The incidence of nosocomial infections in patients with isolated severe traumatic brain injury

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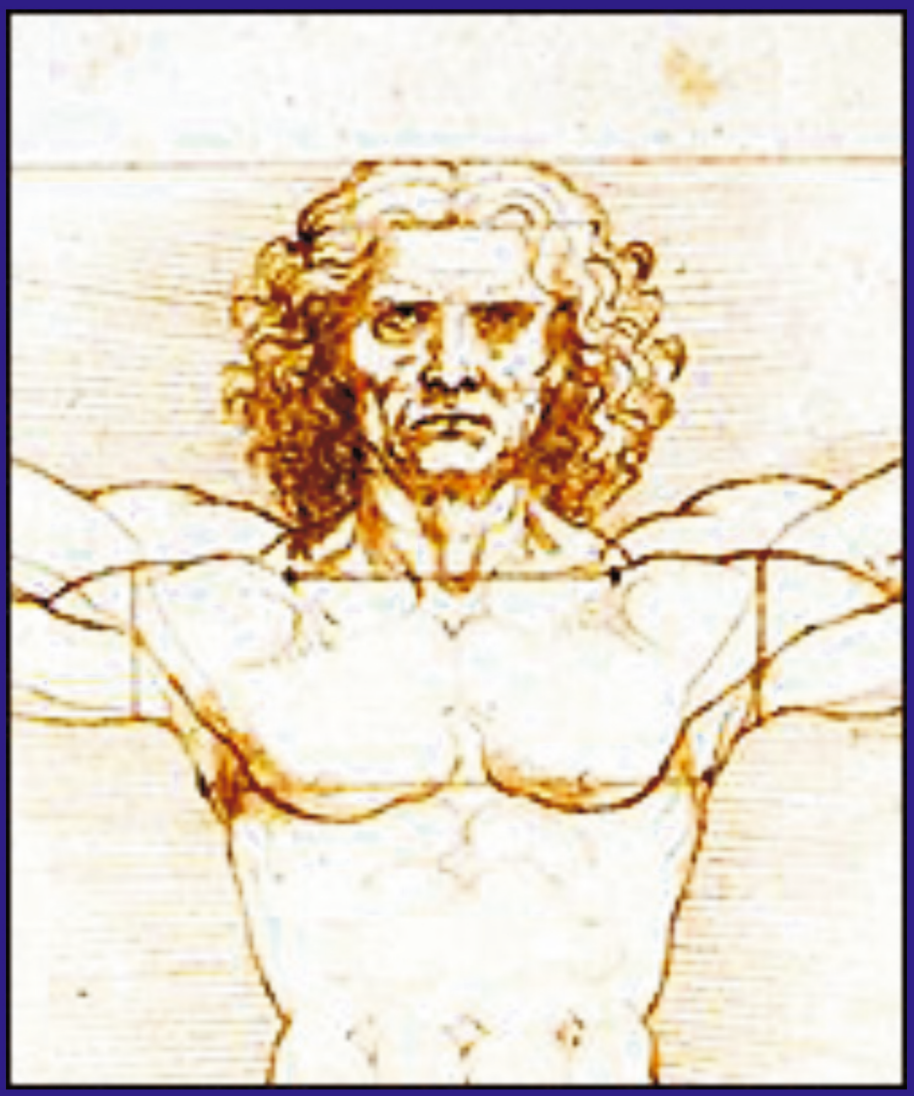

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SADRŽAJ

- **REVIJALNI RAD**

A word from the guest editor / Reč gostujućeg urednika

Poštovani čitaoci,

Izuzetna mi je čast i zadovoljstvo biti jedan od gostujućih urednika decembarskog broja časopisa Sanamed koji je pred Vama.

U ovom broju donosimo nekoliko naučnih i stručnih radova doktora medicine i doktora stomatologije iz Hrvatske sa željom da predstavimo naš rad. Posebna mi je želja bila predstaviti stomatologiju kao struku koja se ne bavi samo zubima, već kao struku koja leči i rehabilituje sve strukture u usnoj šupljini (zube, parodont, vilične kosti, temporomandibularne zglobove, sluznice i pljuvačne žlezde), orofacijalni bol i oralne manifestacije sistemskih bolesti.Oduvek je poznat izraz „Usta su ogledalo zdravlja". Da bi uspešno lečili pacijenta doktori stomatologije moraju imati puno medicinskog znanja, no i doktori medicine trebaju biti upoznati s komplikacijama sistemskih bolesti u usnoj šupljini kao i uticajem oralnih bolesti na opšte zdravlje. Odatle proizilazi još jedan slogan „Nema opšteg zdravlja bez oralnog zdravlja".

Sanamed je časopis, koji objavljuje radove iz područja medicine, stomatologije i farmacije, u kojem će zanimljive i poučne članke naći stručnjaci iz različitih područja. Prednost ovakvih časopisa je što čitatelji imaju dostupne radove iz različitih specijalnosti čime proširuju svoja znanja. Nadam se da ćete i u ovom broju naći zanimljive tekstove.

Zahvaljujem svim autorima i recenzentima na uloženom trudu i vremenu. I na kraju velika zahvalnost uredničkom timu na pozivu da sudelujem u realizaciji ovog broja časopisa što je proteklo u prijateljskoj, saradničkoj i pozitivnoj atmosferi.

Uz želju za još puno uspešnih brojeva koji će naći brojne čitatelje i podstaći ih da i sami napišu članak za Sanamed te

lep pozdrav,

Vanr. prof. Miranda Muhvić Urek, dr. med. dent.
Specijalista oralne patologije
Stomatološki fakultet Univerziteta u Rijeci,
Rijeka, Hrvatska

* * *

Dear Readers,

It is my great honor and pleasure to be one of the guest editors of the Sanamed Journal December Issue that you have in front of you.

In this issue we bring you the scientific and professional articles of medical doctors and dentists from Croatia with the wish to present our work. It is my special wish to present Dentistry as a profession that is not working only on the field of teeth, but also profession that cures and rehabilitates all the structures

in the oral cavity (teeth, periodontal tissues, temporomandibular joints, bone of the jaws, oral mucosa and salivary glands), manages orofacial pain and oral manifestations of the systemic diseases. "Mouth is the mirror of the health" is a well known proverb.

In order to successfully treat patients, dentists have to use their medical training. Also, doctors have to be acquainted with the complications of systemic diseases and their oral manifestations as well as the influence of oral diseases on the general health. From this emerges another proverb: "There is no general health without oral health".

Sanamed is a Journal that publishes articles in the field of Medicine, Dentistry and Pharmacology that can be of interest for experts of various fields. The advantage of this type of Journals is that readers have the access to articles of various expert fields that open their views and knowledge. I hope that you will find in this issue interesting articles.

I thank the all authors and reviewers on the invested effort and time. At the and I want to thank the Editorial Team on the call to participate in the production of this Journal Issue, that we passed in the friendly, cooperative and positive environment.

It is my sincere wish to have a lot of successful issues that will find its way to the readers and encourage them to write their own article for the Sanamed Journal.

Sincerely yours,

Assoc. Prof. Miranda Muhvić Urek, DMD, PhD
Specialist of Oral Pathology
School of Dental Medicine,
University of Rijeka
Rijeka, Croatia

A word from the guest editor / Reč gostujućeg urednika

Kada sam od strane uredništva zamoljen da budem Gost urednik ovogodišnjeg decembarskog broja časopisa Sanamed osetio sam radost i poverenje. Taj predlog sam shvatio kao uvažavanje kao člana naučnog saveta časopisa, kao recenzenta i uvažavanje mojih stručnih i naučnih radova koji su do sada objavljeni u ovom časopisu.

Bez mnogo razmišljanja i sa posebnim zadovoljstvom poziv sam prihvatio. Poziv sam prihvatio jer smatram da je časopis Sanemed za kratko vreme stasao u jedan ugledan medicinski časopis o kome se zna i o kome se priča. To je medicinski naučni časopis osnovan 2006. godine. Po ugledu na monogo starije medicinske časopise u „Sanamedu" se objavljuju originalni naučni i stručni radovi, prikazi bolesnika, pregledi literature, članci iz istorije medicine, prikazi objavljenih knjiga, pisma uredništvu, kao i druge medicinske informacije. Radovi pristigli na adresu časopisa podležu anonimnoj recenziji, a časopis izlazi tri puta godišnje. Novi brojevi časopisa Sanamed dostupni su i u elektronskom obliku, na sajtu časopisa. Časopis je indeksiran u velikom broju citatnih baza i ima kategorizaciju MK52 sa tendencijom daljeg napredovanja.

Ono što želim posebno istaći to je moje divljenje Uredništvu, a posebno glavnom uredniku časopisa i onom manjem broju ljudi oko njega koji su svojim entuzijazmom i svojim samopregornim radom uspeli da ovaj časopis dovedu do onog nivoa koji on ima danas. Naime, sasvim je drugačije, slobodno mogu reći mnogo je lakše, izdavati jedan stručni časopis u velikom gradu u nekom univerzitetskom centru, nego što je to u ovom slučaju. Međutim, ovde se pokazuje da volja za radom i pamet uvek pobeđuju. Zato sam siguran da će Izdavač časopisa Udruženje lekara Sanamed, Novi Pazar, istrajati u svom naporu i da će ovaj časopis tek pokazati svoje vrednosti i zauzeti još više mesto među medicinskim naučnim časopisima.

Na kraju zahvaljujem se uredništvu što mi je ukazalo ćast da budem gost urednik ovog broja časopisa i iskreno Vam želim dalji uspešan rad u prezentaciji stručne i naučne medicinske misli.

Prof. dr Miloš Jovanović,
Klinika za očne bolesti, KCS Beograd
Medicinski fakultet Beograd, Srbija

* * *

When the Editors invited me to be responsible for December 2015 issue of Sanamed Journal as a Guest Editor, I felt joy and trust. I took that proposal as sincere appreciation for the effort I have made as a member of the Journal's Scientific Council, as a reviewer and as author by publishing scientific papers in this journal.

Without hesitation and with great pleasure I have accepted the invitation, especially because I believe that the Sanemed Journal has grown into respected, well known medical journal. SANAMED is a Peer-Reviewed medical journal founded in 2006. The journal publishes: original articles, case reports, literature reviews, articles on history of medicine, articles for practitioners, book reviews, letters to the editor, and other medical information. Papers, received to the address of the Journal, are liable to anonymous reviews. The journal is published both in Electronic and Print format, three times a year. The journal is indexed in many citation bases and is categorized as MK52, with the tendency of further progress.

I would like to particularly emphasize my admiration for the Editorial Board, especially for the Chief Editor and his associates, small number of people, who have managed to bring this Journal to the level he has today with their enthusiasm and their self-sacrificing work . It is quite different, in fact I can freely say it is much easier to publish a journal in a large city, in a university center. However, it is clear that the will to work out and intelligence always win.

I'm quite shure that the Journal publisher, Association of medical doctors "Sanamed" Novi Pazar, will persist in their efforts and that this Journal will yet demonstrate its value and take even higher place among medical journals.

Prof dr Miloš Jovanović
Eye Clinic, Clinical Center of Serbia, Belgrade, Serbia
Faculty of Medicine, University of Belgrade, Serbia

A word from the editor

Respected,

a word from the editor is not a pure formality to fulfill this page. For me, it is an obligation to address, primarily the reader, and then the authors who participate actively in the development of the Sanamed Journal.

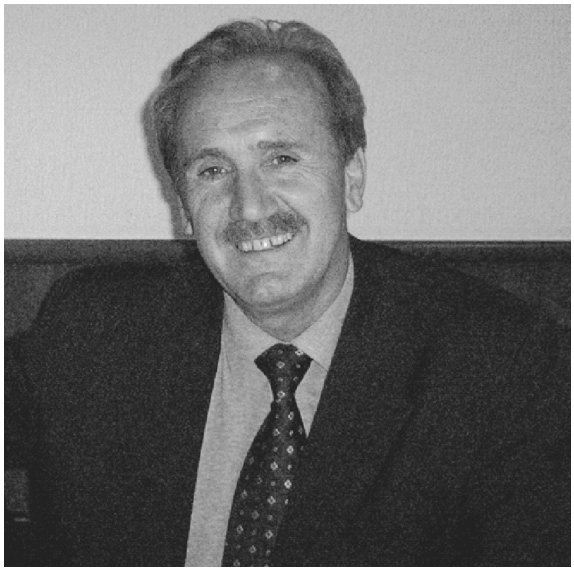
The Journal itself is a treasury of news from various fields of medicine that our authors write, and it all goes through a double blind review, and only some of papers get the green light to be published.

The closest team of people, members of Sanamed Editorial Team, are always active and never are satisfied by the previous issue. That's why we have continuous quality improvement. Our first, and I think the second issue(year 2006 and 2007) were consisted of thematic papers, but it was a problem to collect enough papers that fit into the propositions of the Journal. So, we have changed the policy and gave freedom to all interested authors to write about everything that plain as individuals believe is the important novelty in medicine. That is why our Journal has became a free expression of medical word.

As an editor, I try not to be a critic. But sometimes I cannot avoid it, at least not to express criticism through my dissatisfaction in the part that refers to the desire to see more people who are unique active participants in medical activity.

People just do not like to be criticized for passivity. Medicine is the science that does not allow to stagnate. Medicine requires work that explores unknown, exclude what is unconfirmed, and as someone said, a healthy don't need a little bit of medicine to maintain "a healthy mind in a healthy body".

Today, this idea lost its luster, because in every place you can be threatened by various cosmic radiation, various harmful effects of the products of the



human mind and disorder. The man is placed, without his will, in the role of guinea pig, not knowing that the executor eventually becomes the same.

The Medicine still has great challenges. Excluding the known dangerous diseases which the Medicine has won, an epidemic of malignant diseases is on the scene. Unfortunately, as the elite, we are not active enough in emphasizing the importance of the struggle, with medically proven reasons, against those who produce all these destructive factors which, when exposed to, are leading to a growing number of patients. This is the reason that we are here, in the activities of finding the new formula for health. Science did not give a closing word. And science, in the form of research and innovation, will never end.

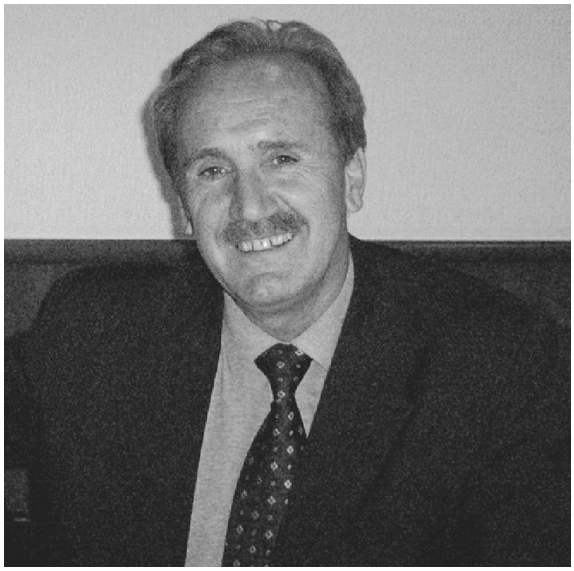
Stay healthy!

With respect,

Prim. dr Avdo Ceranic
Editor in chief

Riječ urednika

Poštovani,



riječ urednika nije puka formalnost kako bi se ispunila ova stranica. Ona za mene predstavlja obavezu da se obratim prije svega čitaocu, a potom, s poštovanjem autorima radova koji aktivno učestvuju u izradi časopisa.

Časopis, sam po sebi čini riznicu novosti iz raznih oblasti medicine koje naši autori pišu, i sve to prođe kroz duplu slijepu recenziju, i tek neki od njih dobiju zeleno svjetlo da budu objavljeni.

Najuži tim ljudi koji uređuje ovaj časopis je stalno aktivan i nikada se ne zadovoljava onim prethodnim. Zato mi i imamo kontinuirani uspon, i svake godine se desi određeni skok u kvalitetu i i nijesmo monotoni.

Naš prvi, i mislim drugi broj (iz 2006. i 2007. godine) činili su tematski objavljeni radovi, ali nam je bio problem to što smo dobijali radove koji se nijesu uklapali u programsku šemu. Zato smo promijenili politiku uređivanja i dali slobodu svim zainteresovanim da pišu o svemu onome što pojedinac smatra da je novost iz medicine. Zbog toga je naš časopis i postao slobodni izraz medicinske riječi, i mislim da ga rado svi prelistavaju i mnogi su ga već upoznali.

Kao urednik, trudim se da ne budem kritičar. Međutim, ponekad ne mogu da izbegnem to da barem ne iskažem kritiku kroz svoje nezadovoljstvo u onom dijelu koji se odnosi na želju da je što više ljudi koji su originali aktivnog učešća u medicinskoj djelatnosti.

Ljudi baš i ne vole da ih neko kritikuje zbog pasivnosti. Medicina po najviše od svih nauka ne trpi da se stoji u mjestu. Medicina traži rad koji istražuje ono što nije poznato, isključuje ono što je nepotvrđeno, a kako bi neko rekao, zdravom ne treba samo malo medicine kako bi održao u zdravom tijelu zdrav duh.

Danas je ova misao izgubila sjaj jer na svakom mjestu možete biti ugroženi od raznih kosmičkih zračenja, od raznih štetnih uticaja produkata ljudskog uma i poremećaja razuma koji je čovjeka stavio, bez njegove volje u ulogu zamorčeta, ne znajući da egzekutor na kraju postaje to isto.

Danas medicina ima velike izazove jer od bezazlene epidemije gripa koja je do skoro bila glavni problem u masovnim tranzitornim oboljevanjima, i kada se izuzmu poznate opasne bolesti sa kojima se medicina izborila, taman kada se pomislilo da je na pomolu jedno zdravo svjetsko društvo, odjednom je na sceni velika svojevrsna epidemija malignih bolesti.

Na žalost, kao elita, malo se ističemo u borbi da se medicinski dokazanim razlozima suprotstavimo onima koji slijepo proizvode sve te razorne faktore kojima kada se izložimo, na ovoj sada maloj planeti Zemlji, dovode do sve većeg broja obolelih. Eto razloga da smo tu u aktivnostima za nove formule za očuvanje zdravlja. Nauka nije sve rekla. A nauci, u formi istraživanja i inovacija, nikad neće biti kraja.

Zdravi bili.

Avdo Ćeranić
Glavni i odgovorni urednik

Čitaj da shvatiš

Piši da preneseš

Uradi da te pamte

Avdo Ćeranić

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THE EFFECT OF FLUCONAZOLE AND AMPHOTERICIN B ON MACROPHAGE FUNCTIONS

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Abstract: **Background:** Different antimicrobial drugs inhibit functions of the microbial cells but, unfortunately, some of these drugs can also affect the host cells, including macrophages. Since these cells represent the baseline defense against microbial agents, it is important that they are fully activated.

Materials and Methods: In the present study we investigated the effect of amphotericin B and fluconazole on the functions of peritoneal macrophages from Balb/c mice treated with these antimycotics. For each antimycotic the therapeutic dose used in clinical practice (calculated on the mouse body weight) and two-fold higher doses were administered intraperitoneally once a day for three consecutive days. The control group was treated with saline in the same way. Four different tests, candidacidal assay, nitroblue tetrazolium test, adherence capability and phagocytic capability, were used to determine macrophage functions.

Results: Our results confirmed positive effect of high dose amphotericin B on phagocytic capability (31.00 ± 4.46%), metabolic changes (27.93 ± 6.63%) and adherence capacity (59.24 ± 8.67%). Lower doses of drug amphotericin B (2 mg/kg) significantly increased the adherence index of macrophages (71.99 ± 5.55%) and intensity of the NBT intracellular reduction (30.20 ± 3.83%). Maximum dose of fluconazole expressed significantly higher phagocytic index (30.77 ± 2.17%), metabolic changes (24.00 ± 4.07%) and candidacidal activities (27.73 ± 6.73%), while lower doses of fluconazole (15 mg/kg) significantly increased the adherence index of macrophages (75.58 ± 5.47%) as well as the phagocytic index (29.23 ± 2.40%). Other results were similar as in control group.

Conclusion: Positive immunomodulatory effects of fluconazole and amphotericin B may be clinically relevant especially in compromised patients who are predisposed to opportunistic fungal infections and require a long-term antimycotic therapy. Synergistic action of macrophages and antimycotics can influence the course of disorders related to immune suppression.

Key words: Amphotericin B, fluconazole, macrophage functions.

INTRODUCTION

Fungal infections pose a growing medical problem because of the markedly increased numbers of immunologically compromised patients due to human immunodeficiency virus, cancer chemotherapy, bone marrow transplantation or other debilitating conditions (1, 2). These infections are commonly associated with significant morbidity and mortality. Many of these infections are caused by, in normal conditions, harmless fungi. The most common infection associated with this group of patients is candidiasis (3–5). Resistance to fungal infections is based on cell-mediated immunity. Macrophages play a key role in the host immune system. They act as a barrier against microbial invasion and dissemination. Their ability to be mobilized into infectious sites from bone marrow and blood, as well as their competence for phagocytosis and killing of microorganisms is often decisive in determining the outcome of infection (1, 6–8). Once activated, they act directly by destroying bacteria, parasites, viruses, fungi and tumor cells with reactive oxidants and hydrolytic enzymes, or indirectly by releasing specific mediators such as interleukin-1, tumor necrosis factor-alpha and others which can regulate other cells' activities. They are also responsible for processing the antigens and presenting the digested peptides to lymphocytes, while playing the leading role in damage repair (9–11). However, chemotherapeutic agents, corticosteroids, and radiation, disrupt these defense mechanisms. If patients are to survive infections associated with neutropenia

and other compromises in host defense due to use of these therapies, it is important to reverse or at least lessen immunosuppresion in this patients (2, 4).

Fungal infections are treated with antifungal drugs. Antifungal agents which are available for treatment of these infections are the polyenes, the azoles and the echinocandins (12–14). Polyene antifungal drug amphotericin B is a standard therapy for invasive Candida infections, but high frequency of renal toxicity limits its use. Recently, newer lipid formulations of amphotericin B with less adverse effects and activities similar to that of standard amphotericin B have become available (15). The triazole fluconazole is a leading drug to prevent and to treat candidal infections. This drug displays predictable pharmacokinetics and an excellent tolerance profile in all groups of patients (12–14, 16).

