she had experienced a sudden loss of vision, 2 months before appointment. After a detailed ophthalmological examination, a total rhegmatogenous retinal ablation of the right eye was diagnosed. The best corrected visual acuity, evaluated on a Snellen chart, was 2/60. The patient was referred to a tertiary-level Institution since a surgical intervention of the ablation was needed. Due to technical inabilities in the above-mentioned Institution, the operation was not performed, and despite the recommendation to perform the intervention in another tertiary level Institution, the patient did not have ophthalmological examinations during the following three months. During the next visit, the Ophthalmologist determined that there was a spontaneous retinal fixation on the retinal pigment epithelium and a partial restoration of the visual function of the affected eye which was evaluated at 0.5.

Keywords: *retinal detachment, retinal breaks, spontaneous resolution of retinal detachment*

SAŽETAK

Ablacija retine je termin koji se koristi za opisivanje razdvajanja neurosenzorne retine od retinalnog pigmentnog epitela, sloja koji se nalazi ispod nje. Regmatogene ablacije retine uzrokovane su prolaskom tečnosti iz vitrealne šupljine kroz rupturu na retini u potencijalni subretinalni prostor između senzorne retine i retinalnog pigmentnog epitela. Učestalost regmatogenih ablacija retine u opštoj populaciji u Evropi iznosi 1 na 10000 stanovnika godišnje. Rizik je najveći u uzrastu od 55 do 70 godina. Bez lečenja može da dovede do slepila na zahvaćenom oku. Individualni rizik zavisi od prisustva ili odsustva faktora kao sto su kratkovidost, pozitivna porodična anamneza, ruptura retine ili ablacija na drugom oku, ablacija staklastog tela, trauma, periferne degeneracije retine visokog rizika i vitreoretinalna degeneracija. Većina nelečenih regmatogenih ablacija retine napreduje do subtotalnog ili totalnog odlubljenja retine i slepila. Prezentujemo veoma redak slučaj potpunog spontanog naleganje senzorne retine na retinalni pigmentni epitel kod pacijentkinje sa totalnom regmatogenom ablacijom retine na desnom oku. Pacijentkinja starosti 52 godine, 2 meseca nakon naglo nastalog gubitka vida pregledana je od strane oftalmologa. Prilikom detaljnog oftalmološkog pregleda dijagnostikovana je totalna regmatogena ablacija retine na desnom oku. Najbolje korigovana vidna oštrina na zavnaćenom oku iznosila je 2/60 po Snelenovim tablicama. Upućena je u stanovu tercijarnog nivoa zbog hirurškog lečenja ablacije. Zbog tehničkih nemogućnosti u datoj ustanovi operacija nije obavljena a uprkos preporuci da se tretman obavi u drugoj ustanovi tercijarnog tipa, pacijentikinja naredna 3 meseca nije odlazila na oftalmološke preglede. Pri ponovnom pregledu oftalmologa utvrđeno je spontano naleganje retine na retinalni pigmentni epitel i delimična restitucija vidne funkcije na zahvaćenom desnom oku koja je iznosila 0.5.

Ključne reči: *ablacija retine, ruptura retine, spontana restitucija ablacije retine*

sciendo
UDK: 617.735-007.281
Ser J Exp Clin Res 2021; 22 (3): 277-280
DOI: 10.2478/sjecr-2019-0017

Corresponding author:
Biljana Vukadinović-Pajović
Clinic of Ophthalmology "PhD Ivan Stankovic"
Clinical Center Zvezdara, Belgrade, Serbia
E-mail:biljka_vuka@yahoo.co.uk

INTRODUCTION

Retinal detachment is separation of the neurosensory retina from retinal pigment epithelium by subretinal fluid. Retinal detachments are classified as: rhegmatogenous, tractional and exudative. The most common are rhegmatogenous retinal detachments (RRDs). They are caused by fluid passing from the vitreous cavity through a retinal break into the potential epitelioretinal interspace between the sensory retina and the retinal pigment epithelium (RPE). The incidence of rhegmatogenous retinal detachment in the general population in Europe is 1 in 10 000 persons per year. Danger is the greatest within the age range 55-70. Without treatment, it may result in the blindness of the affected eye (1). A retinal break is full-thickness defect in the neurosensory retina. Surgical treatment of retinal detachments includes 3 approaches: 1) scleral buckling, 2) vitrectomy and 3) pneumatic retinopexy.