Different antimicrobial drugs inhibit functions of the microbial cells but, unfortunately, some of these drugs can also affect the host cells, including macrophages. Since these cells represent the baseline of defense against microbial agents, it is important that these cells are fully activated (14, 15).

The aim of this study was to investigate the effect of amphotericin B and fluconazole on macrophage functions (adherence, phagocytosis, intracellular killing and digestion of the drug) on experimental mouse model.

MATERIALS AND METHODS

Animals. Female BALB/c mice, 9 weeks old (obtained from the Medical Faculty, University of Rijeka) were used in this study. They were randomly divided in five groups each containing five animal. The animals were kept in plastic cages and were given standard laboratory rodent food and water ad libidum. The Ethical Committee of the Medical Faculty University of Rijeka approved the study and all procedures using mice.

Antimycotics. Two antifungal drugs Amphotericin-B (Amphotericin-B, Bristol-Myers Squibb, Woerden, The Netherlands) and fluconazole (Diflucan, Pfizer, Ambroise, France) were tested.

For each antimycotic, the therapeutic dose used in clinical practice (calculated on the mouse body weight) and twofold higher dose were administrated intraperitoneally once a day, for three consecutive days. Standard preparation of amphotericin B was given in doses of 2 mg/kg/day and 4 mg/kg/day while fluconazole was administrated in doses of 15 and 30 mg/kg/day. Control group was treated with saline (0,85% NaCl) in the same way.

Peritoneal macrophages. 24 h after receiving the last dose of the antimycotic, the animals were sacrificed by cervical dislocation. Peritoneal macrophages were obtained after the peritoneal cavity was washed with 4 ml of RPMI medium (Institute of Immunology, Zagreb, Croatia). The injected medium containing peritoneal cells was slowly aspirated. Quantitative analysis of the cell suspension was performed immediately after collection in a Neubauer chamber.

Macrophage adherence assay. Two plastic test tubes (16 x 160 mm) were filled with 0.2 ml of the same cell suspension. The tubes were incubated for 2 hours in a horizontal position at 37 °C in a humidified atmosphere. After gentle removal, the number of nonadherent macrophages was counted in a Neubauer chamber. The results were expressed as the adherence index (AI).

Phagocytic assay. Two plastic rings, 2 mm high and 16 mm in diameter, were stuck with paraffin onto microscopic slides. The wells were filled with the cell suspension containing peritoneal macrophages in RPMI medium and heat killed *Candida albicans*. The wells were covered with cover slips and incubated at 37 °C for 30 minutes in a humid atmosphere. After incubation the cover slips were removed and the liquid was decanted. The plastic rings were removed and the slides were dried, stained with Wright's stain and examined with immersion. The total number of macrophages and the percentage of ingested *Candida albicans* were counted. More than 100 cells per each well were counted. The results were expressed as phagocytic index (PI).

Candidacidal assay. Plastic tubes were filled with 0.1 ml of cell suspension and 0.005 ml suspension of viable *Candida albicans*. The tubes were then incubated at 37 °C for one hour in a humid atmosphere. After incubation, the suspension was treated with cold distilled water for 15 minutes to cause cells lysis. Light microscopic examination showed blue killed *Candida* while the alive ones remained were colorless. Free *Candida albicans* was colored with Tripan blue. More than 300 *Candida* were counted and the results were expressed as percentage of killed *Candida albicans* at 100 microorganisms.

Nitroblue tetrazolium (NBT)-dye assay. NBT-assay expresses metabolic changes in the macrophages after phagocytosis foreign particles. Metabolic changes include reduction of the colorless NBT in the cytoplasm of macrophages in black color formasan. Plastic tubes were filled with 200 µl of the cell suspension and 200 µl of the nitroblue tetrazolium. The tubes were then incubated at 35E C for 15 minutes in a humid atmosphere and for 15 minutes at room temperature. The suspension was then placed on microscopic slides and dried. Immediately after, dried slides were stained with Wright's stain and examined with immersion. The total number of macrophages and the percentage of formasan positive cells with blue or black inclusions were determined. More than 100 cells per slides were coun-

ted. Results were expressed as percentage of NBT positive cells.

Comparison between groups was performed by Student t-test. Results are expressed as mean and standard deviation. The level of significance was set at 0.05.

All animal experiments were carried out in accordance with Policies and Guidelines for the Care and Use Laboratory Animals. All effort was made to minimize animal suffering.

RESULTS

The effect of fluconazole on macrophage functions

Our results showed that lower dose of fluconazole (15 mg/kg) significantly increased the adherence index of macrophages (75.58 ± 5.47%) as well as the phagocytic index (29.23 ± 2.40%), but did not demonstrate any major alteration in *C. albicans* killing assay and NBT intracellular reduction.

Macrophages treated with maximum dose (30 mg/kg) of fluconazole had significantly higher phagocytic index (30.77 ± 2.17%), metabolic changes (24.00 ± 4.07%) and candidacidal activities (27.73 ± 6.73%) comparing to control group ($p \leq 0.05$).

The effect of amphotericin B on macrophage functions

Lower doses of drug amphotericin B (2 mg/kg) significantly increased the adherence index of macrophages (71.99 ± 5.55%) and intensity of the NBT intracellular reduction (30.20 ± 3.83%), while other results were similar to the control group.

Treatment of macrophages with higher dose of amphotericin B (4 mg/kg) showed that phagocytic capability (31.00 ± 4.46%), metabolic changes (27.93 ± 6.63%) and adherence capacity (59.24 ± 8.67%) were increased significantly.

Results are summarized in Table 1.

DISCUSION

The host response to fungal infections requires co-actions of immune system and antifungal drugs to effectively clear the microorganisms. Antifungal drugs may have broad immunomodulatory properties. Cytokines, effector cells, and antifungals appear to work synergistically to oppose fungal growth. Positive immunomodulatory effects of antifungal drugs may be clinically relevant, especially in compromised patients who are predisposed to opportunistic fungal infections and require a long-term antimycotic therapy (17).

In this study, the most commonly used antifungal drugs were studied for their impact on different macrophage functions. Several studies examined the influence of fluconazole on macrophage activity against *Candida*. It appears that the presence of macrophages provides synergistic activity with fluconazole against *Candida* isolates (14). Garcha presented the data that indicate that the combination of two fungistatic agents, fluconazole and macrophages, can synergize for significant anticandidal activity, especially against fluconazole-susceptible isolates (18). In contrast, investigation presented by Yamaguchi et al. suggested that fluconazole had no immunological effect (19). Results of our investigation confirmed synergic activity of as a stimulant on phagocytosis, oxidative burst and microbicidal activity using both fluconazole and macrophages in immune response. We found that fluconazole acted maximum dose and lower dose of fluconazole, although better results were obtained with maximum dose. Fidan and his co-workers concluded in their research that fluconazole has an immunomodulatory effect connected with the presence of different cytokines (17).

It is well known that Amphotericin B has an immunostimulatory effect to macrophages and enhances their function (17, 19). It also has a stimulatory effect on macrophages to produce cytokine tumor necrosis factor alpha (TNF-α) which may be responsible for the immunomodulatory effects of Amphotericin B (20).

Table 1. *Adherence index, Phagocytic index, NBT-dye assay and Candidacidal assay for amphotericin B and fluconazole*

	Adherence index (AI)	Phagocytic index (PI)	NBT-dye assay (%)	Candidacidal assay (%)
Control	62.21 ± 14.26	22.95 ± 3.55	20.93 ± 1.71	14.10 ± 623
Fluconazole (15 mg/kg/day)	75.58 ± 5.47*	29.23 ± 2.40*	19.20 ± 3.52	11.40 ± 4.40
Fluconazole (30 mg/kg/day)	68.84 ± 8.68	30.77 ± 2.17*	24.00 ± 4.07*	27.73 ± 6.73*
AmphotericinB (2 mg/kg/day)	71.99 ± 5.55*	22.67 ± 3.32	30.20 ± 3.83*	11.13 ± 4.51
AmphotericinB (4 mg/kg/day)	59.24 ± 8.67*	31.00 ± 4.46*	27.93 ± 6.63*	12.60 ± 4.65

Values are expressed as mean ± SD from each group. Student t-test was used to compare data among the groups.
* Significant increased functions comparing to control group at level $p < 0.05$.

We confirmed that both doses of amphotericin B had effect on macrophages, increasing significantly their phagocytic ability and oxidative burst. Our results are also in correlation with the results obtained by Yamaguchi who concluded that amphotericin B has a profound effect on macrophages in vitro and in vivo, and that this action is mediated by cytokines (19).

Antifungals used to treat infections, especially in immunocompromised patients, could have a potent antimicrobial effect to fungi and positive impact on host defense mechanisms such as macrophage functions.

CONCLUSION

It is preferable that drugs used have a slightly stimulatory, rather than an immunosuppressive effect on the cells of the immune system. Since some drugs can suppress macrophage functions, it would be appropriate to determine susceptibility of microorganisms to a certain drug since even minor immunosuppressive effect can additionally complicate the course of the disease. Recent investigation suggested that macrophage functions are connected with activation of different cytokines but further studies should be carried out in order to understand better the mechanism by which target host cells react in response to immunomodulators.

Abbreviations:

AI — adherence index
NBT assay — Nitroblue tetrazolium dye assay
TNF-α — tumor necrosis factor alpha

Sažetak

UČINAK FLUKONAZOLA I AMFOTERICINA B NA FUNKCIJE MAKROFAGA

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Uvod: Različiti antimikrobni lekovi inhibiraju funkcije mikroorganizama, nažalost deluju i na ćelije domaćina, uključujući i makrofage. Obzirom da su makrofazi bazna linija odbrane organizma, potrebno je da budu u potpunosti aktivirani.

Materijali i metode: U istraživaanju ispitivan je učinak flukonazola i amfotericina B na funkcije peritonealinih makrofaga Balb/c miševa. Za svaki antimikrobni lek korišćena je terapeutska doza i dvostruko veća doza. Miševi su tretirani uzastopno tri dana. Kontrolna grupa miševa tretirana je s fiziološkim rastvorom identičnim postupkom. Da bi se odredila funkicija makrofaga korišćena su četiri testa: kandidacidni test, nitroblutetrazolijski test, sposobnost adherencije i fagocitna sposobnost.

Rezultati: rezultati su potvrdili pozitivan učinak amfotericina B na fagocitozu (31.00 ± 4.46%), metaboličke promene (27.93 ± 6.63%) i sposobnost adherencije (59.24 ± 8.67%). Niža doza amfotericina B (2 mg/kg) značajno povećava indeks adherencije makrofaga (71.99 ± 5.55%) i metaboličke funkcije (30.20 ± 3.83%). Viša doza flukonazola značajno povećava fagocitni indeks (30.77 ± 2.17%), metaboličke aktivnosti (24.00 ± 4.07%) i kandidacidne aktivnosti (27.73 ± 6.73%), dok niža doza flukonazola (15 mg/kg) značajno povećava indeks adherencije (75.58 ± 5.47%) i fagocotni indeks (29.23 ± 2.40%). Rezultati su sličnii u kontrolnoj grupi.

Zaključak: Pozitivan imunomodulatorni učinak flukonazola i amfotericina B može biti klinički značajan kod imunološki kompromitovanih bolesnika kod kojih postoji predispozicija razvoja oportunističkih gljivičnih infekcija. Sinergističan učinak makrofaga i antimikotika može uticati na razvoj i tok bolesti.

Ključne reči: Amfotericin B, fluconazol, makrofagne funkcije.

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WHEN TO POSTPONE CATARACT SURGERY: TAKING IN CONSIDERATION PATIENTS' QUALITY OF LIFE

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Abstract: **Purpose:** Assessment of complication in surgery of complicated cataracts and option of postponement of surgery.

Setting: Clinic for eye diseases, Clinical Centre of Serbia

Methods: This was a retrospective observational case series.

Results: In 16 patients subjected to cataract surgery by method of phacoemulsification, three experienced complications during surgery. Two experienced rupture of posterior lens capsule and prolapse of the vitreous body, and one, expulsive hemorrhage. The visual acuity in all three patients was lesser than the preoperative visual acuity. In the second group of 16 patients, after having been acquainted with the survey, the cataract surgery was postponed and the patients were controlled after one year. The cataract progressed just partially in certain patients and all the patients were satisfied with the status of their vision and did not demand surgery.

CONCLUSIONS: Cataract surgery in complicated cases may be accompanied by complications with uncertain postoperative visual results. Therefore, in patients with complicated cataracts and relatively preserved visual acuity, it is necessary to be careful with proposing surgery and often obey their wish to postpone surgery. This should be done particularly with patients of advanced age, patients with poor general status of life and in monoculuses.

Key words: Complicated cataracts; phacoemulsification; surgical complications; postponement of surgery; ophthalmological control.

INTRODUCTION

One could say that presently cataract surgery has almost reached perfection. This applies not only to surgery (phacoemulsification), but also to postoperative functional restoration using implantation of various intraocular lenses (IOL) (1, 2). It is also necessary to emphasize that operative and postoperative complications are minimized. However, in spite of all this the operative and postoperative complications, although rare, can happen and lead to serious impairment of sight in the operated eye (3–10).

DECISION ON CATARACT SURGERY IN SPECIAL CASES

The possibility of the appearance of unforeseen complications during or after surgery is a reason for the surgeon to take extreme care in proposing and undertaking cataract surgery in certain specific cases. The patients know very little if anything about these complications. That is why the surgeon also needs to acquaint them before surgery with the possibility that the cataract surgery might not pass as well as they expect and tell them that sometimes vision can be poorer after surgery or may sometimes end in complete loss of vision. Only after detailed information should the patient make the final decision whether to undergo or postpone surgery and take regular ophthalmological controls. Particular attention needs to be paid with the following patients: 1. patients who lack an eye (anophthalmos), or cannot see with the eye for some other reason and a cataract is present in the sole remaining eye. It is necessary to consider well with such patients whether to operate or subject the patient to regular controls and monitor further progression of the cataract. The following patients fall under this category: a) still actively functional monoculuses with an incipient cataract in the sole eye and visual acuity greater than 0.8 b) retired monoculus patients with a cataract and visual acuity greater than 0.3 c) monoculuses in advanced years and poor general state of health with visual acuity less than 0.3

but still sufficient to perform basic daily living requirements 2. patients with a cataract in both eyes and visual acuity in the better eye greater than 0.6 but with poor general state of health 3. patients with complicated cataracts with a greater percentage of operative and postoperative complications and visual acuity in the better eye greater than 0.3.

We should explain to such patients that there is a greater possibility of complications with cataract surgery and the visual acuity might be worse after the surgery. Simply put, they may have something to lose. They should be suggested to avoid surgery and to report regularly for ophthalmological follow-ups, and only when the visual acuity is so weakened and represents serious daily disturbance, to undergo cataract surgery. They simply have nothing to lose then.

MATERIAL AND METHODS

The present study was approved by the ethical committee of the University Hospital Belgrade and informed consent was obtained from each patient after full explanation of the procedural nature.

Thirty-two patients with an increased possibility of development of complications during cataract surgery were examined at the Clinic for eye diseases, Clinical Centre of Serbia. All the patients underwent previous detailed ophthalmological and internal-medical examination and were provided with detailed explanation of the nature of cataract surgery and the possible benefit as well as possible operative and postoperative complications. After that the patients were given the questionnaire, which they read and answered the existing questions.

1. How well do you see?

a. well
b. relatively well
c. badly

2. How do you see in the distance?

a. well
b. recognition of image difficult
c. badly

3. Can you see to read? Do you see well enough to read?

a. yes, without correction
b. yes, when using glasses for correction
c. cannot see even with correction

4. How well do you orient yourself in space?

a. well
b. with difficulty
c. badly

5. Do you want to undergo surgery?

a. no
b. if you advise
c. yes

6. Are you aware of the possibility of existence of operative and postoperative complications we have discussed that would lead to reduction of preoperative vision or complete loss of vision?

a. yes
b. yes, partially
c. no

7. Did you have a chance to talk to anyone whose operation did not end well?

a. yes
b. no

8. Do you wish to undergo surgery even after having been acquainted in detail with the nature of the operation and possible complications?

a. I do not want to
b. I will postpone the surgery for later
c. I do want to

Following this, 16 patients decide to undergo cataract surgery immediately and the other 16 were in favor of postponement of the surgery and accepted the regular ophthalmological monitoring.

The patients which opted for surgery had phacoemulsification and all the operations were made by an experienced phaco surgeon (MJ). The follow-up of the second group of patients who opted for postponed surgery was performed after half a year and after a year.

This paper presents the results of surgery in the first group of 16 operated patients and findings in the second group of 16 patients, with particular review of the state of the cataract, visual acuity and satisfaction of the patient with the current state of vision.

RESULTS

In the first group of 16 operated patients (Table 1) the operative course passed regularly with 13 patients, and in 10 patients the achieved postoperative visual acuity was normal 1.0, and in 3 patients below normal due to some other accompanying eye disease. However, complications occurred in 3 patients during the surgery, namely, rupture of the posterior lens capsule with vitreous body prolapse in 2 patients (patients under ordinal number 2 and 8), whereas in the third patient an expulsive hemorrhage occurred during the surgery (patient under ordinal number 16). The postoperative visual acuity in the first two patients was poorer with respect to the preoperative and in the third patient amaurosis occurred.

Table 1. *Patients with complicated shape cataract which underwent phacoemulsification*

Case	Sex	Age	Ophthalmic diagnosis	Preoperative VO end IOP		Surgeye	Postoperative VO end IOP		complications
1	M	74	OD: Cat sen incip. PEX OS: Pseudophakia. PEX	0,4 1,0	16,0 14,0	OD	1,0 1,0	14,0 14,0	without
2	F	81	OD: Cat sen incip. Myopia alta OS: St. post rupturam bulbi	0,2 am	12,0 17,0	OD	1/60 am	11,0 16.0	Ruptura caps post. Prol CV
3	M	76	OD: Gl. absolutum OS: Cat sen incip	am 0,4	13,0 13,0	OS	am 1,0	13,0 11,0	without
4	M	82	OD: Cat sen incip OS: Anophthalmus	0,3 /	14,0 /	OD	1,0 /	12,0 /	without
5	F	74	OD: Cat complicata uveitica OS: Pseudophakia. Kerat bullosa	3/60 L+P-	14,0 16,0	OD	1,0 L+P-	11,0	without
6	F	74	OD: Cat sen incip. DCE – Fuchs OS: Pseudophakia. Kerat bullosa	0,3 L+P+	14,0 18,0	OD	1,0 L+P+	12,0 18,0	without
7	F	79	OD: Leucoma corn vasc post cs OS: Cat sen incip	am 0,5	14,0 14,0	OS	am 1,0	14.0 12,0	without
8	M	78	OD: Cat sen incip OS: Cat sen incip	1,0 0,7	15,0 15,0	OS	1,0 1/60	15,0 15,0	Ruptura caps post. Prol CV
9	F	63	OD: Cat complicata uveitica OS: Gl absolutum	0,4 am	16,0 30,0	OD	1,0 am	13,0 30,0	without
10	F	64	OD: Myopia alta, Abl ret inop OS: Myopia alta. Cat brun incip	am 0,2	10.0 12,0	OS	am 0,6	10,0 11,0	without
11	F	64	OD: Myopia alta. Cat brun incip OS: Myopia alta. Atrophio bulbi	0,3 am	12,0 /	OD	1,0 am	11,0 /	without
12	M	86	OD: Cat sen brun. Gl simplex OS: Gl absolutum	0,2 am	16,0 25,0	OD	0,7 am	13,0 25,0	without
13	F	82	OD: Cat sen brun. Gl simplex OS: Gl absolutum	0,2 am	18,0 34,0	OD	0,6 am	16,0 34,0	without
14	F	77	OD: Atrophio bulbi OS: Cat sen incip	am 0,5	/ 14,0	OS	am 1,0	/ 13,0	without
15	M	82	OD: Gl absolutum. Cat compl OS: Cat sen intum. Gl simplex	am 1/60	36,0 20,0	OS	am am	36,0 24,0	Haemorrhagi expulsiva
16	F	78	OD: Cat sen incip. PEX OS: Cat sen incip. PEX	0,9 0,5	17,0 16,0	OS	0,9 1,0	17,0 15,0	without

M = male; F = female;; VO = visual acuity; IOP = intraocular pressure; OD: right eye; OS: left eye; am = amaurosis; CV = vitreous; PEX = pseudoexfoliation syndrome; DCE = degeneratio corneae endoteliales; L+P- = light perception without precise projection; L+P+ = light perception with precise projection

The second group of 16 patients opted after reading the questions and providing the respective answers in the survey not to undergo surgery (Table 2). At the control examination 6 months later only 3 patients (under numbers 7, 11, 13) experienced poorer vision by just one line read on the Snellen chart and at the control 12 months later, whereas the visual acuity dropped by one more line on the Snellen chart in 10 patients. However, all of them retained their decision to have regular checkups and no surgery.

DISCUSSION

In the first group of 16 operated patients, with 13 the phacoemulsification passed without operative complications. In 10 out of these 13 operated patients the postoperative visual acuity was normal (1.0; 6/6), whereas the postoperative visual acuity in 3 patients was somewhat below normal due to other associated ophthalmological diseases. In the patient under ordinal number 10 the visual acuity was 0.6 due to degenerative myopic changes in the posterior eye pole, and in the patient under ordinal number 12 and patient under ordinal number 13 the postoperative visual acuity was 0.7 and 0.6 respectively because of the change on the optic nerve papilla due to open-angle glaucoma.

It is particularly important to note that in 3 patients complications occurred during phacoemulsification, which resulted in decrease of vision with respect to the patients' vision prior to surgery. The patient under ordinal number 2 in the Table, aged 81, had an early cataract and high myopia in the right eye with visual acuity of 0.2. There was a former injury of the eyeball (rupture) which resulted in amaurosis. In other words, this was a monoculus patient. During the phacoemulsification surgery of the right eye the posterior capsule ruptured with a prolapse of the vitreous body. After the definite surgical care the visual acuity was signifi-

Table 2. *Patients with complicated shape cataract with delayed cataract surgery*

Case	Sex	Age	Ophthalmic diagnosis	First examination VO IOP		An eye for a surgery	After 6 months TO IOP		After 12 months VO IOP	
1	F	75	OD: Gl absolutum OS: Cat complicata uveitica	Am 3/60	30,0 16,0	OS	Am 3/60	35,0 16,0	Am 3/60	35,0 16,0
2	F	80	OD: Pseudophakia Kerat bull OS: Cat sen incip. DCE - Fuchs	L+P- 0,5	19,0 13,0	OS	L+P- 0,5	19,0 13,0	Am 0,4	20,0 12,0
3	M	76	OD: Cat sen incip OS: Cat sen incip	0,6 1,0	14,0 14,0	OD	0,6 0,9	14,0 14,0	0,5 0,9	15,0 15,0
4	F	82	OD: Cat compl. Gl caps. PEX OS: Gl absolutum	3/60 Am	14,0 32,0	OD	3/60 Am	14,0 34,0	3/60 Am	13,0 33,0
5	M	72	OD: Cat sen incip. OS: Anophthalmus.	0,6 /	12,0 /	OD	0,6 /	12,0 /	0,5 /	12,0 /
6	M	73	OD: Cat sen incip. AMD OS: Pseudophakia. AMD	0,7 0,2	18,0 12,0	OD	0,6 0,2	17,0 12,0	0,5 0,2	17,0 12,0
7	M	81	OD: Cat sen incip. RD OS: Pseudophakia, RD.Kerat bull	0,4 L+P+	15,0 17,0	OD	0,3 L+P+	15,0 17,0	0,3 L+P+	15,0 18,0
8	F	79	OD: St post rupturam bulbi OS: Cat sen incip	Am 0,5	12,0 15,0	OS	Am 0,5	12,0 15,0	Am 0,4	12,0 15,0
9	F	76	OD: Anophthalmus. OS: Cat sen incip	/ 0,5	/ 16,0	OS	/ 0,5	/ 16,0	/ 0,4	/ 16,0
10	F	64	OD: Myopia alta. Abl ret inop OS: Myopia alta. Cat compl.	Am 0,5	10,0 14,0	OS	Am 0,5	10,0 15,0	Am 0,4	10,0 15,0
11	M	64	OD: Pseudophakia OS: Cat sen incip. PEX	1,0 0,8	15,0 15,0	OS	1,0 0,7	15,0 14,0	1,0 0,7	14,0 14,0
12	F	63	OU: Cat sen brun. Gl caps. St post YAG iridotomiam	0,4 0,6	17,0 17,0	OD	0,4 0,6	17,0 17,0	0,3 0,5	18,0 18,0
13	M	84	OD: Cat sen incip. Chor per acta OS: Cat se incip	0,6 1,0	16,0 16,0	OD	0,6 0,9	18,0 18,0	0,5 0,8	17,0 17,0
14	F	87	OD: Cat sen incip OS: Pseudophakia. Kerat bull	0,6 L+P+	13,0 13,0	OD	0,6 L+P+	13,0 13,0	0,5 L+P+	14,0 14,0
15	F	78	OU: Cat sen incip. PEX. Iridophacodonesis	0,8 0,6	15,0 15,0	OS	0,7 0,6	15,0 15,0	0,7 0,5	16,0 16,0
16	M	81	OU: Cat sen incip. PEX. Iridophacodonesis	0,8 0,6	16,0 16,0	OS	0,7 0,6	16,0 16,0	0,7 0,6	16,0 16,0

AMD = age-related macular degeneration; RD = diabetic retinopathy

cantly lesser and equal to 1/60. For the time being she uses glasses for correction. Patient under ordinal number 8, aged 78, had a very early cataract in both eyes, somewhat more progressed in the left eye, with visual acuity 1.0 in right and 0.7 in left eye. According to the anamnesis he also had a contusion injury of the left eye. After reading the questions from the survey he wanted to undergo surgery of the left eye, which was performed. During the phacoemulsification it proved that there was a dehiscention of the zonula in a part of circumference of the lens and prolapse of the vitreous body. The postoperative visual acuity was 1/60. The intraocular lens was not implanted and the patient corrects the aphakia on the operated eye with contact lens and visual acuity is 1.0. The patient under ordinal number 15, aged 82 had the most difficult surgical complication. She had absolute glaucoma and amaurosis of the right eye and mature cataract and long-standing glaucoma with visual acuity of 1/60 on the left eye. She was in a relatively poor general state of health with arterial hypertension and arteriosclerosis. During the phacoemulsification of the left eye expulsive hemorrhage occurred which resulted in development of amaurosis on that eye as well. The number of 3 patients with surgical complications in the group of 16 operated patients is 18.7%, which is a high percentage, however, it is necessary to bear in mind that these were patients with cataract that was complicated for surgery.

The second group of 16 patients, after detailed ophthalmological examination, talked with the ophthalmologist and once acquainted with the questionnaire, refrained from cataract surgery with an agreement reached with their surgeon of the need of regular ophthalmological follow-up. The reason for refraining from surgery at that moment was a relatively good visual acuity in the eye affected by cataract that was supposed to be operated, which provided the patient a relatively good quality of life, accompanied by fear of surgical complications, and in some cases also a relatively poor general state of health in the advanced years of li-

fe. Among these patients there were 2 with anophthalamus, 4 with amaurosis, 1 with a light perception without precise projection and 2 with light perception with precise projection in the other eye that was lost for sight and was not foreseen for surgery. This was due to various diseases: absolute glaucoma, keratopathy after cataract surgery in that eye, inoperative retinal detachment, injury. The patient aged 75 under ordinal number 1 had amaurosis in the right eye due to absolute glaucoma and a complicated uveitic cataract in the left eye. In addition to this she was in a poor general state of health. Although having quite a low visual acuity of 3/60 for surgery in the left eye, she provided information that she manages quite well at home and in a familiar environment, and that is sufficient to her in this phase of life. She stated that she would undergo surgery only when her vision deteriorated further. The 80 year old patient under ordinal number 3, the 80 year old patient under ordinal number 7 and the 87 year old patient under ordinal number 14 had visual acuity in the eye with a cataract that was supposed to be operated of 0.7, 0.5 and 0.6 respectively. However, in addition to the incipient cataract they also had Fuchs' corneal endothelial dystrophy. Furthermore, in the other eyes of these patients the cataract had already been operated by phacoemulsification and intraocular lens (pseudophakia) implanted, however, decompensation of the cornea took place and bullous keratopathy developed. Their fear of surgery was clear and so was their desire to postpone the operation of the remaining eye, as they stated that they are satisfied with the existing visual acuity and quality of life. The patient aged 82 under ordinal number 4 had visual acuity in the right eye for surgery of 3/60 and amaurosis in the other eye. However, in addition to the complicated cataract in the eye foreseen for operation there was also capsular glaucoma and pseudoexfoliation; hence, due to the possibility of surgical complication the patient refrained from surgery at that moment. The patients under ordinal numbers 5 and 9 had only one eye and an incipient senile cataract in that eye with visual acuity of 0.6 and 0.5. They refrained from surgery because they considered that the existing visual acuity provided them a relatively good quality of life and that they would not take the risk at this moment considering that they did only had one eye. A similar line of thinking was present in patients under ordinal numbers 8 and 10 with amaurosis in the right eye. The patient under ordinal number 6 is interesting. He previously underwent cataract surgery in the left eye, but the visual acuity remained unchanged compared to the visual acuity before surgery and was equal to 0.2, and the reason for this was a progressed dry degeneration of the macula. There was senile cataract in the right eye in an incipient phase but also early degeneration of the macula. This was the reason for refraining from surgery at this moment. The 62 year old patient under ordinal number 12 had incipient senile cataract in both eyes but also capsular glaucoma with performed YAG laser iridotomy in both eyes, and an extremely shallow anterior chamber and posterior sinechia and visual acuity of 0.4 and 0.6. She was satisfied with the existing visual acuity in both eyes, and in addition to this, with the presented possible surgical complications consented with the postponement of surgery at this moment. All the other patients in the table had incipient cataracts in both eyes, relatively preserved visual acuity in both eyes which ranged from 0.6 to 1.0 and pseudoexfoliation with more or less pronounced iridophacodonesis. They considered that the existing visual acuity fulfilled their daily needs and that they would not expose themselves at this moment to the risk of surgery.

All these patients underwent examination by the same surgeon after 6 months and after one year. The cataracts in the eyes that were considered for surgery progressed very slowly so that after 6 months there were only 5 patients with reduced visual acuity by one line on the Snellen charge, and after 12 months there were 9 patients with reduction of one line according to Snellen. Two patients under ordinal number 1 and 5 with least visual acuity and complicated cataract in one functional eye did not have further reduction of visual acuity during the period of one year.

One year after the initial consideration of the need for cataract surgery, all the patients were satisfied with their visual acuity and quality of life it had provided them, so that they refrained from surgery with the need of further regular ophthalmological follow ups.

CONCLUSION

Cataract surgery, although having reached high safety limits, can be accompanied in a certain percentage of cases with the appearance of complications which can result in poor postoperative vision in that eye. This should be borne in mind particularly in cases of cataracts with a higher risk of complications and in case of cataracts in monoculuses.

• In this category of patients, usually in advanced years and with other general illnesses, it is necessary to clarify additionally the increased possibility of complications, conduct the survey proposed in this work and perform surgery only if they consent.

• It is also necessary to bear in mind their relatively reduced general living needs during that period of life and also accept their satisfaction with somewhat reduced vision and quality of life. It is necessary just to control them regularly and subject them to cataract surgery when they are ready for it.

Conflict of interests

All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Sažetak

DOGOVOR SA PACIJENTOM O ODLAGANJU OPERACIJE KATARAKTE U POSEBNIM SLUČAJEVIMA — KVALITET ŽIVOTA

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UVOD: Procena nastanka komplikacija pri operacijama komplikovanih katarakti i mogućnosti odlaganja operacija.

METODE: Praćenje i analiza dve serije pacujenata sa komplikovanim kataraktama, jedne kod koje je izvršena operacija i druge bez operacije.

REZULTATI: Kod 16 pacijenata kod kojih je rađena operacija katarakte metodom fakoemulzifikacije kod tri je nastala komplikacija u toku operacije. Kod dva je došlo do rupture zadnje kapsule sočiva i prolapsa staklastog tela, a kod jednog do nastanka ekspulzivne hemoragije. Kod sva tri pacijenta postoperativna vidna oštrina je bila manja od preoperativne. Kod druge grupe od 16 pacijenata, posle upoznavanja sa anketom, operacija katarakte je bila odložena i na kontroli posle godinu dana katarakta je samo delimično napredovala kod pojedinih pacijenata i svi pacijenti su bili zadovoljni svojim stanjem vida i nisu zahtevali operaciju.

ZAKLJUČAK: Operacija katakte kod komlikovanih slučajeva može biti praćena komplikacijama sa neizvesnim postoperativnim vidnim rezultatom. Zato kod pacijenata sa komplikovanim kataraktama i relativno očuvanom vidnom oštrinom, treba biti oprezan pri predlaganju operacije i često poslušati njihovu želju za odlaganjem operacije. To posebno treba činiti kod pacijenata u poznim godinama života, pacijenata sa lošim opštim životnim statusom i kod monokulusa.

Ključne reči: Komplikovana katarakta, fakoemulzifikacija, operativne komplikacije, odlaganje operacije, oftalmološka kontrola.

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Original article

THE INCIDENCE OF NOSOCOMIAL INFECTIONS IN PATIENTS WITH ISOLATED SEVERE TRAUMATIC BRAIN INJURY

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Abstract: **Introduction:** Traumatic brain injury is the leading cause of death in children and adults in developed countries. Severe traumatic brain injury is classified with Glasgow Coma Scale score 8 and less. About 50% of patients with severe traumatic brain injury developes at least one infection as a complication of primary condition during hospitalization in the Intensive Care Unit, resulting with fatal outcome in 28% of patients. Ventilator — associated pneumonia is the leading infection that affects patients with severe traumatic brain injury, with an incidence between 41% and 74%. Following are sepsis and urinary tract infections.

The aim: To analyze the number of patients with nosocomial infection and isolated severe traumatic brain injury hospitalized in the Intensive Care Unit of the Clinical Hospital Centre Rijeka, Croatia, from 31st January 2013 to 31st December 2014.

Patients and methods: A two – year retrospective study included 46 patients with isolated severe traumatic brain injury and nosocomial infection hospitalized in the Intensive Care Unit of the Clinical Hospital Centre Rijeka,Croatia, in the period from 31st January 2013 to 31st December 2014. All medical data was collected from the Division of Intensive Care Unit, Clinical Hospital Centre Rijeka, Croatia.

Results: From 67 patients with isolated severe traumatic brain injury, 46 (68,65%) of them developed nosocomial infection. There was statistically significant more male patients than female ($p < 0.05$). The average age of infected patients was 57,8 years. The leading were the infections of the respiratory system. Gram – negative bacteria *Proteus mirabilis* and *Pseudomonas aerugnonsa* were the leading pathogens. The average duration of the infection was 5,77 day. Duration of mechanical ventilation accounted for the majority of the patients more than 10 days. The average duration of treatment for all 46 patients was 10,475 days, and for 16 (34,78%) of them, the treatment outcome was lethal.

Conclusion: Nosocomial infections are becoming a major public health problem. The emphasis must be set on the prevention which includes maintaining the hygiene and the antiseptic rules among the medical personnel of the Intensive Care Unit. Already developed infections must be adequately treated so the negative treatment outcomes can be reduced.

Key words: isolated severe traumatic brain injury, Glasgow Coma Scale, Intensive Care Unit, nosocomial infections, gram – negative bacteria.

INTRODUCTION

Traumatic brain injury (TBI) presents traumatically induced structural damage of brain as a result of external force. It is usually followed by temporary or permanent cognitive brain dysfunction. Some of the early onset clinical signs that can indicate TBI are quantitative loss of consciousness, immediate memory loss before or after the injury, alteration in mental state, neurological sequelae and presence of intracranial lesions (1).

In developed countries, TBI is the leading cause of death in children and adults (2). In European countries, every year is hospitalized about 1,6 milion people with TBI. That formes a brain injury rate of 235/100 000 per year (3). Epidemiological data from Center for disease control and prevention, shows that in the United States TBI makes 30% of all injury deaths (4). The most vulnerable groups are children aged 0 to 4, older adolescents between the ages of 15 and 19, and people older than 75 years. Incidence is highest between the ages of 15 and 30, with the greatest risk between the ages of 15 and 24. Men have 1,4 times greater risk compared to

female (5). The most common cause of TBI are traffic accidents, accounting for 50%. Falls are the second leading cause with 20% to 30%. Incidence of TBI caused by falls is increasing as the population ages. On that way contusions of brain, that are more frequent in older patients, are becoming the most common biomechanical mechanism of TBI. Violence is the third leading cause, accounting for 7% to 10%. The incidence of injuries due to firearms rises on the fourth place (6).

Using the most widely applied system for observation and assessment of the level of consciousness called Glasgow Coma Scale (GCS), TBI is divided into the three levels. Scoring the opening of the eyes, verbal and motor response, the total sum from 13 to 15 places the patient into the group with the mild TBI. Total score from 9 do 12 places the patient into the group with moderate TBI. Severe TBI is classified with total score 8 and less (7). Studies indicate that the severity of the injury is proportional to the treatment outcomes; the more difficult injury is related with greater chance of complications and death. Patients with severe TBI are 37 times more likely to die of neurological sequels such as seizures, 12 times more often from sepsis, 4 times more often from pneumonia, and 3 times more often from other respiratory (except pneumonia) and digestive difficulties than healthy population (8). Using the combination of clinical examination and radiological diagnosis, that includes native computed tomography of the brain, it can be achieved prompt diagnosis, and therefore adequate therapy. The aim is to prevent secondary brain injury, primarily hypotension and hypoxia, in order to prevent the patients deterioration and complications like nosocomial infections and potential death (6).

Patients with severe TBI have a high risk for development of nosocomial infections. Nosocomial infections are defined as infections occurred in the hospital environment at least 48 hours from receiving patient for treatment. Approximately 9% to 37% of patients admitted to an Intensive Care Unit (ICU), will acquire one or more infections. Risk factors are invasive intensive monitoring, intravenous therapy, mechanical ventilation, and according to some studies, the release of catecholamines after stimulation of the sympathetic nervous system during brain injury that results with induction of systemic immunosuppression (9, 10). The incidence of people with severe TBI is only 10%, but is associated with the highest mortality rate which ranges between 30% and 54% (11). About 50% od patients with severe TBI develops at least one infection as a complication of primary condition during hospitalization in ICU, resulting with fatal outcome in 28% of patients (9, 12, 13).

Nosocomial, ventilator – associated pneumonia (VAP) is the most common infection that affects patients with severe TBI. The incidence ranges between 41% to 74%. The main risk factors for this type of infection are endotracheal intubation and mechanical ventilation. During the first week of hospitalization the risk for developing VAP is 15%, and in the second week rises on 20% and more. VAP is dived into the two groups. First one is early – onset VAP that occurs in the first 48 to 72 hours from the beginning of intubation and ventilation. It is the result of microaspiration of colonized oropharyngeal secretions and it is caused by pathogens that are sensitive to antimicrobial therapy (13). The second one is late – onset VAP that develops after 72 hours from the beginning of intubation and ventilation. This type of infection is a result of long lasting intubation and ventilation, as well as prophylactic application of broad – spectrum antibiotics. Pathogens are highly virulent and multiresistant. The most common pathogen is gram – negative bacteria *Pseudomonas aerugionsa*, whose incidence reaches up to 47% (14, 15). Therapy includes de – escalating antibiotic therapy (13).

Patients with severe TBI present one of the most vulnerable group of patients for development of the second most common nosocomial infection called sepsis, whose incidence ranges between 10% and 41%. The leading cause is bacteremia, while something less frequent causes are fungemia, viremia, and parasitemia (9, 16). Early diagnostic is essential for prompt prevention and treatment of this type of infection. Diagnostic criteria for sepsis are documented or suspected infection that is associated with some of the following variables like general, inflammatory, hemodynamic, organ dysfunction and tissue perfusion variables (17, 18). Treatment includes adequate intravenous antimicrobial therapy, drainge of abscesses, debridement of necrotic tissue or removal of infected foreign body. The most common is combination of a penicillin/β – lactamases inhibitors or third – generation cephalosporins with an aminoglycosides. It is essential to maintain adequate perfusion with intravenous fluids and inotropic and vasopressor agents (18).

The third most common nosocomial infections are urinary tract infections (UTIs) that are catheter – associated, with an incidence about 15%. Studies show that bacteriuria occurs in patients who require a bladder catheter for longer than 48 hours (19). The leading pathogens are gram – negative bacteria such as *Escherichia coli*, *Enterobacter species*, *Proteus species*, *Klebsiella species*, non – lactose – fermenting bacteria such as *Pseudomonas aeruginosa*, and some other organisms such as staphylococcal species and *Enterococcus*. Bacteriuria can lead to bacteremia, and subsequently in sepsis in about 5% of the time. Therapy also includes combination of a penicillin/β – lactamases inhibitors or third – generation cephalosporins with an aminoglycosides.

Prevention of ICU – acquired UTIs is important because UTIs are associated with increased mortality (13).

The aim of this two – year retrospective study was to analyze the number of patients with isolated severe TBI hospitalized in the Intensive Care Unit of the Clinical Hospital Centre Rijeka, Croatia from 1st January 2013 to 31st December 2014, who developed infection during their hospitalization. The aim was also to analyze the type of infection and leading pathogens, as well as the duration of infection and treatment outcomes.

PATIENTS AND METHODS

This retrospective study was undertaken at Department of Anesthesiology, Reanimatology and Intensive Care, Division for Intensive Care Unit, Clinical Hospital Centre Rijeka, Croatia. It was included 67 patients with isolated severe TBI who where hospitalized in the period from 1st January 2013 to 31st December 2013, and between 1st January 2014 and 31st December 2014. General informations which included the name, surname, gender and age of every patient where considered. From 67 patients with severe TBI, 46 of them developed nosocomial infection. We analyzed GCS score at admission to the ICU, types of nosocomial infections, and the leading pathogens for every hospitalized infected patient with severe TBI during analysis of the study. We analyzed most commonly used antimicrobial drugs in treatment of infected patients, as well as the duration of infection, mechanical ventilation and treatment during the hospitalization in the ICU, so as the treatment outcomes. Privacy rights of all patients where maintained with respect to all ethical and moral standards in accordance with the Declaration of Helsinki.

We collected medical data of all patients from database of Department of Anesthesiology, Reanimatology and Intensive Care, Division for Intensive Care Unit, Clinical Hospital Centre Rijeka, Croatia. All medical records were analyzed using Microsoft Excel. Statistical analysis was performed using STATISTICA 12 (StatSoft, Tulsa, USA). For calculation of statistical significance we used Mann – Whitney non – parametric test for small independent samples, and a chi – squared test for the test of independence of two variables. $P < 0,05$ was considered statistically significant.

RESULTS

During the period of time from 1st January 2013 to 31st December 2013, at Department of Anesthesiology, Reanimatology and Intensive Care, Division for Intensive Care Unit, Clinical Hospital Centre Rijeka, Croatia, there was 36 hospitalized patients with severe TBI, out of whom 25 (69,44%) developed nosocomial infection. From 1st January 2014 to 31st December 2014, the total number of patients with severe TBI was 31, and 21 (67,74%) of them developed nosocomial infection during the hospitalization (Figure 1).