A limited retinal detachment left untreated may follow one of four potential outcomes:

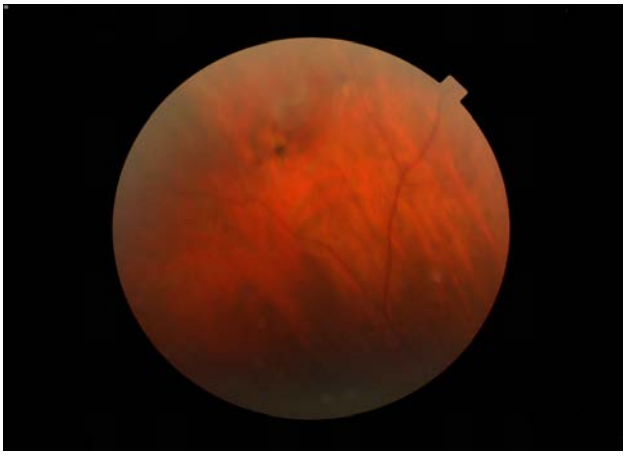
1. Usually, most untreated clinical rhegmatogenous detachments progress to near total or total detachment and blindness.
2. Occasionally, the detachment indefinitely remains a subtotal detachment with stable borders and the creation of demarcation lines. This most commonly occurs with detachments caused by inferior breaks, particularly small breaks or dialyses.
3. Rarely, subretinal fluid settles inferiorly away from the break due to a superior retinal break and the site of the original break flattens.
4. Very rarely, spontaneous reattachment occurs and it is usually associated with a very small break and excellent presumed "pumping" of the retinal pigment epithelium or closure of the break by the scar tissue (2).

CASE PRESENTATION

This paper presents the case of a female patient aged 52 who was admitted due to a sudden decay of vision which had occurred two months earlier.

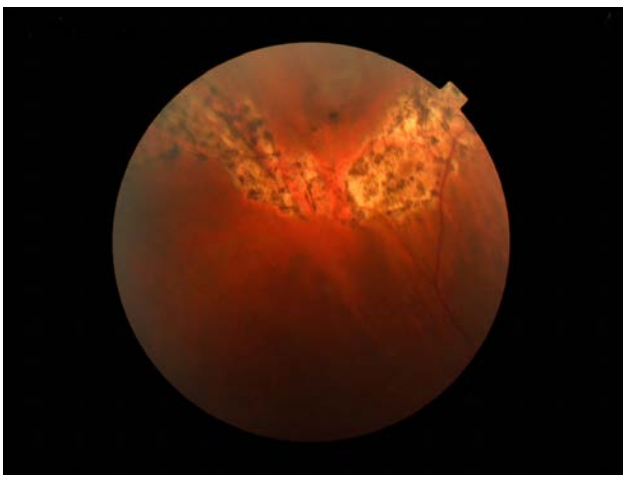
The patient had been treated for depression and hypothyroidism and was using the following therapy: *Elorica* ,*Risperidone* and *Letrox* tablets. The best corrected vision acuity, evaluated on a Snellen chart, was 2/60 for the right eye an 1.0 for the left eye. The intraoclular pressure was 14 mmHg in both eyes. The slit-lamp examination revealed the presence of blurred type of tobacco dust in corpus vitreum. Examination of the fundus confirmed the complete retinal detachment with a huge retinal break in the upper temporal quadrant. The examination of the left-eye fundus did not reveal any significant pathological changes. The patient was emergently referred to a tertiary-level Institution for the surgical treatment of the retinal detachment but she was not admitted due to technical inabilities of the Institution to perform the surgical intervention needed to treat the ablation. The next visit to the competent Ophthalmologist took place after 3 months. On this occasion, the examination of the fundus revealed that there was a total reattachment of the previously detached retina to pigment epithelia with a huge U-shaped rupture present in the upper temporal quadrant. In the lower half of the retina, there was a diffuse retinal pigment alternation inside the sharply limited convex edge. The best corrected visual acuity, evaluated on a Snellen chart, was 0.5 for the right eye. The fundus photograph of the affected eye is presented in the Figure 1.

Figure 1. Fundus photography. U-shaped rupture in the upper temporal quadrant of the right eye



The Laser Photocoagulation (LCP) was conducted for the rupture barrage and the entire peripheral retina circumference. The following parameters were set: LCP spot diameter at 200 μm, power at 280-300 mV, exposition time at 0.2 seconds. Seven hundred spots were placed. Regular check-ups were scheduled once a month. Fundus photography of both eyes was conducted. It detected pigmented LPC spots, through the entire circumference of the peripheral retina and a large U-shaped rupture in the upper temporal quadrant of the right eye (Figure 2).