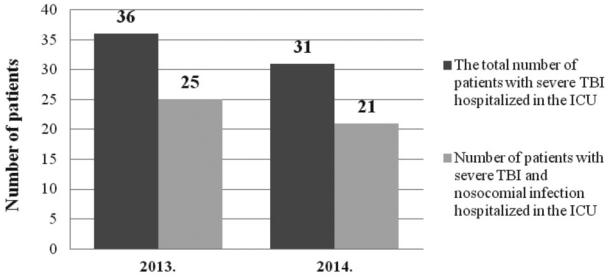

Figure 1. *The ratio of the total number of patients with isolated severe TBI compared to the number of patients with severe TBI and nosocomial infection hospitalized in the ICU during the period between 1st January 2013 and 31st December 2014*

Of the 25 patients with severe TBI and nosocomial infection that were hospitalized in the ICU during the 2013, 19 (76%) of them were male gender, and the remaining 6 (24%) were members of the female gender. Out of total number of 21 patient with severe TBI and nosocomial infection during 2014, 16 (76,19%) of them were male gender, and 5 (23,80%) of them were female gender. Overall, during 2013 and 2014, there was 35 (76,08%) members of male gender, and 11 (23,91%) members of female gender with severe TBI and nosocomial infection. There was statistically significant more male gender participant than female (Figure 2).

Of all patients with isolated severe TBI and nosocomial infection in 2013, the largest number of patients was between ages 80 and 89, and the second were patients between ages 50 and 59. The average age of patients in 2013 amounted 58,08 years, while the median was 57 years. Analyzing the year 2014, the highest number of patients was also between ages 80 and 89. Second largest group was between ages 60 and 69. The

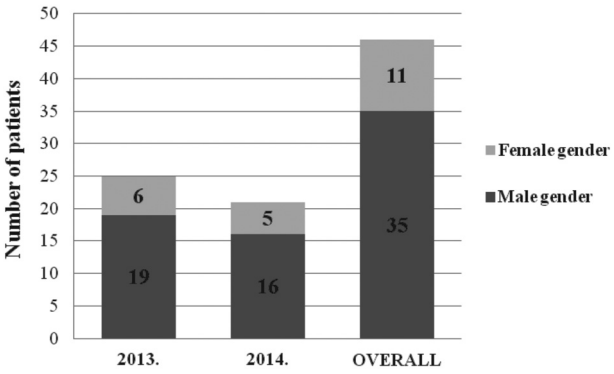

Figure 2. *The ratio of patients with isolated severe TBI and nosocomial infection hospitalized in the ICU during 2013 and 2014 according to gender*

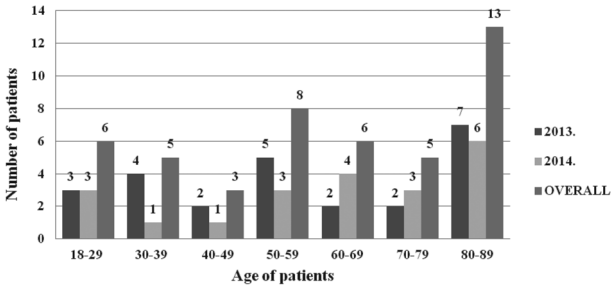

Figure 3. *The age distribution of patients with severe TBI and nosocomial infection hospitalized in the ICU during 2013 and 2014*

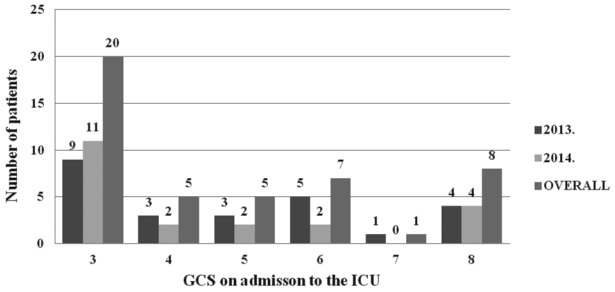

Figure 4. *GCS score on the admission to the ICU of the patients with severe TBI and subsequently developed nosocomial infection hospitalized during the year 2013 and 2014*

average age for 2014 was 57,52 years, while the median was 67 years. Overall, the largest number of patients was between 80 and 89 years old. The average age was 57,8 years, whil2013e the median was 62 years (Figure 3).

During the admission of patients with severe TBI who subsequently developed nosocomial infection in 2013, GCS for the highest number of patient accounted for 3. Also, the same GCS score amounted for the highest number of patients in 2014. Overall, for 2013 and 2014, the highest number of patients were scored GCS 3 (Figure 4).

Table 1. *The leading types of nosocomial infections in patients with severe TBI that were hospitalized in the ICU during year 2013 and 2014*

Type of the infection	2013 (n = 25)	2014 (n = 21)	OVERALL (n = 46)
Ventilator - associated pneumonia (VAP)	6	8	14
Sepsis	2	1	3
Urinary tract infection (UTI)	7	3	10
Other infections - ordinary and mucopurulent bronchitis	10	9	19

Respiratory tract infections are proved to be the most common. Leading nosocomial infection for the year 2013 and 2014 was ordinary and mucopurulent bronchitis (41,30%). Second most common infection was VAP (30,43%). The following are UTIs, which were presented in the 21,73%, and sepsis, which accounted for 6,52% (Table 1.). In the year 2013, the leading cause of respiratory tract infections were bacteria Proteus mirabilis and Pseudomonas aeruginosa. Sepsis was caused by Candida albicans and Proteus mirabilis, while Escherichia coli was the leading cause of the UTIs (Table 2.). Analyzing the year 2014, Pseudomonas aeruginosa was proved to be the major cause of respiratory tract infections and sepsis. Bacteria Entero-

Table 2. *Overview of the leading pathogens considering the type of infection in patients with sever e TBI hospitalized in the ICU in the period between 1st January and 31st December 2013.*

Pathogen	Ventilator - associated pneumonia (VAP)	Sepsis	Urinary tract infections (UTI)	Other infections (ordinary and mucopurulent bronchitis)
Escherichia coli	1	0	4	1
Pseudomonas aeruginosa	0	0	0	3
Klebsiella pneumoniae	0	0	2	2
Proteus mirabilis	2	1	0	1
Proteus vulgaris	0	0	0	1
Staphylococcus aureus	1	0	0	1
Enterococcus faecalis	0	0	1	0
Haemophilus influenzae	0	0	0	1
Stenotrophomonas maltophila	1	0	0	0
Serratia marcescens	0	0	0	0
Candida albicans	1	1	0	0
OVERALL	6	2	7	10

Table 3. *Overview of the leading pathogens considering the type of infection in patients with sever e TBI hospitalized in the ICU in the period between 1st January and 31st December 2014.*

Pathogen	Ventilator - associated pneumonia (VAP)	Sepsis	Urinary tract infections (UTI)	Other infections (ordinary and mucopurulent bronchitis)
Escherichia coli	0	0	1	0
Pseudomonas aeruginosa	4	1	0	4
Klebsiella pneumoniae	0	0	0	0
Proteus mirabilis	0	0	0	1
Proteus vulgaris	0	0	0	0
Staphylococcus aures	0	0	0	0
Enterococcus faecalis	1	0	2	0
Haemophilus influenzae	0	0	0	0
Stenotrophomonas maltophila	0	0	0	0
Serratia marcescens	2	0	0	2
Candida albicans	1	0	0	2
OVERALL	8	1	3	9

coccus faecalis is determined as leading cause of UTIs (Table 3.).

The most commonly used antimicrobial medications to treat infected patients in the ICU during 2013 and 2014, were the beta – lactam antibiotics involving meropenem, cloxacillin, and a combination of piperacillin and tazobactam. In the second place where cephalosporins such as cefazolin, cefepime, ceftriaxone. Less frequently used group of antimicrobial medications were non – beta lactam antibiotics including teicoplanin and vankomycin. Other used medications where aminoglycosides, quinolones, medications against anaerobic bacteria and fungal infection (Figure 5).

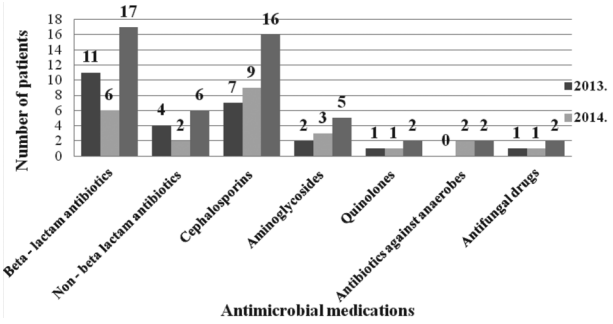

Figure 5. *Antimicrobial medications used in the treatment of patients with nosocomial infection and isolated severe TBI hospitalized in the ICU during the year 2013 and 2014*

Duration of infection in days, overall in the 2013 and 2014, was for the majority of patients longer than 7 days with an average of 5,77 days (Figure 6).

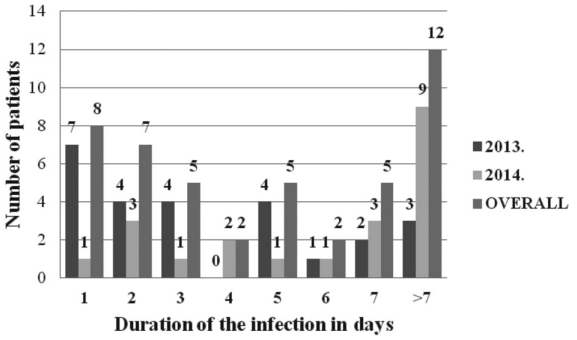

Figure 6. *Duration of the infections in days in patients with isolated severe TBI and nosocomial infection hospitalized in the ICU during 2013 and 2014*

Overall in 2013 and 2014, duration of mechanical ventilation for patients with infection was for most of them more than 10 days (Figure 7).

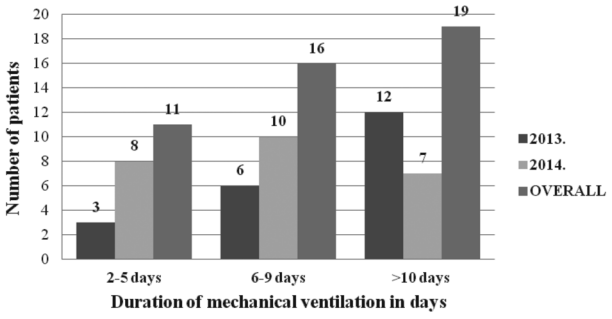

Figure 7. *Duration of mechanical ventilation in days in patients with isolated severe TBI and nosocomial infection hospitalized in the ICU during 2013 and 2014*

The average duration of treatment of patients in the ICU, was in 2013 and 2014 overall 10,475 days (Figure 8).

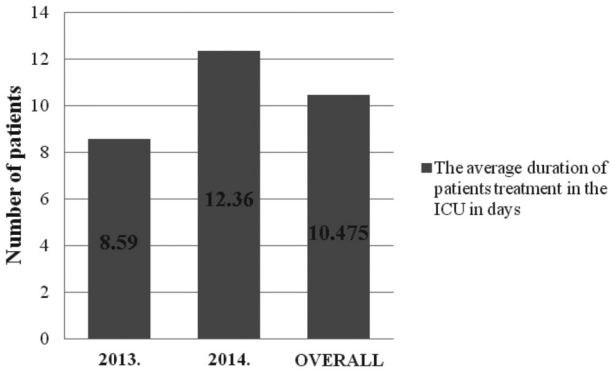

Figure 8. *The average duration of treatment of patients with nosocomial infetion and isolated severe TBI hospitalized in the ICU during 2013 and 2014*

From 46 patients with isolated severe TBI and nosocomial infection, 29 (63,04%) was dismissed to the Department of Neurosurgery. For 16 (34,78%) patients treatment outcome was lethal, and 1 (2,17%) patient was dismissed to the Department of Pulmolonary Medicine (Figure 9).

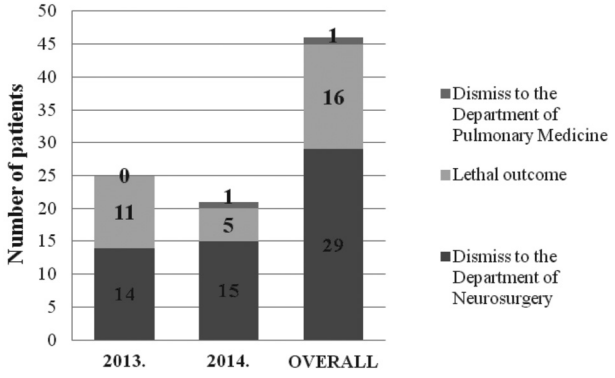

Figure 9. *Treatment outcomes in patients with severe TBI and nosocomial infection hospitalized in the ICU during 2013 and 2014*

DISCUSSION

Based on the results of analysis that was undertaken at the Department of Anesthesiology, Reanimatology and Intensive Care, Division of Intensive Care Unit, Clinical Hospital Centre Rijeka in a period of time between 1st January 2013 and 31st December 2013, the incidence of nosocomial infections in patients with severe TBI was 69,44%. During the period between 1st January 2014 and 31st December 2014, incidence was 67,74%. These results show a higher incidence of nosocomial infections in patients with severe TBI compared to global studies, where the percentage of infections in patients with severe TBI is about 50% (9, 12, 13). The results can be explained by the presence of multiresistant pathogens that are found in the ICU, and are transmitted primarily through medical personnel, despite their efforts to maintain hygiene and antiseptic rules. Medical personnel must be familiar with the standards of control of hospital infections.

According to gender of infected patients with severe TBI, during 2013 and 2014, overall was hospitalized 76,08% members of male gender, and the remaining 23,09% were female members. There was statistically significantly more male gender members than female ($p < 0.05$). Results are confirmed by the fact that members of male gender have 1,4 times higher risk for the development of severe TBI, and consequently of nosocomial infections (5).

Analyzing the age distribution of patients with nosocomial infection and severe TBI, it was observed that the incidence of nosocomial infections was highest at the oldest patients between ages 80 and 89. On the second place was working population aged between 50 and 59 years old, and in third young people aged between 18 and 29 years old. The average age of all infected patients with severe TBI was 57,8 years, and median was 62 years. Comparing the results with the global literature, we confirm that the most vulnerable group of patients is the one aged 75 and more, as well as the population aged between 15 and 30 years old (5). An average age of 57,8 years is associated with the fact that it is the active working population, increasing on that way the risk of accidents and consequent injury.

Out of 46 patients with nosocomial infection and severe TBI, 20 (43,47%) of them had on the admission to the ICU, GCS score 3. Severe TBI is defined as GCS score 8 and less. The lower GCS score is proportional with higher risk for development of complications, including nosocomial infections, thus increasing the risk of lethal outcome (8).

From all 46 patients with nosocomial infection and severe TBI, 14 (30,43%) had been diagnosed with VAP, 3 (6,52%) of them with sepsis, and UTI had 10 (21,73%) patients. The leading infection was ordinary and mucopurulent bronchitis which occurred in a total of 19 (41,30%) patients. As is confirmed by other studies, including our own, the most common are respiratory tract infections which predispose endotracheal intubation and mechanical ventilation. Ordinary and mucopurulent bronchitis consequently leads to VAP. Following infections are sepsis and UTI, and that corresponds to the incidence recorded in the world literature (9, 12, 13, 20, 21). The leading pathogens were *Proteus mirabilis* in a year 2013, and *Pseudomonas aeruginosa* for the year 2014. These bacteria belong to the group of gram – negative multiresistance pathogens that are the leading etiological causes of nosocomial infections (12, 13).

Most commonly used antimicrobial drugs were beta – lactamic group of antibiotics, and cephalosporins, which is in accordance with the world literatue (13).

The average duration of infection, overall in 2013 and 2014, was 5,77 days. Overall, duration of mechanical ventilation was more than 10 days, and average length of patients treatment in days was 10,475 days. It is essential to start with adequate treatment and to set early tracheostomy so the hospitalization can be shorter, and consequently the risk of negative treatment outcomes can be reduced (12).

Treatment outcome was for 29 (63,04%) of 46 patients dismiss to the Department of Neurosurgery, for 16 (34,78%) patients outcome was lethal, and 1 (2,17%) patient was dismissed to the Department of Pulmonary Medicine. According to global literature, mortality from severe TBI is between 31% and 54%, and if it is complicated with nosocomial infection it rises to 70% (11,13). Comparing this records with results of our analysis, we conclude that lethal outcome in patients with nosocomial infection and severe TBI is at the lower limit, which indicates on early and adequate therapy and positive treatment outcomes.

CONCLUSION

Based on our retrospective study, we can conclude that the incidence of nosocomial infections in patients with severe TBI can be equated with an incidence that is recorded in the global literature. The leading cause of this posttraumatic complications is presence of multiresistant pathogens in the ICU. Severe TBI complicated by nosocomial infections leads to prolonged hospitalization, thus raising the cost of treatment. On that way, nosocomial infections in patients with severe TBI are becoming one of the major global health problems. The emphasis must be set on prevention of nosocomial infections, where the key role has medical personnel of the ICU. Maintenance of hygiene and antiseptic rules is one way how the nosocomial infections can be prevented among this difficult group of patients. Medical personnel must be familiar with the standards of control of hospital infections. Also, proper care of the patient such as placing the patient in the appropriate position, and use of a mobile bed, may help prevent the development of nosocomial infections. Already developed nosocomial infection should be recognized and adequately treated in order to improve patients treatment course, and to reduce the number of potential negative treatment outcomes.

DECLARATION OF INTEREST. None.

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ABBREVIATIONS

GCS — Glasgow Coma Scale
ICU — Intensive Care Unit
TBI — Traumatic Brain Injury
UTI — Urinary Tract Infection
VAP — Ventilator – Associated Pneumonia

Sažetak

UČESTALOST BOLNIČKIH INFEKCIJA KOD PACIJENATA SA IZOLOVANOM TEŠKOM POVREDOM MOZGA

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Uvod: Traumatska povreda mozga je vodeći uzrok smrti kod dece i odraslih u razvijenim zemljama. Teška traumatska povreda mozga se Glasgow koma skalom klasifikuje skorom 8 i manje. Oko 50% pacijenata sa teškom traumatskom povredom mozga razvije barem jednu infekciju kao komplikaciju primarnog stanja tokom hospitalizacije u Jedinici intenzivnog lečenja, što u 28% slučajeva rezultira fatalnim ishodom. Vodeća infekcija kod pacijenata sa teškom traumatskom povredom mozga je pneumonija vezana za asistiranu ventilaciju, sa incidencom 41% i 74%. Slede sepsa i infekcija urinarnog trakta.

Cilj: Analizirati broj pacijenata sa bolničkom infekcijom i izolovanom teškom traumatskom povredom mozga, hospitalizovanih u Jedinici intenzivnog lečenja Klinike za anesteziologiju, reanimatologiju i intenzivno lečenje Kliničko bolničkog centra Rijeka, Hrvatska, od 31. januara 2013. do 31. decembra 2014. godine.

Pacijenti i metode: Dvogodišnja retrospektivna studija je uključila 46 pacijenata sa izolovanom teškom traumatskom povredom mozga i bolničkom infekcijom, hospitalizovanih u Jedinici intenzivnog lečenja Klinike za anesteziologiju, reanimatologiju i intenzivno lečenje Kliničko bolničkog centra Rijeka, Hrvatska, od 31. januara 2013. do 31. decembra 2014. godine. Svi medicinski podaci prikupljeni su iz Jedinice intenzivnog lečenja Kliničko bolničkog centra Rijeka, Hrvatska.

Rezultati: Od 67 pacijenata sa izolovanom teškom traumatskom povredom mozga, 46 (68,65%) od njih dobilo je bolničku infekciju. Broj muških pacijenata je statistički značajno veči od broja ženskih pacijenata ($p < 0.05$). Prosečne godine starosti pacijenata su 57,8 godina. Vodeće su su bile infekcije respiratornog trakta. Gram – negativne bakterije, *Proteus mirabilis* i *Pseudomonas aerugnonsa*, su se pokazale kao najčešći patogeni uzročnici. Prosečno trajanje infekcije bilo je 5,77 dana. Trajanje mehaničke ventilacije je kod većine pacijenata trajalo više od 10 dana. Prosečno trajanje lečenja kod svih 46 pacijenata bilo je 10.475 dana, kod 16 (34,78%) od njih, ishod lečenja bio je letalan.

Zaključak: Bolničke infekcije postaju veliki ozbiljan problem javnog zdravlja. Akcenat mora biti na prevenciji koja uključuje održavanje higijene i poštovanje pravila antisepse među medicinskim osobljem Jedinice intenzivnog lečenja. Već razvijene infekcije moraju biti adekvatno lečene kako bi se redukovali negativni ishodi lečenja.

Ključne reči: izolovana traumatska povreda mozga, Glasgow koma skala, Jedinica intenzivnog lečenja, bolničke infekcije, gram – negativne bakterije.

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Original article

OCULAR HYPERTENSION RISK FACTORS AND THERAPY?

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Abstract: **Introduction/Aim:** The goal of our study was to analyze the epidemiological characteristics of ocular hypertension, as well as the influence of chronic risk factors on glaucoma development (conversion to glaucoma). We tried to make some entries for solving this complex ophthalmological problem. **Material /Methods:** From 2009 to 2015, a retrospective control study was performed on 121 patient with diagnoses of bilateral ocular hypertension and without disease progression/conversion of glaucoma (by standard protocols of diagnosis and basic procedures) on tertiary level at Clinic of Ophthalmology, Clinical Centre of Kragujevac, Serbia. The authors analyzed epidemiological characteristics: sex, age groups, positive/negative family history and personal history with chronic risk factors (one and/or two) of ocular hypertension. The data obtained from this study were statistically analyzed in SPSS program, version 20.0. **Results:** As for the patients, 69 of them (57.02%) were male and 52 female (42.98%). Dominant age group was between 40 9 (42.15%) and then group between 50 9 (40.50%) years of age. Anamnesis data indicated the absence of family anamnesis in 71 (58.68%) patients. Risk factors for ocular hypertension were presented in 103 (85.13%) patients, 18 of them (14.87%) did not respond. One risk factor - cardiovascular disease was noted in 83 (68.59%), two risk factors - cardiovascular diseases and diabetes mellitus in 20 patients (16.53%) and PEX syndrome at other respondents. **Conclusion:** Ocular hypertension is not a common disease, but with risk factors, such as older age, positive family history, and chronic risk factors syndicated, represents a serious clinical and social problem, so the question remains for ophthalmologists - pro or against therapy? Those in favor of therapy would state the safety and protection from conversion/progression of glaucoma; but those against therapy would only mention adequate monitoring of patients.