Figure 2. Fundus photography. LPC spots, through the entire circumference of the peripheral retina and a large U-shaped rupture in the upper temporal quadrant of the right eye



On a control check after 2 months, there was a decline in the best corrected visual acuity which was 0.3 at this point. The eye fundus examination revealed the Epiretinal Membrane (ERM) in the macula area, whose presence was confirmed with the Optical Coherence Tomography (OCT) (Figure 3). The OCT findings for the left eye showed the regular morphology of the macula. Computerized visual field was performed for both eyes. The following values were determined: MD -5.77 dB, PSD 4.43 dB for the right eye and MD -2.38dB, PSD 3.89 dB for the left eye (Figure 4). After the treatment and examination, the patient was referred to a tertiary Institution where she was examined by a Vitreoretinal Surgeon and continued her regular check-ups there.

Figure 3. OCT right eye. ERM

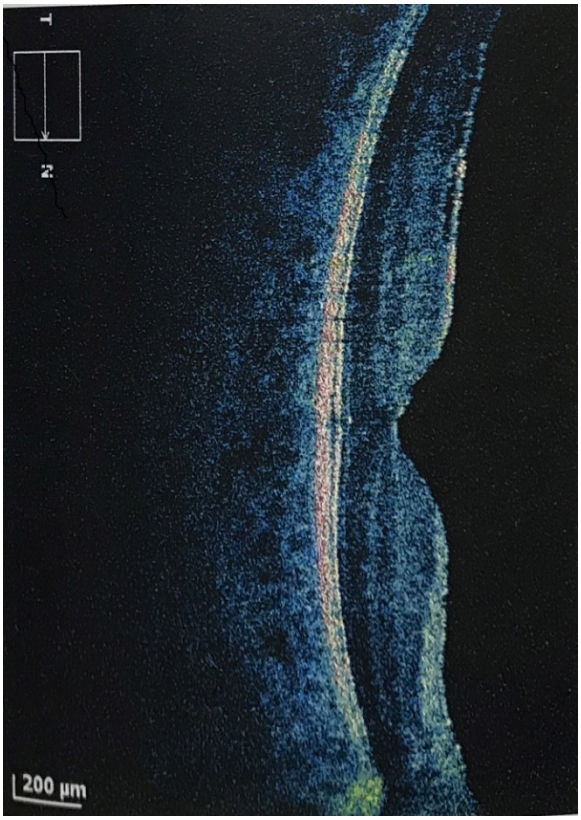
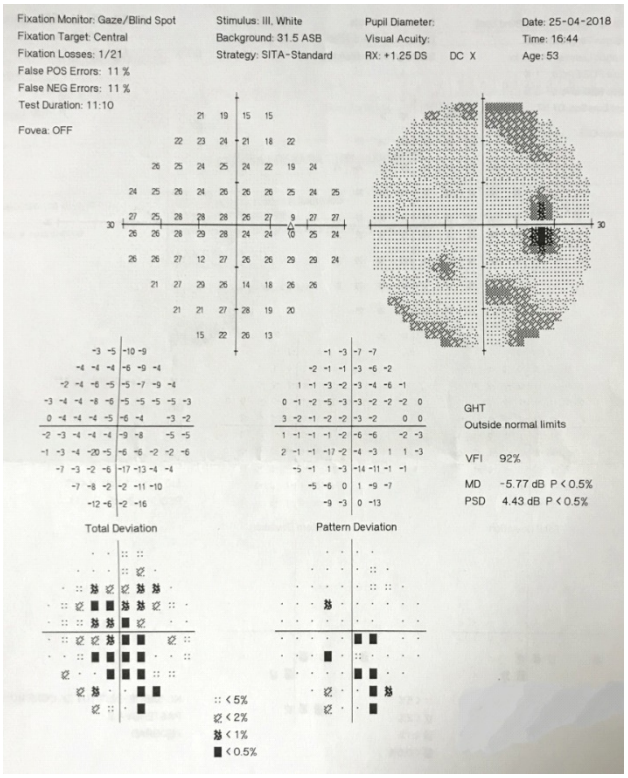


Figure 4. Computer visual field right eye



DISCUSSION

Spontaneous reattachment of retina after the total retina ablation is a rare phenomenon. Only a few isolated examples have been detected in the relevant references. Ryosuke Ochi et al. described a case of spontaneous resolution of retina ablation in 4-year-old boy with Coats disease four months after the boy had been diagnosed with total retina ablation. The authors suggested that the retina reattachment resulted from a decline in the retina abnormal blood vessels permeability and the good functional ability of the retinal pigmented epithelium (3). The Retinal Pigment Epithelium (RPE) consist of a single line of mononuclear hexagonal cells.

Cells are interconnected with occludent bonds that prevent the passage of water and ions. They form an external hemato-ocular barrier. Roles of the RPE can be summarized as follows: (1) the RPE cells are rich in mitochondria and they actively participate in the oxidative metabolism because they contain antioxidant enzymes, and thus reduce the formation of free radicals that can damage lipid membranes, (2) they form and maintain a photoreceptive matrix which is important for the retinal adhesion, (3) they participate in the production of growth factors through which the RPE controls the vascular endothelium, its permeability, recovery and proliferation (reparative processes). The RPE also plays an important role in the transport of water and electrolytes since it pumps the fluid from a retina to choruses against the strong hydrostatic or osmotic pressure. RPE membranes contain selective ionic channels and transfer systems for the transmission of ions, metabolites, glucose and amino acids. The sodium-potassium pump is active on the apical part of RPE cells while the chlorine-bicarbonate exchange takes place at the basal membrane of pigment cells. Thanks to these pumps, water and ions are moving transcellularly. A good functional ability of RPE results in maintaining the dryness of a subretinal space (4). In 2012, an isolated case of a spontaneous reattachment of ablated retina caused by a rupture was reported. It had been diagnosed during the pregnancy and the reattachment occurred after the delivery. In this particular case, physiological changes induced during the delivery are suspected to be a mechanism of the resolution of total retina ablation which had occurred during the pregnancy (5). Diffuse retinal pigment alterations inside the sharply limited convex edge are the most common finding after the

reattachment of an ablated retina in all cases described in the current references. In 2015, a case of a 60-year-old man was reported where the patient had a spontaneous reattachment of retina, after rhegmatogenous ablation, with gradual correction of visual function and a fully restored retina (6). Song Ee Chung et al. tried to explain mechanism of the Spontaneous Reattachment of Rhegmatogenous Retinal Detachment (SRRRD). Initially, both focal vitreoretinal adhesion and vitreoretinal traction induce a retinal break in the peripheral retina in an eye without a complete PVD. This is followed by an influx of liquefied vitreous into the retinal break, constituting the development of retinal detachment. However, the direction of vitreoretinal traction changes to parallel the elevated retinal surface. Eventually, vitreoretinal traction is relieved and the retinal break is closed by vitreous fibers running parallel to the retinal plane. As with the interruption of fluid currents through the subretinal space, the SRRRD develops, and the thin membrane proliferates over the retinal break. They suspect that the proliferative membrane is a result from the fibroglial and retinal pigment epithelial hyperplasia (7). In 2007, Cho Hee Yoon et al. published an overview of fifteen suspected cases of spontaneous retina reattachments after rhegmatogenous ablations which is a real rarity in the current references. Examinations of these patients had confirmed the presence of diffuse alternations in retinal pigment inside the sharply limited convex edge. Lesions were placed in the lower retina in ten out of fifteen patients, limited to six or less hours. Changes on retina, associated with rhegmatogenous ablation, were present on the other eye in seven patients (8).

CONCLUSION

Spontaneous retina reattachment after a rhegmatogenous ablation (SRRRD) is a rare event that involves the relief of vitreoretinal traction, closure of retinal breaks, and reabsorption of subretinal fluid. Spontaneous retina reattachment after a total rhegmatogenous ablation is a rare phenomenon which must be taken into consideration in different diagnoses of the patients diagnosed with the diffuse alternation of retinal pigment inside the sharply limited convex edge in the fundus. In addition, the findings of small retina ruptures in non-vitrectomized eye can be associated to the spontaneous retina resolution after rhegmatogenous retina ablation.