Key words: ocular hypertension, epidemiology characteristics, risk factors, therapy.

INTRODUCTION/AIM

Ocular hypertension is defined as intraocular pressure higher than 22 mmHg with normal clinical appearance of the optic nerve head and no defects in frequency doubling by the perimetry tests. (1).

The disease doesn't prefer gender, but is more common in men, of middle-older-age, mostly without a positive family history and with associated the chronic risk factors, so it is up to the clinics to decide whether they are for or against the treatment (2). If the therapy is not applied, the mandatory general principal of ophthalmologist is to monitor their intraocular pressure, optic head condition and visual field defects (3).

The aim of this study is to determine what can create the risk of harmless ocular hypertension progression towards multi factorial glaucoma diseases of today, and to present an important discovery.

MATERIAL AND METHODS

The retrospective study conducted in the period from 2009 to 2015, included 121 patient from Clinic of Ophthalmology in Kragujevac, those with bilateral ocular hypertension but without disease progression at referent tertiary level as determined by the ambulatory-polyclinic observation of the patients. Patients were selected and followed up using standard protocols of patients who came to the Clinical Centre of Kragujevac, Serbia.

The criteria according to which the patients were selected to be included in the study were: IOP higher than 22 mm Hg - ocular hypertension, daily fluctuations and target IOP, but without functional and morphological damage and the progression of disease.

The patients who were functional mono-oculus for any reason, those with secondary glaucoma, as well as those who had any eye-surgical treatment were excluded.

IOP values were measured by Goldman applanation tonometer, while CCT values were determined using the ultrasonic pachymeter (ultrasonic pachymeter by renowned German manufacturer - Heidelberg Engineering, referent values 500–555 μm).

By measuring the central corneal thickness, we excluded the possibility that among our patients with thicker corneas there were candidates with ocular hypertension and therapy, and that among our patients with thinner corneas were potentials glaucoma patients with determined necessity for the therapy.

The regional Ethic Committee of Clinical Centre in Kragujevac (central Serbia) approved this study.

Patients were categorized into groups based on intraocular pressure, daily fluctuations, target IOP, cup-to--disc ratio (obtained by indirect fundus examination - morphological damages), and visual field parameters (obtained by three Octopus perimetry tests - functional damages).

Authors analyzed the epidemiological characteristics: sex, age group, family history related to ophthalmologic problems (ocular hypertension or glaucoma) and the personal history with the chronic risk factors (cardiovascular diseases, diabetes mellitus and PEX syndrome).

The data obtained in this study were statistically analyzed in the SPSS program, version 20.00. The frequency analysis was performed by Chi-square test (p-values include the exact value unless it is less than 0.05).

RESULTS

There was no statistically significant difference between the sex representation in our study - 69 males (57.02%) and 52 females (42.98%) ($\chi^2 = 2.338$, $p = 0.122$), (Table 1).

Dominant age groups were between 40-49 (42.15%) and 50-59 (40.50%) years of age (the average age was 47.31 years ± 0.79). The analysis of age indicated a statistically significant difference between age groups ($\chi^2 = 13.950$, $p = 0.001$), (Table 1). Authors also conducted the partial analysis and found that the number of patients in the first age group was significantly different from the number in the second ($\chi^2 = 12.500$, $p = 0.000$), and the third age group ($\chi^2 = 1.200$, $p = 0.001$). However the number of patients in the second and third age groups were slightly different ($\chi^2 = 0.040$, $p = 0.841$), so that there was no statistical significance.

The anamnesis data indicated that 71 (58.68%) patient had no family history with ophthalmologic problems, while 50 (41.32%) respondents had such history, (Table 1). The analysis by positive/negative family history indicated no statistically significant difference ($\chi^2 = 3.645$, $p = 0.056$). The conclusion that family history had no influence could be disputable, because the p-value was very close to the limit value of 0.05. The risk factors were noticed in 103 (85.13%) patients, while 18 (14.87%) of them did not show any.

We had 83 (68.59%) patients with one chronic risk factor (cardiovascular diseases) and 20 (16.53%) patients with two chronic risk factors (cardiovascular diseases and diabetes mellitus), while PEX syndroma was noted in other patients - 20 (14,88%). There were no patients with all three risk factors, (Table 1).

Our results indicated that the largest number of patients had one risk factor: cardiovascular disease or diabetes mellitus; but the small number of them had two risk factors (cardiovascular disease and diabetes mellitus), with a statistically significant difference in number of these patients – ($\chi^2 = 38.534$, $p = 0.000$). Among the patients with one risk factor for ocular hypertension, patients with PEX and diabetes mellitus were similar and with statistically significantly difference ($\chi^2 = 9.389$, $p = 0.002$) in correlation with patients with only cardiovascular disease. These date indicated that patients with PEX or diabetes mellitus had

Table 1. *The epidemiological characteristics (age, gender, family history) and risk factors for ocular hypertension (cardiovascular diseases, diabetes mellitus, PEX syndroma)*

Age	30–39 years	40–49 years	50–59 years	Sex		Family history		Risk factors			Number of patients
	Ocular hypertension	Ocular hypertension	Ocular hypertension	M	F	+	–	Cardiovas. diseases	DM	PEX Sy	
2009–2011	2	13	12	14	13	12	15	4	5	10	27 22.31%
2011–2013	3	15	15	18	15	13	20	6	5	15	33 27.28%
2013–2015	16	23	22	37	24	25	36	21	13	24	61 50.41%
Σ6	21 17.36%	51 42.15%	49 40.50%	69 57%	52 43%	50 41%	71 59%	Σ31	Σ23	Σ49	Σ121

different other conditions which can ameliorate eye condition- positive condition for ocular hypertension development. The analysis showed that incidence of cardiovascular disease and diabetes mellitus were not significantly different ($\chi^2 = 1.185$, $p = 0.276$). It also indicated that greater number of our patients had cardiovascular disease than diabetes mellitus, but without statistical significant difference ($\chi^2 = 4.050$, $p = 0.044$).

Correlation of the risk factors and the values of intraocular pressure was not the aim of our study.

All CCT values, determined by ultrasonic pachymeter, were in referent values 500–555 ìm, as daily fluctuations and target IOP, so we did not use those data for the statistical analysis, too.

The treatment of ocular hypertension is an intrigant question. We cannot exactly give the suggestion with the very beginning of the therapy, as well as which medications can be used in these cases. Our suggestion is to watch over all of the results and measurements, with the deep insight in the health of every patients. The treatment of ocular hypertension was not the aim of this study, because we merely wanted to clarify the risk factors.

DISCUSSION

A number of patients did not differ significantly by gender, but differed by age groups in favor of the second and third groups (the older patients). It was concluded that the older patients (as it is commonly known), and the patients with one or two risk factors needed the anti glaucoma therapy as the preventive therapy for the diagnosis of ocular hypertension.

Negative family history also had a great impact on the potential number of the other risk factors, such as cardiovascular diseases, diabetes mellitus and PEX syndrome.

The risk factors are the main in the evolution of ocular hypertension and represent an obstacle in the progress. They are also taking into the account making decisions about the treatment for prevention of the disease progression or conversion in glaucoma.

Many authors determined the prevalence of pseudoexfoliation syndrome (PEX) in Lithuanian urban population and its association with ischemic heart disease (IHD), arterial hypertension (AH) and diabetes mellitus (DM). No clear PEX syndrome association with IHD, AH and DM was proven after controlling the effect of age (1).

Ocular hypertension is frequent (about 3.6%) in the adult Chinese population with the age of 40+years. Associated factors are diabetes mellitus and arterial hypertension. The diabetes mellitus and arterial hypertension should be checked in ocular hypertensive subjects (2).

However, some of studies available on systemic findings in glaucoma patients are contradictory, making further research necessary to identify the exact role of such disturbances in pathogenesis of the damage. Moreover, it is not always clear whether we are dealing with coincidence or true association between glaucoma and the particular systemic disease, which is why the authors presented this retrospective study (3).

Popa et al., cited that the arterial hypertension, diabetes mellitus, atherosclerosis and vasospasms in developed glaucoma were the main risk factors (4). We considered the same risk factors to determine the development from clinical diagnosis of harmless ocular hypertension to the potential glaucoma.

Ocular hypertension is present when intraocular pressure is above the range considered as normal (22 mmHg), without detectable changes of visual field and no damage to the eye structures. The term is used to distinguish between people with elevated pressure but without a developed glaucomatous disease and those without it. There is an increased risk for glaucoma among the patients with elevated ocular tension and that is why, according to the authors opinion, regular comprehensive eye examinations are essential for the overall eye health (5).

Evaluating the results of ocular fundus examinations for signs of hypertensive retinopathy in combination with the assessment of the presence or absence of other known vascular risk factors may allow clinicians to further individualize the risk profile of each individual patient, thus permitting more accurate risk stratification and potentially guiding treatment strategies, as to be used in our future researches (6).

These data suggested that, although diabetes and metabolic abnormalities may be associated with the small increase in intraocular pressure, they were not significant risk factors for glaucomatous optic neuropathy (7, 8). The other authors showed that metabolic syndrome was a risk factor for high ocular tension (9), which was also the case with our patients, as to be used in our future researches, too.

Zhao et al., recommended a single evening dose of the combination of latanoprost and timolol in reducing IOP in Chinese subjects with primary open angle glaucoma or ocular hypertension, whose intraocular pressure was insufficiently reduced with β-blocker mono therapy or β-blocker-based dual therapy (10), which according to our opinion is justified when the transmission from harmless ocular hypertension to glaucoma has already taken place.

Tzamalis A. et al., indicated that the type of tonometry could also help us in making a decision in which cases to treat ocular hypertension. The difference between dynamic contour tonometry (DCT) and Gold-

mann applanation tonometry (GAT) IOP measurements is found statistically significantly higher in patients receiving Carbonic Anhydrase Inhibitors (CAIs) either as monotherapy or as a part of a combined ocular hypotensive treatment, while DCT and GAT readings remain unaffected (11).

Patients with diabetes mellitus, as well as with cardiovascular disease should be considered as high risk patients for converting ocular hypertension to glaucoma. Therefore, it is necessary to conduct serious examinations in order to decide when to start glaucoma treatment (12, 13).

Based on our findings and other relevant data, it is our suggestion that protocols for ocular hypertension should be precisely filed allowing ophthalmologists to have exact entries for deciding when to treat ocular hypertension and when to establish glauocomatous diagnosis (14).

Long-term IOP fluctuations do not appear to be significantly associated with the risk of developing glaucoma in untreated ocular hypertensive patients. With this study we also established that IOP fluctuation did not exactly determine the conversion of ocular hypertension in glaucoma (15).

St mer et al., noted that we should treat the patients with IOP higher than 32 mm Hg, but also that we should seriously consider their ophthalmological condition by using some kind of risk calculator. It is necessary to consider the risk factor but we also need to take into account the IOP values. The principal of atchful waiting is the best for the patients with ocular hypertension, and the treatment should start immediately if morphological or functional progression has been noted (16).

The data suggested that also we must consider all risks, as well as benefits and alternatives for this serious ophthalmological problem (17, 18).

Studies in this ophthalmological area are very interesting for ophthalmologists because they help us resolve very difficult problems. The EGPS (European Glaucoma Prevention Study) did not demonstrate that reducing intraocular pressure with dorzolamide actually prevented the onset of glaucoma, compared to the individuals receiving a placebo. The investigators of the OHTS (Ocular Hypertension Treatment Study) found that the treatment of ocular hypertension could be delayed with topical medication when treated patients were compared with an observation group. EGPS also suggested that age, thin corneal thickness measurements, large cup-to-disc ratio and mean IOP are the main criteria for determining the treatment. However, the ultimate decision when to apply the treatment can also be determined by other factors such as life expectancy, the general health of the patient and the number of risk factors (19).

It is also very important to determine the target IOP for every individual patient. Target IOP can presume the outcome of ocular hypertension (20).

CONCLUSION

Ocular hypertension is often missed to be diagnosed as a disease, due to the presence of a number of risk factors such as age, associated chronic risk diseases, etc, which poses a dilemma before ophthalmologists, to apply a therapy or not?

The question of the therapy for ocular hypertension stays open for now and only adequate monitoring and more frequent controls of these patients can help us to detect the disease in early stage and proceed with the initial therapy that would serve as a preventive therapy against individual disease conversion/progression. If we decide not to apply the therapy to our ocular hypertensive patients, we then definitely should proceed with monitoring them through ophthalmological and cardiovascular examinations.

With this study the authors attempted to determine the risks of harmless ocular hypertension progressing into glaucoma disease. The results can serve for establishing more solid grounds for making decision in relation to the application of therapy and for further investigations into this matter.

Abbreviations

PEX syndrome — pseudoexfoliative syndrome
IOP — intraocular pressure
CCT — central corneal thickness
CVD — cardiovascular disease
DM — diabetes mellitus
IHD — schemic heart disease
AH — rterial hypertension
EGPS — European Glaucoma Prevention Study
OHTS — Ocular Hypertension Treatment Study

Conflict of interest

We confirm that no actual or potential conflict of interest exists in relation to this article.

Sažetak

OKULARNA HIPERTENZIJA — FAKTORI RIZIKA I TERAPIJA?

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Uvod/Cilj: Cilj studije je bio da se analiziraju epidemiološke karakteristike okularne hipertenzije, kao i uticaj hroničnih faktora rizika za okularnu hipertenziju (konverzije u glaukom). Pokušali smo da napravimo neke odrednice za rešavanje ovog kompleksnog oftalmološkog problema.

Materijal i Metode: Retrospektivna, kontrolisana studija u periodu od 2009. do 2015. uključila je 121 pacijenta sa obostranom kliničkom dijagnozom okularne hipertenzije, bez progresije bolesti/konverzije u glaukom, upotrebom standardnih protokola i osnovnih dijagnostičkih procedura na tercijalnom nivou, Klinike za Oftalmologiju, Kliničkog Centra Kragujvac, Srbija. Analizirane su epidemiološke karakteristike: pol, starosne grupe, pozitivna/negativna porodična anamneza i individualni hronični faktori rizika (jedan i/ili dva) za okularnu hipertenziju. Podaci studije su statistički obrađeni i analizirani u SPSS programu, verzija 20,00.

Rezultati: Od ukupnog broja pacijenata, muškaraca je bilo 69 (57,02%), a žena 52 (42,98%). Dominantna starosna grupa je bila od 40–49 godina sa najvećom učestalošću pacijenata 42,15%, a zatim starosna grupa od 50–59 godina sa učestalošću 40,50%. Anamnestički podaci ukazuju da je 71 pacijent (58,68%) bilo bez pozitivne porodične anamneze. Faktori rizika okularne hiperztenzije, kao hronične bolesti su nađeni kod 103 (85,13%), a bez kod 18 (14,87%) pacijenata. Sa jednim faktorom rizika (kardiovaskularna bolest) je bilo 83 (68,59%), sa dva faktora rizika (kardiovaskularna bolest i šećerna bolest) je bilo 20 (16,53%), a sa PEX sindromom ostali ispitanici. **Zaključak:** Okularna hipertenzija kao samostalno oboljenje nije česta, ali sa faktorima rizika, kao sto su starije doba, pozitivna porodična anamneza i udruženi hronični faktori rizika (jedan i/ili dva), predstavlja ozbiljan kliničko-socijalni problem, a pred oftalmologe postavlja pitanje, za ili protiv terapije? Odgovor za terapiju, je zaštita od konverzije i progresije u glaukom, a odgovor protiv terapije, je samo adekvatno praćenje pacijenata.

Ključne reči: okularna hipertenzija, epidemiološke karakteristike, faktori rizika, terapija.

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THE CONNECTION BETWEEN PERFECTIONISM AND ANXIETY IN UNIVERSITY STUDENTS

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Abstract: **Introduction:** Perfectionism is a relatively stable personality trait which refers to setting high personal standards and the pursuit of perfection. Anxiety as personality trait represents propensity to observe objectively harmless situations as endangering and to react signifficantly more intensive than the particular situation requires. Earlier results have shown positive correlation between exam anxiety and negative perfectionism (fear of failure). Also, some gender differences where found regarding perfectionism and anxiety, showing girls as more anxious and more perfectionists than boys.

Aim: The aim of this research was to examine if there is any correlation between perfectionism and anxiety, what is it's level and direction. Also, we wanted to examine if there are any gender differences regarding these two personality traits.

Method: Systematic non-experimental research. The study involved 202 students of Belgrade University, 158 girls (78%) and 44 boys (22%). Perfectionism level was measured with Multidimensional Perfectionism Scale, by Frost et al., while anxiety was measured with Enler Multidimensional Anxiety Scale - Trait. Statistical analysis included Pearson correlation and t-test of independent samples.

Results: The results show moderate positive correlation between anxiety and perfectionism ($r = 0.29$, $p = 0.01$), and slightly higher positive correlation between anxiety and negative aspects of perfectionism ($r = 0.40$, $p = 0.01$). There is a gender difference shown in anxiety level between female and male students, i.e. Girls have shown significantly higher anxiety level than boys ($t = 3.39$, $p < 0.01$, $\eta^2 = 0.05$). Regarding perfectionism, only significant gender difference was on the subdimension doubt about the action ($t = 2.11$, $p = 0.04$, $\eta^2 = 0.02$), showing girls as more likely to express this trait than boys.

Conclusion: Based on this research we conclude that more anxious persons are more of perfectionists (especially negative perfectionists) than those who are less anxious. Also, our results describe female students as generally more anxious than male students.

Keywords: perfectionism, anxiety, gender differences, connection.

INTRODUCTION

Perfectionism is a relatively stable personality trait which refers to setting high personal standards and pursuit of perfection (1). Hewit and Flett (2) thought perfectionism represents striving for flawlessness, which in extreme cases extends to all aspects of life, while Burns (3) thought perfectionism in all cases of non-adaptive and undesirable traits. Today, there are also authors who strongly doubt perfectionism can be positive, healthy and functional, i.e. adaptive (1). Various authors agree that perfectionism is a stable trait, independent of the current emotional state of the person, which was confirmed by studies (1, 2, 4). Alfred Adler spoke about the innate aspiration for perfection, which is the main driving force of personality development (5). In the seventies and eighties, perfectionism was generally considered negative trait and in this period of time it was mainly associated with poor outcomes (low self-esteem, procrastination, guilt, shame and feelings of failure) or psychopathological phenomena (addictions, depression, anorexia, personality disorders) (1, 6). During the nineties, perfectionism was mostly described as a multidimensional construct, so accordingly, new perfectionism scales were multidimensional too (2, 7). Factor analysis of these tests showed that all dimensions may be reduced to two factors: one was related to positive aspirations, and the other was related to maladaptive evaluation concerns (1). Slade and Owens (8) distinguish positive perfectionism, which is the result of striving for success and negative perfectionism, which is due to fear of failure, and Hamacheck (9) cal-

led these normal and neurotic perfectionism. Perfectionism was associated with various problems and phenomena in different studies, such as global self-esteem, depression level, demographic variables (10, 11). These studies showed connection between the positive aspects of perfectionism and global self-esteem (10), as well as positive correlation between negative aspects of perfectionism and depression level. It was also found that people living in the cities and those with better economic status set their personal standards significantly higher (sub dimension of positive perfectionism) (11). The same study (11) revealed gender differences regarding perfectionism, showing that girls had significantly higher scores on scales of positive perfectionism than boys (11).

Anxiety is a term used in a wide variety of meanings. It can be defined as a state of distressing and unpleasant expectations and premonition, worry and uncertainty, which lasts longer than fear, where feelings of vulnerability arise from either person's environment or person's internal conflicts and can lead to significant psychological and somatic changes (12). Spielberger's model of anxiety distinguishes state anxiety and general anxiety - anxiety as a trait. State anxiety is subjective, consciously perceived state of fear and worry associated with increased alertness of the autonomic nervous system, and can be triggered by an external or internal stimulus perceived as a danger or a threat (13). Anxiety as a trait is a tendency to perceive objectively harmless situations as threatening and to react to them much more intensively than a situation objectively requires (14). Endler's interaction model also distinguishes trait anxiety and state anxiety, but presumes their multidimensionality (15). In this study we considered anxiety as trait. Understanding anxiety is essential in understanding of either normal or pathological functioning of personality. Among other things, researchers have found negative correlation between anxiety and self-respect (14), and positive correlation between anxiety and depression (16). Anxiety may have a protective function, since it was significantly negatively correlated with the propensity to make risking decisions (17). Some studies indicate to gender differences in emotional reactions and anxiety occurrence. For instance, study (14) in a sample of young musicians showed that girls react more anxious to some stress. Very important fact for our research is the result showing positive correlation between anxiety in test situation and negative perfectionism (4).

THE AIM OF THE STUDY

The aim was to examine if there are any correlations between perfectionism and anxiety and their subscales, and then to determine its intensity and direction. We also wanted to examine if there are any gender differences regarding these two personality traits.

METHOD

This was a systematic non-experimental research. We collected data through questionnaires in Belgrade in October and November 2013. The survey was conducted on a sample of Belgrade University students. Of 202 students 158 or 78% were girls and 44 or 22% were boys.

To estimate perfectionism level we used Multidimensional Perfectionism Scale (MPS), constructed by Fost and associates, and translated to Serbian and adapted by Stojiljković and Maksić (18). The coefficient of reliability of the total score, measured by the authors, was 0.90, and the reliability of subscales from 0.77 to 0.93. The instrument contains 35 claims and the task of respondents is to check the degree of agreement with the statement on a five-point Likert scale. Information gathered on this scale tells us about the total perfectionism level and its subdimensions. The scale includes the following subscales: concern over mistakes, personal standards, parental expectations, parental criticism, doubts regarding action and organization. The authors have conducted factor analysis, which showed that personal standards and organization may be considered subdimensions of positive perfectionism, and concern over mistakes, parental expectations, parental criticism, as well as doubts concerning the action as dimensions of negative perfectionism (7). Higher scores on MPS indicate higher perfectionism.