REFERENCES

1. Nicolas, F., Peter W. Rhegmatogenous Retinal Detachment-an Ophthalmologic Emergency. Dtsch Arztebl Int. 2014; 111(1-2): 12-22.
2. Brinton, D. A. , Hilton, G. F.,Wilkinson, C. P. (2009). *Retinal Detachment: Principles and Practice (3rd ed.).* Oxford : Oxford University Press.
3. Ochi, R. , Sato, B., Mimura M., Morishita, S., Fukumoto, M., Kida, T., Sugasawa, J., Ikeda, T. A Case of Coats' Disease with Spontaneous Retinal Reattachment after Total Detachment. Case Reports in Ophthalmology. 2015; 6(2): 200-203.
4. Paovic Stanojevic, A., M D., Milenkovic, S., Kontic, Đ., Cvetkovic, D., Hentova Sencanic P., Paovic, J. (2008). Eye Physiology. Beograd: Medicinski fakultet Univerziteta u Beogradu.
5. Schmoll, C., Hegde, V., Bennett, H., Singh, J. Spontaneous resolution of a rhegmatogenous retinal detachment after normal labor and childbirth. Retinal Cases & Brief Reports. 2012; 6(1): 1-3.
6. Mercanti, A., Renna, A., Prosperi, R., Lanzetta, P. An unusual and spontaneous resolution of a total rhegmatogenous retinal detachment. Ophthalmic Surg Lasers Imaging Retina. 2015; 46(4): 489-92.
7. Chung, S., Kang, W., Chan-Hui Y. A Developmental Mechanism of Spontaneous Reattachment in Rhegmatogenous Retinal Detachment. Korean J Ophthalmo*l.* 2012; 26(2): 135-138.
8. Cho, H., Chung, S., Kim, J., Park, K., Kim, S., Kang, S. Spontaneous reattachment of rhegmatogenous retinal detachment. Ophthalmology. 2007; 114(3): 581-6.

INSTRUCTION TO AUTHORS

Serbian Journal of Experimental and Clinical Research is categorized as M51 on the list of categorized national scientific journals of the Ministry of Education, Science and Technological Development of the Republic of Serbia.

Serbian Journal of Experimental and Clinical Research only publishes papers that have not been previously published. Any attempt of plagiarism or self-plagiarism shall be penalized (publication of papers is banned to all authors for a certain period of time depending on the degree of plagiarism and the management of the institutions in which the authors work are informed about this, as well as their professional associations).

Only papers written in English are accepted, with the title, affiliations, abstracts and keywords both in Serbian and English.

Since the Journal has started with electronic editing and publication of papers sent to the address:
https://www.editorialmanager.com/sjecr/default.aspx,
all papers are submitted to the Editorial Board in this way EXCLUSIVELY.

All authors, reviewers and editors must be registered system users with a unique e-mail address. Authors can register via the link:
https://www.editorialmanager.com/sjecr/default.aspx.

Technical instruction to use the e-UR system: electronic editing of papers can also be accessed at:
http://www.editorialmanager.com/sjecr/.

When submitting the paper to the electronic editing system *SerJExpClinRes*, it is necessary to enclose a statement that all technical requirements have been met, including a statement signed by all authors and co-authors that the paper has not been published, in whole or in part, or accepted for publishing in another journal. The statement on the individual contribution of the author has to be signed by each author of the paper, scanned and sent as a supplementary file (requested in the system as Cover Letter). Also, the authors are obliged to submit a signed statement on non-existence of conflict of interest. By this procedure, all authors become responsible for meeting all set requirements, followed by the decision on acceptance for further editorial procedure. The system of journal electronic editing *Editorial Management* includes the use of the CrossCheck service, so all the papers are automatically checked to plagiarism or self-plagiarism, prior to the first step of the editorial process.

Accepted papers are published in the order determined by the Editorial Board on the suggestion of Editor-in-Chief. SerjexpClin publishes exclusively: original articles, review papers and case reports.

Each original scientific paper and case report has to contain the following parts: ABSTRACT, INTRODUCTION, THE AIM OF THE PAPER, PATIENTS AND METHODS, RESULTS, DISCUSSION, CONCLUSION and REFERENCES. Review paper does not necessarily have to contain all stated segments; it can have an independent structure.

Times New Roman font 10pt is used for manuscript writing, and a new paragraph is indented for better visibility.

Submitted papers are first forwarded to the editor, and then to, at least, two reviewers. Comments and suggestions of the editor and reviewers (without the names of the reviewers) are delivered to the author for final modification of the paper.

After professional and editorial processing and before publishing, the accepted paper is referred to the corresponding author for authorial reading. At this stage, it is not possible to make major changes, but only to correct letters and other minor mistakes. If the corrected text is not returned within seven days, it will be considered that the author has no objections.