Anxiety level was estimated using Endler Multidimensional Anxiety Scale - Trait (EMAS-T). Scale refers to anxiety as a trait and it was constructed by the Endler and associates as one of the three parts of Endler's Multidimensional Anxiety Scales, in addition to the scale relating to anxiety as a state (EMAS -S) and scale related to the perception of the type and intensity of the threat posed by specific situation (EMAS - P). EMAS-T scale consists of four subscales: social evaluation/assessment, physically dangerous situations, new/unfamiliar situations and everyday situations. Each subscale consists of 15 items where respondents on the Likert five point scales assess the extent to which data statement describes their reactions and attitudes in thus defined situations. The scales were translated into Croatian and adapted by Sorić and associates (19). Higher scores on EMAS – T indicate higher anxiety.

The data were analyzed in SPSS 20.0 (Statistical Package for the Social Sciences). Method of linear correlation - Pearson coefficient examined interconnection between the dimensions of perfectionism and anx-

iety. Method t-test for independent samples examined differences between the sexes in terms of perfectionism and anxiety level.

RESULTS

Perfectionism and anxiety

Pearson's correlation coefficient between the total scores on the scales EMAS-T and MPS is 0.29 and is statistically significant at the level of 0.01 (Table 1). The correlation between anxiety and negative perfectionism is something greater and statistically significant, also on level 0.01. The statistically significant correlation between positive perfectionism and anxiety was not ascertained.

Total perfectionism significantly positively correlated with anxiety in assessment situations and anxiety in new situations scales (Table 2). There were no significant correlation between perfectionism and anxiety in situations of physical danger and anxiety in everyday situations. Therefore, bigger perfectionists are more prone to show anxiety in assessment and unfamiliar situations.

From Table 3, we see that there were no significant correlation between positive perfectionism and any of anxiety subscales. Negative perfectionism correlated significantly and positively with anxiety in situations of assessment with 0.48 correlation coefficient (Pearson's r), while the correlation with anxiety in new situations and anxiety in everyday situations is somewhat lesser, but also statistically significant and positive.

As for the correlation between the four types of anxiety and six subdimensions of perfectionism, it should be emphasized that the organization as subdimension of positive perfectionism significantly negatively correlated with anxiety in everyday situations (Pearson's r = –0.28).

Table 1. *Correlation (Pearson's r) between anxiety and general perfectionism, positive perfectionism and negative perfectionism*

	Anxiety
Perfectionism (general)	0.29**
Positive perfectionism	–0.07
Negative perfectionism	0.40**

** significant at the 0.01 level

Table 2. *Correlation (Pearson's r) between perfectionism and four subscales of anxiety (of EMAS-T)*

	Perfectionism
Anxiety in assessment situations	0.27**
Anxiety in situations of physical danger	0.08
Anxiety in new situations	0.20**
Anxiety in everyday situations	0.13

** significant at the level 0.01
EMAS-T: Endler Multidimensional Anxiety Scale - Trait

Gender and perfectionism

The only statistically significant gender difference in terms of the dimensions of perfectionism was obtained on the dimension doubt about the action. Here the value of t statistics is 2.11 and it is significant at the 0.05 level. Thus, according to our results, girls significantly more express this trait than boys. To determine what is the size of the gender effect on the expression of doubt about the action we calculated eta squared, and it is 0.02, which indicates a rather small influence of gender on the expression of doubt about the action.

Gender and anxiety

When it comes to anxiety, it was shown that there are differences between boys and girls, both in terms of general anxiety trait, where the value of the t statistic is 3.39 ($p \leq 0.01$), and the eta - squared of 0.05. The situation is similar when it comes to subdimensions of anxiety, except the anxiety in everyday situations. These

Table 3. *Correlations (Pearson's r) between positive and negative perfectionism and anxiety subscales (of EMAS-T)*

	r		r
Pos. Perfectionism - Anxiety in assessment	–0.10	Neg. Perfectionism - Anxiety in assessment	0.38**
Pos.Perfectionism - Anxiety in situations of physical danger	0.09	Neg. Perfectionism – Anxiety in situations of physical danger	0.05
Pos. Perfectionism - Anxiety in new situations	–0.02	Neg. Perfectionism - Anxiety in new situations	0.25**
Pos. Perfectionism - Anxiety in everyday situations	–0.14	Neg. Perfectionism - Anxiety in everyday situations	0.23**

** significant at the level 0.01
EMAS-T: Endler Multidimensional Anxiety Scale – Trait

significant differences speak in favor of anxiety being more prominent in girls than in boys. Calculated eta squared points to a moderate size of the influence of gender on the presence of anxiety.

DISCUSSION

Our research has confirmed the existence of a positive correlation between perfectionism and anxiety in general, but also between their subdimensions. Total perfectionism was significantly positively associated with anxiety in assessment situations and new/unfamiliar situations. Slightly higher correlation than in the case of general perfectionism was found between negative perfectionism and overall anxiety, which is consistent with the results obtained in earlier studies (4). This connecttion between anxiety and negative aspects of perfectionism is particularly evident in assessment situations, unfamiliar and everyday situations. Thus, students who tend to display anxiety in these situations are persons who are more likely to show indicators of negative perfectionism than others. Only in the case of manifestation of anxiety in situations of physical danger there were no relationship between the level of the negative perfectionism aspect. Although we haven't found significant relationship between general anxiety and positive perfectionism, we found a significant negative correlation between organization and anxiety in everyday situations. Speaking common sense, it is expected that the less organised people will be more likely to feel anxious in everyday situations.

In contrast to the results of previous studies (11), where it was found that girls had significantly higher scores on scales of positive perfectionism than boys, we did not find a significant difference between boys and girls in terms of general perfectionism. The only indication of perfectionism which is more pronounced in girls is the tendency to have doubts about taking some action, although the intensity of the impact of gender on this feature is not particularly large ($p < 0.05$, eta squared = 0.02). So, we can only conclude that the girls in terms of taking some action or initiation of dealing with something and somewhat are more thoroughly and more punctilious, but also indecisive and more prone of reluctance than boys. When it comes to the presence of anxiety, it was shown that it is significantly more expressed in female and this is true for general anxiety, and also anxiety in the assessment situations, anxiety in physically dangerous situations and anxiety in new/unfamiliar situations. This is consistent with results of previous studies (14), where on a sample of young musicians researchers have found that girls show significantly higher levels of anxiety than boys.

CONCLUSION

We examined the connection between perfectionism and anxiety in a sample from the student population, as well as gender differences in the expression of these two personality traits. The results of this research confirmed that these two traits are moderately positively correlated with each other. Therefore, we can conclude that the anxious persons are generally more of perfectionists, especially of a people who express negative aspects of perfectionism, which are thought to arise as a consequence of the fear of failure. It was found that female students are generally more anxious thane male students. In terms of perfectionism, girls showed significantly higher level of doubt about the action.

DECLARATION OF INTEREST. None

Abbreviations

MPS — Multidimensional Perfectionism Scale

EMAS-T — Endler Multidimensional Anxiety Scale - Trait

EMAS-S — s-endler multidimensional anxiety scale - state

EMAS-P — p-edler multidimensional anxiety scale - perception of the threat

Sažetak

POVEZANOST PERFEKCIONIZMA I ANKSIOZNOSTI KOD STUDENATA

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Uvod. Perfekcionizam je relativno stabilna osobina ličnosti koja podrazumeva postavljanje visokih ličnih standarda i težnju ka savršenstvu. Anksioznost posmatrana kao crta ličnosti predstavlja sklonost da se situacije koje su objektivno bezopasne opažaju kao ugrožavajuće i da se na njih reaguje znatno intenzivnije nego što to situacija objektivno nalaže. Raniji rezultati pokazuju da je anksioznost u ispitnoj situaciji u pozitivnoj vezi sa negativnim perfekcionizmom (strahom od neuspeha). Takođe, ranija istraživanja pokazuju da postoje razlike između polova u pogledu izraženosti ovih osobina, u oba slučaja u korist devojaka.

Cilj. Cilj istraživanja bio je da se ispita da li postoji povezanost između perfekcionizma i anksioznosti, kakvog je intenziteta i smera. Pored toga, želeli smo da ispitamo postoje li razlike između polova u pogledu izraženosti ove dve osobine ličnosti.

Metod. Sistematsko neeksperimentalno istraživanje. Uzorak je činilo 202 studenta Beogradskog Univerziteta, od toga 158 devojaka (78%) i 44 mladića (22%). Izraženost crte perfekcionizma merena je testom Multidimenzionalna Skala Perfekcionizma, Frosta i saradnika, dok je anksioznost merena testom Endlerova Multidimenzionalna Skala Anksioznosti - Crte. Statističke tehnike koje smo koristili u analizi su Pirsonov koeficijent korelacije i t-test nezavisnih uzoraka.

Rezultati. Rezultati pokazuju umerenu pozitivnu korelaciju anksioznosti sa ukupnim perfekcionizmom ($r = 0.29$, $p = 0.01$), kao i nešto intenzivniju, takođe pozitivnu, korelaciju anksioznosti sa negativnim aspektima perfekcionizma ($r = 0.40$, $p = 0.01$). Nađena je razlika između polova u pogledu anksioznosti, tj. da je kod studentkinja anksioznost značajno više izražena nego kod muških studenata ($t = 3.39$, $p < 0.01$, $= 0.05$). Kada je u pitanju perfekcionizam, jedina značajna razlika između polova nađena je u pogledu subdimenzije sumnja i vezi akcije ($t = 2.11$, $p = 0.04$, $= 0.02$), koja pokazuje da je ova crta izraženija kod devojaka nego kod mladića.

Zaključak. Dakle, na osnovu ovog istraživanja mogli bismo zaključiti da su anksioznije osobe uglavnom i veći perfekcionisti (pogotovo negativni perfekcionisti) nego manje anksiozne osobe, kao i da su studentkinje generalno anksioznije od studenata.

Ključne reči. perfekcionizam, anksioznost, pol, povezanost.

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Case report

ORAL MANIFESTATIONS OF CROHN´S DISEASE: A CASE REPORT

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Abstract: Crohn's disease is a chronic inflammatory bowel disease still with unknown etiology. In 0.5–20% of patients, extra intestinal lesions in the oral cavity can be presented in forms of orofacial granulomatosis, cobblestone and corrugated oral mucosa, mucosal tags, deep linear ulcerations with hyperplastic folds, pyostomatits vegetans, aphthous ulcers, angular cheilitis, labial/facial edema and gingival erythema/edema. We describe a case of a 28-year-old male who was presented with oral lesions of Crohn's disease and treatment procedure. The patient was candidate for biologic treatment so dental procedures and preparation of the patient for treatment are described. Good communication and cooperation between the patient's doctor and dentist are important for successful treatment.

Key words: Crohn´s disease; inflammatory bowel disease; oral manifestation.

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory granulomatous disease with primary intestinal involvement but it may involve any part of bowel system from mouth to anus (1, 2).

The etiology of disease is still unknown but genetic factor, environmental factors and immune response in the bowel wall seems to be main causes of CD (3, 4).

The disease is characterized by phases of exacerbation and remission, with the symptoms of diarrhea, stomach pain, weight loss and elevated body temperature (1, 5). One third of patients can exhibit extra intestinal manifestations of the disease (6). The most frequent manifestations affect the joints, skin, eyes and hepatobiliary system. Changes in the oral cavity, blood vessels, heart, lungs and genitourinary and endocrine system have been also described (6, 7).

Oral lesions of CD were first described in 1969 by Dyer *at al* (8). In the same year Dudeney (9) reported another case of patient suffering from CD who had oral manifestations. The prevalence rate of oral manifestations is estimated to be between 0.5 to 20% (5, 10, 11), although some studies mention up to 80% (12, 13). They include orofacial granulomatosis, cobblestone and corrugated oral mucosa, mucosal tags, deep linear ulcerations with hyperplastic folds, pyostomatitis vegetans, aphthous ulcers, angular cheilitis, labial/facial edema and gingival erythema/edema (10, 14, 15). Presence of cobblestone mucosa and mucosal tags are highly suggestive to CD (16).

There is a male predilection and the oral outbreaks often start in young ages (17). Up to 60% of patients with CD may present oral manifestations years before the appearance of intestinal disease (5, 17). Oral manifestations are unpleasant bitter, disagreeable, displeasing, and distasteful for the patients; restrict their nutrition and oral hygiene.

The aim of this paper is to present a case of patient with oral manifestation of CD and treatment procedure.

CASE REPORT

A 28-years-old male patient was referred to the Department of Oral medicine at the Dental clinic Rijeka due to pain in the mouth. Oral complains and lesions have been presented for 10 days.

The patient medical history revealed that he has been suffering from CD for five years. He has been subjected to resection of terminal ileum and sigmoid colon in 2010. Post-surgical remission was maintained with azathioprine therapy for four years. Two months after stopping the azathioprine therapy, (four months prior of arrival in our clinic) the disease became active and the infliximab was recommended. During the period of patient's preparation for infliximab therapy the patient was referred to the Oral medicine Dental Office for treating lesions in the oral cavity and excluding oral

foci of infection. He has never before experienced oral lesions since he was diagnosed with CD.

Clinical exam revealed erythema and inflammation with white to yellow small pustules on the right buccal mucosa, what was recognized as pyostomatitis vegetans. Furthermore, in the lower right quadrant on the vestibular gingiva and in the fornix a thickened, inflamed and cobblestone oral mucosa with ulcerations was presented (Figure 1). Under local anesthesia (2% lidocaine) an incision biopsy of the altered mucosa and gingiva was performed. Swabs were taken from the oral mucosa for the microbiological analysis.

Patient was prescribed a topical antiseptic therapy (0.2% chlorhexidine gluconate solution three times per day), corticosteroid (0.05% betamethasone ointment three times per day), and systemic corticosteroid (prednisolone 30 mg) with proton pump inhibitor.

On recall visit after seven days the sutures were removed. Clinically the erosions were epithelized and the inflammation diminished. The patient continued the prescribed therapy for additional 7 days. The biopsy of the buccal lesion revealed: dense lymphoma histiocytic inflammatory cell infiltration in the vicinity of the basal membrane. In the gingiva sample histiocytic granulomas were presented, that all together indicated the presence of Crohn's disease.

Patient's dental status was taken, vitality tests were performed, and the panoramic radiogram was analyzed. No pathological changes were found on the teeth or on the surrounding bone. Microbiological results were negative and from the dental point of view the patient was eligible to start the biologic therapy.

On the second recall after 14 days the oral mucosa was normal without pathological changes (Figure 2).

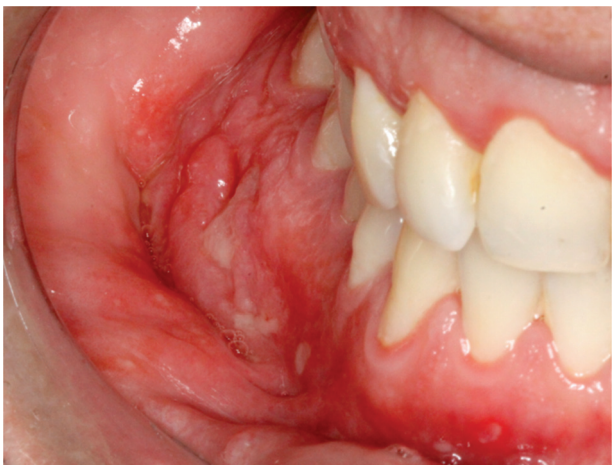

Figure 1. *Clinical appearance at time of first presentation. White to yellow small pustules on the inflamed buccal mucosa and cobblestone lesions with ulcerations on the vestibular gingiva and in the fornix*

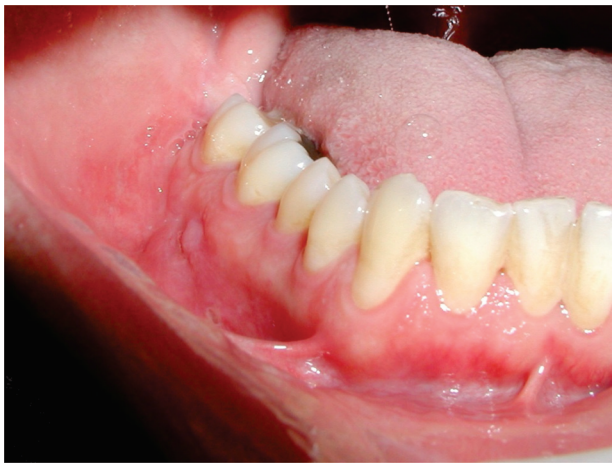

Figure 2. *Clinical appearance at second recall. There was no oral lesions. The site of gingival biopsy is visible*

Topical therapy was stopped while the systemic prednisolone therapy remained and it was gradually tapered down under gastroenterology specialist supervision. Patient was instructed to come for consult after one month, when there was no oral lesions presented.

After routine preparation for biologic (anti-TNF) therapy (screening for tuberculosis and viruses), infliximab induction therapy was administered by which the remission of Cohn's diseases was achieved. Infliximab maintenance therapy was continued by re-administration every eight weeks. Now, he is in stable remission.

DISCUSSION

We presented the case of a patient who developed oral manifestations of CD in the phase of reactivation of the disease, after interrupting of maintenance azathioprine therapy during four years.

Although, in the mouth of patients with CD a vast variety of specific and nonspecific lesions can be presented, in our case the pyostomatitis vegetans, cobblestone mucosa and ulcerations were observed. In the literature it is reported that the oral lesions can appear either before, coincide, or after the onset of symptoms and lesions in the gastrointestinal system (17–21). The severity of oral lesions can indicate the activity level of chronic inflammatory processes in the intestine (22).

Oral lesion can be managed by topical corticosteroids such as triamcinolone acetonide and betamethasone (23). The topical application of corticosteroids sometimes is not sufficient and a systematic administration of corticosteroids is needed (e.g. prednisolone) (23, 24). Some authors state that the topical application of corticosteroids is not sufficient, and treatment must start from the beginning with systemic corticosteroid therapy (25). In the presented case, it was decided to start simultaneously with topical and systemic cortico-

steroid therapy what resulted in healing of oral lesions. After 14 days the topical therapy was halted, while the systemic corticosteroid was gradually tapered down.

Administration of medium high and high doses of systematic corticosteroids results on disappearance of lesions, however the lowering of dosage or stopping the treatment can result in exacerbation of the lesions (26). For the modern therapy it is unacceptable to keep the patient in remission with corticosteroids due to numerous side effects. The azathioprine therapy that was administered for 4 years after withdrawal brought the patient to acute disease exacerbation including oral lesions. The anti-TNF therapy was the choice for our patient.

However, the initiation of biologic therapy requires strict preparation procedures including detection of manifest and hidden potential focal infections (27). The preparation includes exam of oral cavity and teeth (27). Patient have to present restored teeth, healthy periodontal tissue and oral mucosa, and the possible oral foci have to be eliminated. The presence of oral foci due to immunosuppressive action of the biologic therapy can lead to distant focal infections that can jeopardize the patient's health and life. Therefore, the dental exam was performed and the foci of oral origin were excluded in our patient.

CONCLUSION

In the presented case the findings in the oral cavity were manifestations of the primary disease and the patient was treated for the primary disease (with corticosteroids, and subsequently anti-TNF biologic medication). Since the patient was candidate for biologic therapy the foci of oral origin were excluded. For the successful treatment of extra intestinal/oral lesions of Cohn's disease good communication between gastroenterology specialist and the dentist/oral medicine specialist is essential.

Sažetak

ORALNA MANIFESTACIJA KRONOVE BOLESTI — PRIKAZ SLUČAJA

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Kronova bolest je hronična zapaljenska bolest creva još uvek nepoznate etiologije. U 0,5–20% pacijenata mogu se javiti ekstraintestinalne lezije u usnoj duplji u obliku orofacijalne granulomatoze, kaldrmaste i talasaste oralne sluznice, sluzničkih nabora, dubokih linearnih ulceracija s hiperplastičnim naborima, piostomatitis vegetansa, aftoznih ulceracija, angularnog heilitisa, otoka usana i lica te crvenila i otoka gingive. U ovom radu opisan je slučaj 28-godišnjeg pacijenta koji je razvio oralne lezije u sklopu Kronove bolesti i postupak lečenja. Pacijent je bio kandidat za biološko lečenje te je u radu opisan stomatološki postupak pripreme pacijenta za lečenje. Za uspešno lečenje bitna je dobra komunikacija i saradnja između pacijentovog doktora i stomatologa.

Ključne reči: Kronova bolest; Oralne manifestacije; zapaljenska bolest creva.

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Case report

CATARACT SURGERY AND INTRAOCULAR LENS POWER CALCULATION IN A PATIENT WITH ANTERIOR MEGALOPHTHALMOS WITH NORMAL SIZED CRYSTALLINE LENS: CASE REPORT

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Abstract: Cataract surgery and intraocular lens power calculation is challenging in patients with anterior megalophthalmos and cataract, with postoperative refractive surprise frequently reported. Deep anterior chamber in these patients substantially influence effective lens position. To minimize possibility of refractive surprise, we used Haigis formula that takes into account anterior chamber depth in the lens power calculation for our patient. Cataract was managed by phakoemulsification with standard intraocular lens implanted in the capsular bag. Postoperatively, satisfying refractive result was achieved and refractive surprise was avoided.

Key words: Anterior megalophthalmos, cataract surgery, intraocular lens, power calculation.

INTRODUCTION

Anterior megalophthalmos is a rare bilateral hereditary disorder in which megalocornea (defined as horizontal corneal diameter greater than 13 mm) is associated with enlarged anterior segment of the eye (1). While in the simple megalocornea there are no additional ocular abnormalities, in the anterior megalophthalmos various other findings are present including iris hypoplasia, stromal atrophy, iris transillumination defects, pigment dispersion syndrome, myopia, cataract, lens subluxation and luxation, and glaucoma. Clinical diagnosis of anterior megalophthalmos can be confirmed by biometry findings of low vitreous index (vitreous length/axial length x100 < 69%) (2).

Intraocular lens calculation is challenging in these patients, with postoperative hyperopic refraction frequently reported (3). Many commonly used formulas doesn't take into account anterior chamber depth (ACD) when calculating intraocular lens (IOL) power. This can cause erroneous estimation of effective lens position in these unusual eyes (8). We therefore used Haigis formula (9) to calculate IOL power in this particular patient, to minimize possibility of refractive surprise. Large capsular bag is often present in these eyes, adding inaccuracy in prediction of final IOL position, if in-the-bag placement is planed.

In this report we described a case of anterior megalophthalmos with normal-sized cataractous lens. Cataract was managed by phakoemulsification with standard intraocular lens implanted in the capsular bag. Postoperatively, satisfying refraction was achieved within 0.25 D of targeted in both eyes.

CASE REPORT

A healthy 30-year-old man was referred to our department because of the bilateral vision loss due to advanced cataracts. His visual acuity was reduced to counting fingers at 1 m in the right eye, and at 3 m in the left.

Slit-lamp biomicroscopy of both eyes revealed signs of anterior megalophthalmos: enlarged corneas, deep anterior chamber, iris transillumination defects and white cataract in the right eye (Figure 1), while incipient in the left. Refraction of his right eye could not be obtained, and of the left eye was mildly myopic. Anterior segment biometry data was collected by Allegro Biograph (Wave Light) as follows: average keratometry OD: 37.79 D (8.79 mm; n = 1.332), and OS: 37.92 D (8.76 mm; n = 1.332). Anterior chamber depth (ACD) and lens thickness (LT) for the right eye were 5.03 mm and 3.96 mm, and for the left eye 5.21 mm and 4.05 mm, respectively. Axial length of the right eye was 25.80 mm, and 26.80 mm of the left, measured by immersion echography. Horizontal white-to-white

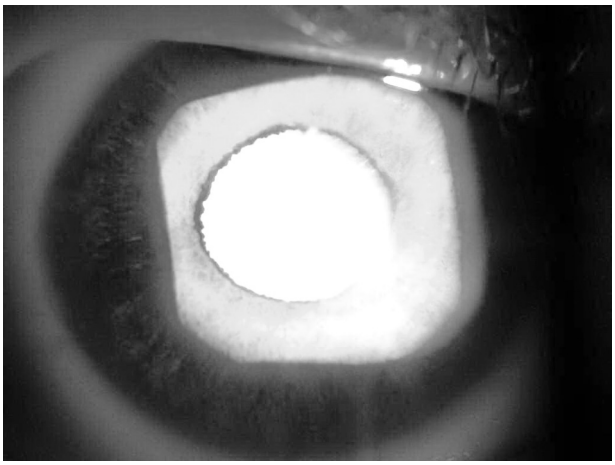

Figure 1. *High magnification slit-lamp image of the anterior segment reveals white cataract and transillumination iris defects associated with anterior megalophthalmos*

for the right and the left eye was 13.56 mm and 13.24 mm, respectively. Intraocular pressure was 16 mmHg bilaterally, measured by Goldmann applanation tonometer. There were no phacodonesis in any eye, but iridodonesis was present in both.

Calculated vitreous index was 65.15 % for the right, and 65.45% for the left eye, confirming diagnosis of anterior megalophthalmos. UBM of the anterior segment revealed normal crystalline lens of 9.26 mm equatorial diameter in the right eye, concave iris configuration and elongated stretched zonules (Figure 2). Findings were similar for the left eye, with diameter of 9.24 mm.

Power of the intraocular lens was estimated with various formulas utilizing Biograph proprietary software, aiming emmetropia. Haigis formula indicated 21.5D IOL for the right eye, while other formulas predicted lower power IOLs for emmetropia. Calculation for the left eye was 18.0D. Prediction error of some

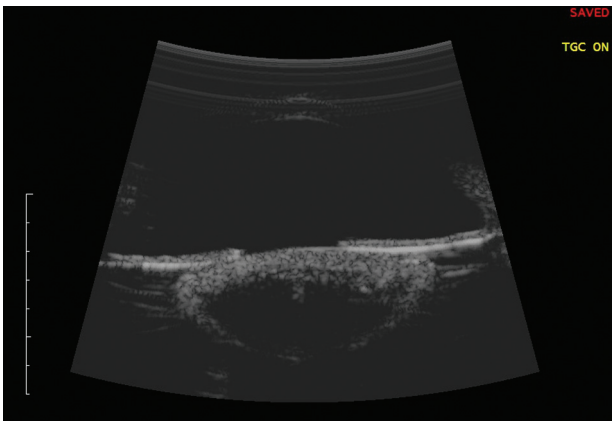

Figure 2. *Preoperative UBM of the right eye showing deep anterior chamber, normal-sized crystalline lens with anterior cortical opacities, and elongated zonules*

Table 1. *Prediction of postoperative refraction of some commonly used formulas for SA60AT Acrysof lens. Input data (mm): AL 25.80, ACD 5.03, LT 3.96, Ave. K 8.79*

IOL power	SRK II 119.0	SRK T 118.8	Holladay I 1.64	Hoffer Q 5.41	Haigis –0.091, 0.231, 0.179
21.50	–1.66	–1.39	–1.10	–0.57	0.00
21.00	–1.26	–1.00	–0.73	–0.22	0.35
20.50	–0.86	–0.62	–0.37	0.13	0.69
20.00	–0.46	–0.25	0.00	0.47	1.03
19.50	–0.06	0.12	0.35	0.81	1.37

Comment: All formulae except Haigis would suggest lower power IOL to achieve emmetropia, leading to hyperopic surprise.

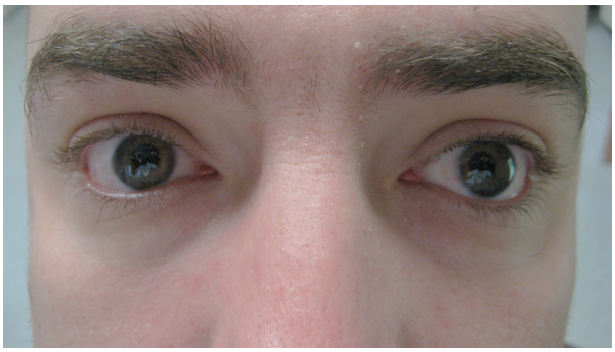

Figure 3. *Postoperative appearance of both eyes*

commonly used formulas for the patient right eye are listed in Table 1.

Cataract surgery of the right was performed in sub-Tenon anesthesia. Temporal clear corneal incision was made by 2.4 mm knife, anterior capsule was stained with trypan-blue dye, DisCoVisc viscoelastic was injected into the anterior chamber, paracenthesis incision was performed for second instrument placement, and continuous circular capsulorhexis was successfully finished. Viscoelastic material was added between iris and anterior capsule, to prevent lens iris diaphragm retropulsion syndrome (LIDRS), which is expected to occur in such a case. Phaco probe was inserted through the main incision and nucleus was chopped and aspirated. Cortical material was then aspirated with unimanual irrigation/aspiration handpiece. Single piece foldable intraocular lens Acrysof SA60AT (Alcon Laboratories, Inc.) of 21.5D was implanted in the capsular bag. Subsequently, viscoelastic material was removed and operative wounds were hydrated using balanced salt solution (BSS). A month later, second eye was operated in the same manner.

Postoperative course was unremarkable with both eyes. Best corrected visual acuity of the right eye reco-

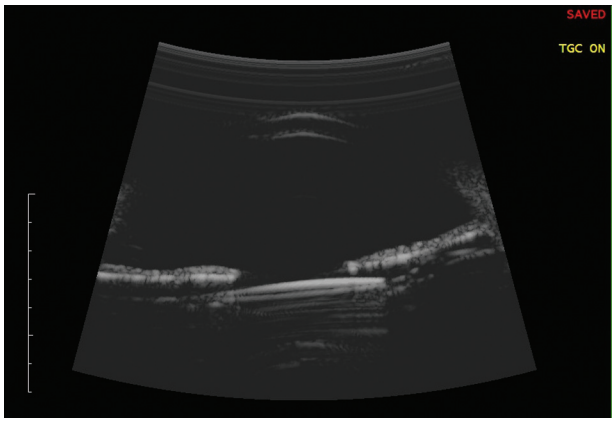

Figure 4. *UBM of the operated eye shows in-the-bag position of the IOL*

vered to 1,0 Snellen with –0.25 Dsph at the first postoperative visit and stayed so during 6 months of follow up. Postoperative spherical equivalent of the left eye was +0.25 Dsph, with uncorrected distance visual acuity of 1,0 Snellen at final exam 5 month after the surgery (Figure 3 and 4).

DISCUSSION AND CONCLUSION

Cataract extraction in eyes with anterior megalophthalmos is complex because of hyper-deep anterior chamber, zonular laxity and poor visualization. Enlargement of the ciliary ring is often associated with a wide capsular bag, so various methods to secure intraocular lens implant in these circumstances were described in literature: iris fixated artificial lens (10, 11), sutured posterior chamber IOL (12, 13), anterior capsulorhexis capture of the IOL (14), and custom-made intraocular lens with very wide haptic diameter (4). However, crystalline lens is not always large. Zare M.A. and colleagues (3) recently reported a case of normal-sized cataractous lens (10,21 mm) in an anteriorly-megalophthalmic eye, and they showed the significance of preoperative ultrasound biomicroscopy (UBM) imaging in cataract surgery planing in these patients.

Deep anterior chamber in patients with anterior megalophthalmos substantially influence effective lens position, so we used Haigis formula that takes into account ACD in the lens power calculation.Rather than using a single constant, the Haigis formula recommends IOL power based on a three-variable (a0, a1 and a2) function.

The a0, a1 and a2 constants are set by optimizing a set of surgeon- and IOL-specific outcomes for a wide range of ALs and ACDs. By double-regression analysis, the a0, a1 and a2 constants are adjusted to match the results for a specific surgeon and IOL. This means that the mathematics of the Haigis formula can be adjusted for each surgeon/IOL combination.

Normal size of the crystalline lens, as in our patient, allows secure and stabile in the bag placement of an IOL which, in turns, aids in accuracy of power calculation. Additional power adjustments are only needed if the IOL is planed to be iris -fixated or capsulorhexis captured, as is the cases with large or unstable capsular bag. One such a case was reported by Galvis V. and coauthors (10). Haigis formula was used in that case to calculate Artisan iris fixating lens power, with excellent refractive result.

Various other formulas are used to calculate IOL power, many of them are based only on two parameters, namely keratometry and axial length. This may explain hyperopic refractive result in some of these unusual eyes. On the other side, formulas that includes other relevant parameters (ACD, lens thickness, white-to-white measurement and other) like Haigis, Holladay II and Olsen (15), have a potential to more accurately predict postoperative refraction. In a case report of de Sanctis and Grignolo (16), Holladay II formula has been shown to be very accurate in their patient with X-linked megalocornea. Assia and coauthors (6) recently described a case of cataract surgery with IOL implantation in anterior megalophthalmos. After having hyperopic refractive surprise with SRK-T formula, they back-calculated IOL power using Holladay II formula, and concluded that IOL selection and refractive result would be similar. It remains unclear whether preoperative ACD was used in power calculation in that case. However, authors suggested the use of Holladay II formula to calculate IOL power in megalophthalmic eyes with very deep anterior chamber and wide WTW. Review of refractive results of reported cases of cataract surgery in eyes with anterior megalophthalmos, where IOL was placed in the capsular bag, is shown in Table 2.

Table 2. *Previous and current reports of in-the-bag IOL placement in anterior megalophthalmos*

Author/year	Formula	Achieved refraction (SE)
Zare, 2011	SRK-T	OD +0.75 D
Marques Vaz, 2007	n/a	OD +0.75 D OS +1.75 D
Assia, 2009	SRK-T	OD +2.25 D (+2.90 D from target) OS +1.00 D (+2.25 D from target)
Hegde, 2012	SRK II	OD +2.50 D
Javadi, 2000	SRK-T	1. OD –1.75 D OS –2.50 D 2. OD –0.825 D OS +0.25 D 3. OS –0.50 D
Orczykowska, 2013	SRK-T	OS +1.00 D
De Sanctis and Grignolo, 2004	Holladay II	OD +0.48 D from target OS –0.25 D from target
Current, 2015	Haigis	OD –0.25 D (–0.25 D from target) OS +0.25 D (+0.25 D from target)

There are fewer reports of myopic postoperative surprise. Javadi et al. (17) reported postoperative myopic surprise in the majority of their cases. Axial length was measured by ultrasound, but it wasn't stated wether it was accomplished by contact biometry, what may be the source of error. The other two published reports of myopic refraction after surgery are cases with sutured IOL, either through iris and capsule, or between iris and capsule (12, 13). Myopic refraction can be explained in these eyes by anterior shift of sutured IOL.

An interesting approach to IOL power calculation was utilized by Jain et al. (14). They used SRK II formula, and added 2 D to emmetropic calculation. The IOL optic was sulcus fixated and captured through the capsulorhexis. Final refraction was emmetropic in one eye, and mildly myopic in the other.

We showed in our case that the error that may result from the classical formulas using only the K-reading and the axial length for the prediction of ELP can be avoided by using Haigis formula in these extreme eyes. Secure capsular bag fixation of the standard intraocular lens provided stabile and satisfying refractive outcome.

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Abbreviations:

ACD — Anterior chamber depth
LT — Lens thickness
OD — Oculus dexter
OS — Oculus sinister
IOL — Intraocular lens
UBM — Ultrasound biomicroscopy
ELP — Effective lens position
WTW — White-to-white
BSS — Balanced salt solution
D — Diopter
K — Keratometry
LIDRS — Lens-iris diaphragm retropulsion syndrome

Sažetak

OPERACIJA KATARAKTE I PRORAČUN DIOPTRIJSKE SNAGE INTRAOKULARNOG SOČIVA KOD PACIJENTA SA PREDNJIM MEGALOFTALMUSOM: PRIKAZ SLUČAJA

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Operacija katarakte i proračun dioptrijske snage intraokularnog sočiva kod pacijenata sa prednjim megaloftalmusom su veoma delikatni, a refraktivna iznenađenja su u literaturi često navođena. Duboka prednja očna komora kod ovih pacijenata značajno utiče na efektivni položaj implantiranog sočiva. Da bi smanjili mogućnost za neželjeni refraktivni ishod operacije katarakte, kod prikazanog pacijenta korišćena je Haigisova formula koja uključuje parametar dubine prednje očne komore za kalkulaciju dioptrijske snage sočiva. Katarakta je operisana metodom fakoemulzifikacije, sa implantacijom veštačkog sočiva standardnih dimenzija u kapsularnu kesicu. Postoperativno je postignut zadovoljavajući refraktivni i funkcionalni rezultat.

Ključne reči: Prednji megaloftalmus, hirurgija katarakte, intraokularno sočivo, kalkulacija.

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SALIVA AS A DIAGNOSTIC FLUID

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Abstract: Saliva is a readily available oral fluid with many functions, from digestion, maintenance of oral tissues' integrity, to caries prevention. Changes regarding its secretion may be divided into qualitative and quantitative: both of them are a consequence of certain conditions/diseases (e.g. internal factors) or nutrients/drugs ingested (e.g. external factors). During the last 15 years, technological advances gave a significant momentum to utilization of saliva as a diagnostic tool. Analysis of saliva, just like the blood analysis, has two main objectives: to identify the subjects suffering from a certain disorder, and to follow the development and progress of therapy. This paper provides an overview of possibilities for the use of saliva for diagnostic purposes and gives specific examples of some clinical investigations, with the final aim to stimulate the use of this noninvasive means for the health care promotion.

Key words: caries, diagnosis, disease, oral fluid, saliva.

INTRODUCTION

Saliva is a complex fluid originating from three major and several minor salivary glands, gingival crevicular fluid, bacterial products, epithelial cells and food debris (1). In addition, it contains minerals, electrolytes, buffers, enzymes and their inhibitors, growth factors, cytokines, immunoglobulins, mucin, and other glycoproteins (2, 3). About 93% of its volume is secreted by major salivary glands, while the remaining 7% originates from minor salivary glands. The main component of the saliva is water — 99%. Secretion of the saliva may be influenced by numerous physiological and pathological factors, either reversibly or irreversibly. Saliva plays an important role in maintaining the integrity of oral cavity, as well as digestion and control of oral infections (4). The role of saliva in caries protection may be viewed from 4 aspects: dilution and elimination of sugars and other compounds, buffering action, balance between demineralization and remineralization process, and antimicrobial function. Saliva may present an option for diagnostics of specific disorders and diseases. Finally, it enables tracking of disease pathogenesis. Although the main component of the saliva is water, it plays an important role in lubrication and reparation of oral mucosa, formation and swallowing of the food bolus, and control of the oropharyngeal microbial population.

CLINICAL IMPORTANCE OF QUALITY AND QUANTITY OF SALIVA IN ORAL HEALTH MAINTENANCE

Just as much as the quantity, the quality of saliva holds a great importance since every single component plays a role in its various specific functions. Normal quantity of saliva may be reduced significantly affecting the individual quality of life and oral health. Leading signs and symptoms related to hyposalivation are "dry mouth syndrome" or xerostomia, thirst, difficulty swallowing and chewing, especially when eating dry foods, a need to sip drinks frequently, difficulty wearing dentures, mouth soreness and irritation, and burning mouth sensation.

Reduced salivary flow may be caused by many physiological and pathological mechanisms.

Salivary gland function is naturally reduced in elders. Furthermore, decreased secretion is related to the intake of certain medications, diabetes and hypertension. More than 400 commonly prescribed drugs may affect salivary secretion. Head and neck radiotherapy cause irreversible destruction of the glandular parenchyma. Certain systemic disorders, such as some autoimmune disorders (namely Sjögren syndrome) lead to a progressive destruction of salivary glands, while others cause vascular or neurological alterations showing short or long- term repercussions on salivary secretion: these include hypertension, depression, malnourishment, dehydration and diabetes.

Salivary secretion has its physiological peak in the time of tooth eruption and is related to hyperstimulation of peripheral receptors in oral mucosa. This hyperstimulation may also be observed during the first trimester of pregnancy and menstrual bleeding.

Pathological causes of hypersalivation are divided into oral and non-oral. The former include the initial stages of prosthetic rehabilitation with a denture, toothache, irritation and/or pain in the oropharyngeal region. On the other hand, certain neurological disorders such as Parkinson's disease, epilepsy, encephalitis, or some tumors, as well as exogenous toxins (bismuth, mercury, silver, gold, arsenic or endotoxins during uremia) and pilocarpine may trigger hypersalivation.

During the last 15 years, technological advances gave a significant momentum to utilization of saliva as a diagnostic tool. Measurement and tracking of the molecular components within the saliva, and their comparison to the components of the serum enabled the analysis of microorganism, chemical and immunological markers (5, 6). Consequently, saliva became not just an indicator of oral health but also a powerful tool for measuring basic indicators of overall health. Nowadays, there is a growing interest for investigations regarding the use of saliva for diagnostic purposes. Analysis of saliva, just like the blood analysis, has two main objectives: to identify the subjects suffering from a certain disease, and to follow the development and progress of therapy. Advantages of using the saliva as a diagnostic medium compared to the blood are simple and non-invasive sampling procedure (devoid of stress or risks) easily acceptable for the patient, low cost, and use for investigation purposes. One of the most important advantages for using the saliva as a diagnostic tool is its simple, non-invasive sampling process.

Various components within the saliva, besides protecting tissue integrity, enable detection of local and systemic conditions and diseases. Saliva is especially useful for qualitative diagnostics and detection of certain markers in numerous diseases, such as viral infections (HIV, hepatitis), some hereditary diseases (cystic fibrosis), autoimmune disorders (Sjögren syndrome), and malignancies. For example, p53 is known as a tumor suppressor protein and antibodies targeted against it have been detected in patients with squamous cellular carcinoma in the oral cavity, thus helping the early detection and monitoring of this disease (7, 8).

There are several reports describing possible uses of salivary creatinine levels in detection of renal diseases (9, 10, 11).

Saliva also represents a useful medium for diagnosis of certain oral diseases, and monitoring of drug and hormone levels. Specific salivary tests for antibodies (anti-viral and anti-bacterial), steroid hormones (estrogen, progesterone and testosterone), exogenous toxins (cadmium and mercury), tobacco and some drugs (ethanol, lithium) have a sufficient sensitivity to reflect their blood levels (12). Qualitative changes in its composition provide necessary information related to diagnostics of certain oral diseases. Namely, increased albumin levels in whole saliva were demonstrated in patients on chemotherapy who developed stomatitis later on, posing as a significant marker for future prognosis of this complication (13). Increased levels of salivary nitrates and nitrites, and reduced activity of nitrate reductase were detected in patients with oral carcinoma when compared to healthy subjects.

Detection of increased numbers of certain bacterial species in the saliva is related to increased possibility of caries development, especially on the root surface (4).

Saliva may be collected with or without stimulation; one of the best methods for unstimulated saliva collection is passive drool into the measuring sterile vial (14). Collection of stimulated saliva is performed following chewing or stimulation of taste buds.

One of the most common methods used in research is collection of the whole unstimulated saliva (WUS) which represents the pool of saliva from all — major and minor- salivary glands.

Although WUS represents both local and systemic pathophysiological states in the moment of saliva collection, some factors such as hyposalivation in elders, use of certain drugs, periodontitis, fear and anxiety may affect the results obtained during such research.

Due to the relationship between oral and overall health, clinicians mostly use saliva as diagnostic means, although it is still debated that we could profit even more from such analyses (15, 16).

In the past, mostly used diagnostic means was blood serum, however saliva holds many advantages over both serum and urine (2).

Saliva is readily collected during clinical or laboratory work in quantities sufficient for various tests. These tests hold certain advantages over serum analysis since saliva collection is non-invasive, therefore preventing fear, uneasiness and anxiety which patients feel when involved in other analyses.

Cytokines play role in pathogenesis of numerous oral diseases such as bacterial, viral and fungal infections, as well during the pathogenesis of immunological disorders of the oral cavity and development of precancerous lesions.