Upon editor's approval, after received positive paper reviews, the paper is accepted in the system, and the corresponding author receives information about the paper accepted for publication to the email address.

DOI number is assigned to the paper and, after proofreading and text break according to the Journal instructions, the paper is published as Ahead of Print first on the Journal page at Sciendo platform:
https://content.sciendo.com/view/journals/sjecr/ahead-of-print/issue.xml and then in one of the next issues of the Journal.

All papers, regardless of the source language, are cited in English, and the source language is stated in brackets, after the title. We do not accept citation of abstracts, secondary publications, oral presentations, unpublished papers, official and confidential documents. Citation of papers accepted for publication, in the procedure of preparation for printing, can be accepted by stating the title and putting *in press* in brackets after the name of the journal.

The examples of correct referencing:

For journal papers:

e. g. Shoji F, Haro A, Yoshida T, Ito K, Morodomi Y, Yano T, et al. Prognostic significance of intratumoral blood vessel invasion in pathologic stage IA non-small cell lung cancer. Ann Thorac Surg 2010; 89(3): 864–9.

For books:

e. g. Kleiner, F.S., Mamiya C.J. & Tansey R.G. (2001). Gardner's art through the ages (11th ed.). Fort Worth, USA: Harcourt College Publishers.

For conference papers:

e. g. Field, G. (2001). Rethinking reference rethought. In Revelling in Reference: Reference and Information Services Section Symposium, 12-14 October 2001 (pp. 59-64). Melbourne, Victoria, Australia: Australian Library and Information Association.

GUIDE TO PREPARING FIGURES

Figure and legend must fit within this box

6.89 inches (17,5 cm.)

or **or**

COLUMN 1 **COLUMN 2**

3.36 inches (8,54 cm.) **3.36 inches (8,54 cm.)**

FILE FORMATS

We prefer ai, eps, pdf, svg, layered psd, tif and jpg files. Please submit each figure as an individual file separate from the manuscript text.

FIGURE LAYOUT AND SCALING

We will use your suggested layout as a guide, but it may be necessary to rearrange or change the size of your figures because of production constraints.

When laying out your figure:

- Avoid wide variation in type size within a single figure.
- Maximize the space given to the presentation of the data.
- Avoid wasted white space.

LABELS

All text should be in a typeface Times New Roman.

- Panel parts are 10 point Bold **A B C D**
- Axis labels are 6 to 9 points six, seven, eight, nine
- Minimum font size is 6 points Minimum 6 points

IMAGE TYPES

When possible, supply vector-based files such as those produced by CorelDRAW, Adobe Illustrator or similar software.

Vector files give us maximum flexibility for sizing your figures properly.

They maintain high print-quality resolution at any size. Do not rasterize line art or text.

Vector or line art: eps, ai, pdf, svg

Raster (bitmap)

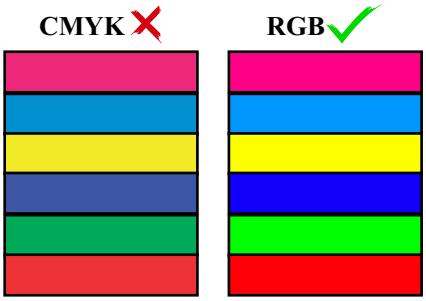
RESOLUTION

Photographic images should have a minimum resolution of 300 dots per inch (dpi) at final print size (see column widths above). Embedded images within a vector file should also have a minimum resolution of 300 dpi. Up sampling artwork (artificially increasing file size or resolution) will not improve quality and causes production problems.

300 dpi 72 dpi

COLOR CONVERSION

Full color artwork should be provided in RGB format (not CMYK) as your paper will be published online only.



LINE WEIGHTS

At final print size, line weights can be no thinner than .28 pt.

.28 pt

CLEAN SOURCE FILES

Please delete unwanted data from files. Do not hide unwanted data in masks or layers. Hidden images or data can show up in the production process. Crop out extraneous elements that are outside the image area.

sciendo

Serbian Journal of Experimental and Clinical Research

2000

FACULTY OF MEDICAL SCIENCES
Svetozara Markovica 69, 34000 Kragujevac, SERBIA
P.O. Box 124
Tel. +381 (0)34 30 68 00 • Tfx. +381 (0)34 30 68 00 ext. 112
e-mail: sjecr@medf.kg.ac.rs

https://medf.kg.ac.rs/sjecr