Research demonstrated a significant increase in the levels of interleukin-6 (IL-6) and interleukin-2 (IL-2) in the saliva of patients with Sjögren syndrome and decreased levels of IL-2 in patients under treatment with pilocarpine (17).

Saliva of HIV-positive patients with oral candidiasis holds elevated values of interferon gamma (IFN-γ) compared to other HIV-positive patients with healthy mouth and otherwise healthy controls. In addition, increased values of IFN-γ were found in saliva of HIV-positive patients with oral villous leukoplakia, compared to HIV-positive patients without pathological oral findings (18).

Saliva of patients suffering from recurrent aphthous ulcerations which developed as a consequence of destructive autoimmune reaction reportedly has decreased values of vascular endothelial growth factor (VEGF) — the cytokine which plays a role in angiogenesis and healing (19).

In our previous researches we predominantly used saliva for the purpose of cytokine detection in particular oral diseases. In patients with oral lichen planus (OLP), we tested the levels of salivary tumor necrosis factor-alpha (TNF-α). This study was undertaken to quantify the salivary levels of pro-inflammatory marker in the reticular and the erosive/atrophic forms of OLP, compared with age-matched healthy control volunteers. Whole saliva from 40 patients with active lesions of OLP, as well as from 20 healthy persons, was investigated for the presence of TNF-α by enzyme immunoassay. Salivary TNF-α levels were significantly increased in patients with OLP in comparison with healthy subjects. The presence of TNF-α showed positive correlation to clinical forms of OLP, being significantly higher in the erosive/atrophic type than in the reticular type of disease. Saliva provides an ideal medium for the detection of pro-inflammatory markers of the oral cavity. In patients with OLP, TNF-α levels in saliva were elevated, correlating with the severity of illness. Salivary TNF-α analysis may be a useful diagnostic tool and a potential prognostic marker in OLP (20).

Since burning mouth syndrome (BMS) is quite common diagnosis in the field of oral medicine, and taking into account painful symptoms in many patients who do not express any clinical changes on the oral mucosa, we have undertaken a study focusing on salivary levels of IL-2 and IL-6. Affected patients often presented multiple oral complaints, including burning, dryness, and taste alterations. The etiology of BMS is still unknown. Role of various cytokines has been implicated in the development of BMS. The aim of this study was to evaluate levels of salivary IL-2 and IL-6 in patients with BMS, compared with age-matched healthy volunteers (control group). Whole saliva from 30 patients with BMS, age range 55 5, was tested for the presence of IL-2 and IL-6 by enzyme immunoassay. Control group consisted of 30 healthy participants, aged 55 5 years. Saliva IL-2 concentrations in BMS were significantly increased in patients compared to healthy subjects: mean 34.1 9.7 versus 7.3 3.0 pg/mL; P < .001. Patients with BMS had significantly higher concentrations of IL-6 compared to control: mean 30.8 5.6 versus 5.2 2.8 pg/mL; P < .001. In patients with BMS, IL-2 and IL-6 levels in saliva were elevated, correlating with the severity of illness (21).

In yet another study we compared the levels of proinflammatory cytokines in patients with burning mouth syndrome before and after low level laser therapy (LLLT) (22). The aim of this study was to determine the levels of proinflammatory cytokines TNF-α and IL-6 in WUS in subjects with BMS before and after treatment with LLLT. BMS is characterized by a continuous, painful burning sensation in a clinically normal-appearing oral mucosa. A sample consisting of 40 consecutive subjects was selected on a voluntary basis from the pool of patients who presented for diagnosis and treatment of BMS. For determination of salivary levels of TNF-α and IL-6, an enzyme-linked immunosorbent assay (ELISA) was performed. After 4 weeks of LLLT, the salivary levels of TNF-α and IL-6 in the experimental group decreased significantly ($p < 0.001$). There was no significant difference in the experimental group regarding visual analogue scale.

Regarding quite frequent questions on negative effects of amalgam fillings and their possible influence on pathological changes on the oral mucosa, we ran a research on correlation between oral lichenoid reaction and amalgam fillings. The aim of this study was to perform a clinical assessment of the association between oral lichenoid reactions (OLR) and amalgam restorations and to determine the salivary concentrations of IL-6 and IL-8 before and after replacement of the amalgam restorations. The study included 20 patients with OLR and 20 healthy volunteers. All patients were skin patch tested by an experienced physician. Saliva samples were collected, prepared and analyzed for IL-6 and IL-8 concentrations using enzyme-linked immunosorbent assay. Sixteen out of 20 patch-tested patients showed a sensitization to inorganic mercury or amalgam. Total replacement of all amalgam fillings was carried out on 20 patients with fillings based on composite resin, gold, porcelain or a combination of these. Sixteen out of 20 patients showed complete healing of OLR; three patients had marked improvement, whereas one patient showed no improvement. Levels of IL-6 detected before replacement were significantly higher than IL-6 levels following the replacement ($P = 0.003$). The IL-8 levels measured before replacement procedure were significantly higher than the IL-8 levels after replacement of the fillings ($P < 0.001$).On the basis of clinical observations, restorative therapy resulted in tissue healing. Following the replacement of amalgam fillings with fillings based on other restorative materi-

als, levels of both IL-6 and IL-8 shifted towards normal, as measured in healthy subjects (23).

In order to prove the efficacy of the biostimulative laser therapy, we ran a research correlating the clinical signs to biostimulative therapy and levels of TNF-α and IL-6. The aim of this study was to monitor therapeutic response by determining the levels of proinflammatory cytokines TNF-α and IL-6 in whole unstimulated saliva in patients with denture stomatitis (DS), before and after laser therapy. DS is an inflammatory condition that occurs in subjects who wear dentures (usually upper), and it is a common oral mucosal lesion. A potential noninvasive treatment for DS patients is laser phothotherapy. A group of 40 consecutive subjects was selected on the voluntary basis from the pool of patients who presented for the diagnostics and treatment of DS. A clinical examination was performed according to the standard clinical criteria. Lesions described as palatal inflammation were diagnosed as Newton type II denture stomatitis. The patients were randomly assigned to either an experimental group (20 patients receiving the real LPT) or a control group (20 patients receiving inactive/placebo laser treatment). In order to determine the salivary levels of TNF-á and IL-6, ELISA testing was performed. Following treatment with LPT for 4 weeks, the levels of TNF-α and IL-6 decreased significantly ($p < 0.001$) and were significantly different from controls ($p < 0.001$).The results of this study suggest that LPT may be an effective choice of therapy (24).

CONCLUSION

During the past 10 years we ran several investigations where we used saliva as a diagnostic tool, and consequently we have proved that it may be regarded as the perfect medium to be explored for health and disease monitoring. The translational applications and opportunities are enormous. The ability to monitor health status, disease onset and progression, and treatment outcome through noninvasive means is the most desirable goal in the health care promotion and delivery.

Abbreviations

WUS — whole unstimulated saliva
IL-6 — interleukin-6
IL-2 — interleukin-2
IFN-γ — interferon gamma
VEGF — vascular endothelial growth factor
OLP — oral lichen planus
TNF-α — tumor necrosis factor-alpha
BMS — burning mouth syndrome
LLLT— low level laser therapy
OLR — oral lichenoid reactions
DS — denture stomatitis
LPT — laser phototherapy laser phototherapy

Sažetak

SALIVA KAO DIJAGNOSTIČKI MATERIJAL

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Pljuvačka je dostupna oralna tečnost sa brojnim funkcijama, od varenja, preko održavanja integriteta tkiva, do prevencije karijesa. Promene koje se odnose na sekreciju pljuvačke mogu biti kvalitativne i kvantitativne: obe promene su posledica određenih stanja/bolesti (unutrašnjih faktora) ili hranljivih materija/lekova unetih u organizam (spoljašnji faktori). U poslednjih 15 godina, napreci u oblasti tehnologije dali su veliki doprinos korišćenju pljuvačke u dijagnostičke svrhe. Analiza pljuvačke, kao i analiza krvi, ima dva glavna cilja: da identifikuje supstance organizma koji trpe zbog određene bolesti, i da prate napredak i terapijski učinak. Ovaj rad obezbeđuje pregled mogućnosti koje pruža korišćenje salive u dijagnostičke svrhe i daje primere određenih kliničkih istraživanja, sa glavnim ciljem da stimuliše korišćenje ovog neinvazivnog sredstva u unapređenju zdravlja populacije.

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Review article

PNEUMOTHORAX — DIAGNOSIS AND TREATMENT

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Abstract: **Introduction:** Pneumothorax is defined as the presence of air in the pleural cavity, ie, the space between the chest wall and the lung itself. Pneumothorax is classified ethiologically into spontaneous pneumothorax and traumatic pneumothorax. Spontaneous pneumothorax is further classified into primary and secondary. Traumatic pneumothorax may result from either blunt trauma or penetrating injury to the chest wall. It can also be caused by iatrogenic injuries. Spontaneous pneumothorax is a significant health problem because of the high recurrence rate (this is so called recurrent pneumothorax).

The aim of the study: the review of modern diagnosis and surgical management of pneumothorax.

Methodology: This is a review article. We used Medline and Pubmed databasis for retrieving the literature.

Conclusion: Pneumothorax, either spontaneous or traumatic, demands urgent intervention in order to normalize lung function and save life of the patient.

Keywords: pneumothorax, chest drainage, thoracotomy.

INTRODUCTION

Pneumothorax is defined as the presence of air in the pleural cavity, ie, the space between the chest wall and the lung itself. Itard first recognized pneumothorax in 1803, and Laennec himself described the full clinical picture of the condition. In the second part of XIX century it was believed that tuberculosis was the the main cause of pneumothorax since it was present mostly in patients with tuberculosis. On the other hand, Forlanini (Europe, in 1882) and John B. Murphy (the USA, in 1898) pointed out the useful results of pneumothorax in tuberculosis treatment (collapse therapy) (1, 2).

Althoug pathophysiological processes of pneumothorax are not fully known, it is is known that pleural pressure is negative with values –2 to –40 cm H2O. If a communication developes between the pleural space and an alveolus, air will flow into the pleural space until a pressure gradient no longer exists or until the communication is sealed. Without the negative intrapleural pressure holding the lungs against the chest wall, their elastic recoil properties cause them to collapse. The main physiologic consequences od pneumothorax are a decrease in the vital capacity and a decrease in the partial pressure of arterial oxygen (PaO2). In the otherwise healthy individual, the discease and the vital capacity is well tolerated. If the patient's lung function is compromised before the pneumothorax, however, the decrease in the vital capacity may lead to respiratoty insufficiency with alveolar hypoventilation and respiratory acidosis. In a tension pneumothorax, the intrapleural air pressure exceeds atmospheric pressure. The mechanism by which a tension pneumothorax develops is probably related to some type of a one-way valve process in which the valve is open during inspiration and closed during expiration. If extra thoracic air pressure remains relatively higher than the pressure in the pneumothorax over a period of time, then the air in pleural space and the ambient atmosphere will begin to approach equilibrium. This can cause mediastinal shift, compression of the superior vena cava, compression of the contralateral lung. The reduced preload (volume returning to the heart) causes a reduced stroke volume and therefore reduced cardiac output. This may result in hemodynamic collapse and obstructive shock (3).

CLASSIFICATION OF PNEUMOTHORAX

According to aetiology pneumothorax is classified into spontaneous and traumatic (Table 1). Spontaneous pneumothorax is further classified into primary and secondary. Traumatic pneumothorax may result from either blunt trauma or penetrating injury to the

Table 1. *Classification of pneumothorax*

Spontaneous
Primary *(a rupture of a subpleural bleb)*
Secondary
Chronic obstructive pulmonary disease (COPD)
Cystic fibrosis
Bronchial asthma
Connective tissue diseases (Marfan Syndrome)
Interstitial lung diseases (*Eosinophilic granuloma*)
Pneumocystis carinii pneumonia (in AIDS patients)
Pneumonia with lung abscess
Pulmonary hydatid disease
Lung cancer (metastatic sarcoma)
Esophageal perforation
Catamenial pneumothorax
Neonatal pneumothorax
Traumatic
Iatrogenic
Central venous catheter insertion
Pacemaker implantation
Transthoracic needle biopsy
Transbronchial needle aspiration
Thoracocentesis
Laparoscopic surgery
Barotrauma
Blunt trauma
Road traffic accident trauma, falls, sports injuries
Penetrating trauma
Shot wounds, stab wounds

Source: Spasić M, Milisavljević S, Gajić V. Analiza učestalosti javljanja i načina lečenja pneumotoraksa u petogodišnjem periodu u Kragujevcu. Med Pregl 2012; LXV(Vol 5–6): 238–43.

chest wall. It can also be caused by iatrogenic injuries (3). This condition occurs in 7.4 to 18 per 100 000 men each year and 1.2 to 6 per 100 000 women each year. The incidence of secondary spontaneous pneumothorax is 6.3 per 100 000 men each year and 2 per 100 000 women each year (4). Some British studies that have been done recently show the incidence of primary spontaneous pneumothorax of 24 per 100 000 in men and 9.8 100 000 in women (5).

PRIMARY SPONTANEOUS PNEUMOTHORAX

Primary spontaneous pneumothorax (PSP) commonly occurs in tall, thin, adolescent men (male-female ratio 6:1). Smoking is associated with a risk of developing pneumothorax in healthy smoking men (5). Because the gradient in pleural pressure is greater from the lung base to the lung apex in taller individuals, the alveoli at the lung apex are subjected to a greater mean distending pressure in taller individuals. Over a long period, this higher distending pressure could lead to the formation of subpleural blebs (6). The ocurrence of PSP seems to be related to the level of cigarette smoking. The relative risk of a pneumothorax is 100 times higher in heavy smokers (more than 20 cigarettes/day) than in nonsmokers (7).

Some studies suggest that there is a familial tendency for the development of primary spontaneous pneumothorax. In some cases of PSP the mode of inheritance for the tendency for primary spontaneous pneumothorax is either autosomal dominant with incomplete penetrance or X-linked recessive (8). Primary spontaneous pneumothoraces are believed to be the result of rupture of sub-pleural blebs (9). Sub-pleural blebs and bullae are found in up to 90% of cases at thoracoscopy or thoracotomy and in up to 80% on computerised tomography (CT) scanning of the thorax (10, 11). The pathogenesis of the blebs remains unclear. There are suggestions that they may be congenital or inflammatory in origin or the result of disturbance of collateral ventilation (12). According to some studies, precipitating factors may be atmospheric pressure changes, physical activity, and exposure to loud music (13). Sadikot et al, study showed a recurrence rate of 39% during the first year (14). It also indicated that there was 54% risk of recurrence of pneumothorax in 4 years. According to their studies, factors that have been proposed to predispose patients to primary spontaneous pneumothorax (PSP) include smoking and patient's height. The peak age for the occurence of primary spontaneous pneumothorax is the aerly 20' and it rarely occurs after age 40. Primary spontaneous pneumothorax usually develops while the patient is at rest. Main symptoms are chest pain and dyspnea. This pain may be mild or severe, sharp and steady ache in character, and usually resolves within 24 h even though pneumothorax still exists (15). It is interesting that many patients with a primary pneumothorax do not seek medi-

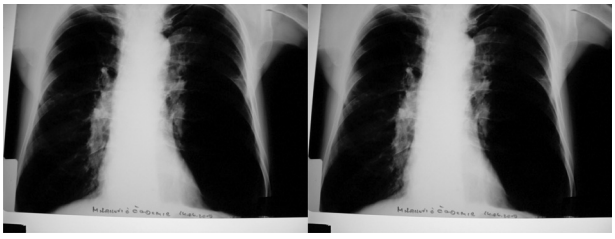

Figure 1. 1a *Spontaneous pneumothorax in the left lung;* ***1b*** *Bilateral pneumothorax*

cal attention for several days- more than 50% of patients waited more than 24 hours after their symptoms started to seek help, and 18% waited more than a week after the symptoms appeared (16) (Figure 1a, 1b).

SECONDARY SPONTANEOUS PNEUMOTHORAX

Secondary spontaneous pneumothorax (SSP) occurs in patients with underlying lung disease.

The incidence of secondary spontaneous pneumothorax is similar to that of primary spontaneous pneumothorax. It usually occurs in older people, after the age of 60 (13). Some research show that the peak incidence for males occures in the seventh decade of life, 60/100.000 each yearn (5). Many lung diseases can cause SSP: chronic airway and alveolar diseases (COPD, bronchial asthma, cystic fibrosis); infectious lung diseases (tuberculosis, pneumocystis carinii, lung abscess leading to pneumothorax with pleural empyema); interstitial lung diseases (idiopathic fibrosing alveolitis, sarcoidosis, histiocytosis X, lymphangio leiomyomatosis); systemic connective tissue diseases (rheumatoid arthritis, ankylosing spondylitis, scleroderma, Marfan- and Ehlers Danlos-syndrome); malignant lung and chest diseases (bronchial cancer, sarcoma) (13). The most common lung disease that causes spontaneous pneumothorax is chronic obstructive pulmonary disease (COPD).

Degradation of elastic fibres of visceral pleura contributes the occurence of pneumothorax in COPD (15). SSP occurred in many HIV-infected patients.

Pneumocystis carinii (PCP) infection has been considered to be the main aetiological factor for this association, because of a severe form of necrotising alveolitis that occurs in which the subpleural pulmonary parenchyma is replaced by necrotic thin-walled cysts and pneumatoceles. These patients can develop bilateral pneumothorax (15). The relative risk of recurrence of secondary spontaneous pneumothorax is 45% higher than the one of PSP (15). Risk factors for reccurence of SSP include age, pulmonary fibrosis and emphysema (17). Because lung function in these patients is already compromised, secondary spontaneous pneumothorax (SSP) often presents as a potentially life-threatening disease. The clinical signs and symptoms of secondary pneumothorax are more intense and severe. Dyspnea is the main symptom, and chest pain on the same side as the affected lung is present in most patients. Some of the most clinically significant symptoms that may develop include hypotension, tachycardia, cyanosis, hypoxemia with or without hypercapnia, and acute respiratory distress. The physical findings are often subtle and may be masked by the underlying lung disease, especially in patients with COPD (13) (Figure 2a, 2b).

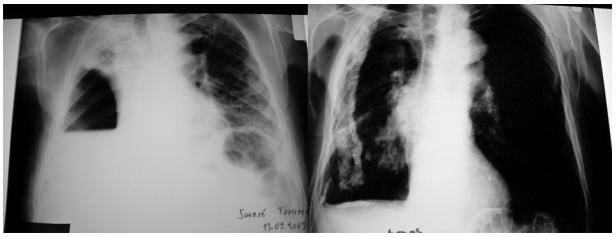

Figure 2. 2a *Hydropneumothorax in the right lung Tuberculosis "destroyed lung"; **2b** Fibrothorax in the right lung After the thoracic drainage*

CATAMENIAL PNEUMOTHORAX

Catamenial pneumothorax is a spontaneous type of pneumothorax that starts at the onset of or within 24 to72 hours after onset of menses and is usually recurrent. Catamenial pneumothorax was first described by Maurer in 1958. The initial pneumothorax usually does not occur until the woman is in her thirties. Lillington introduced in 1972 the term catamenial pneumothorax to describe the already reported phenomenon (18). This pneumothorax was considered to be a rare type with the incidence 1–5% in women in reproductive age (18). Recent studies have shown that in 25% of cases the recurrent catamenial pneumothorax was related to time of menstruation (19), so the incuidence is not so low as it was believed. These pneumothoraces are usually right sided (according to some authors, in 95%) (20). The pathophysiology of catamenial pneumothorax is uncertain. Three distinct mechanisms have been proposed based on metastatic, hormonal and anatomic model (18). The metastatic model hypothesizes migration of endometrian tissue via the peritoneal cavity through transdiaphragmatic lymphatic channels, via diaphragmatic fenestrations, or hematogenously into the pleural space. Congenital fenestrations are more common in right hemidiaphragm making intratho- racic endometriosis right sided. Endometrial deposits have been identified in in the pleural space in 13% to 62,5% of t he cases (19, 20, 21). The hormonal hypothesis was proposed by Rossi and Goplerud in 1974. It suggests that high serum levels of prostaglandin F2 at ovulation leads to vasospasmassociated ischemia with tissue injury and alveolar rupture. However this cannot explain the preponderance of right sided involvement. Also there are no non-steroidal anti-inflammatory medications (NSAIDs) capable of preventing recurrence of catamenial pneumothorax in respective reported series. Thus, this hypothesis was rejected (18). The anatomic model for catamenial pneumothorax is based on the influx of air into the pleural space from the peritonela

cavity via diaphragmatic fenestrations (18). Also concomitant pneumoperitoneum is found in some patients with catamenial pneumothorax (18). Diaphragmatic defects were found in 50%–62,5% of patients. To prevent recurrence, diaphragmatic defects should certainly be closed (19, 21). Patients with catamenial pneumothorax develop chest pain and dyspnea within 24 to 72 hours of the onset of the menstrual flow. It is usually recurrent and correlated with menses (18).

NEONATAL PNEUMOTHORAX

Spontaneous pneumothorax is present shortly after birth in 1% to 2% of all infants. It is twice as common in boys as in girls. The incidence of neonatal pneumothorax is higher in cases of preterm birth and low birth weight. (15%). Also, the cases of infants with fetal distress and respiratiry distress syndrom have higher incidence (19%) (15). The pathogenesis of neonatal pneumothorax is related to the mechanical problems of first expanding the lung. Transpulmonary pressures have average values 40cm H2O during the first few breaths of life, with occasional transpulmonary pressures as high as 100 cm H2O. If bronchial obstruction occurs, high transpulmonary pressures may lead to rupture of the lung (15). The signs vary from none to severe acute respirator distress. In the infant with a small pneumothorax, mild apneic spells with some irritability or restelssness may be present. Large pneumothoraces incur varying degrees of respiratoty distress, and, in severe cases, marked tachypnea, grunting, retractions, and cyanosis are present (15). The most reliable clinical sign of neonatal pneumothorax is a shift of the apical heart impulse away from the side of the pneumothorax (15) (Figure 3a, 3b)

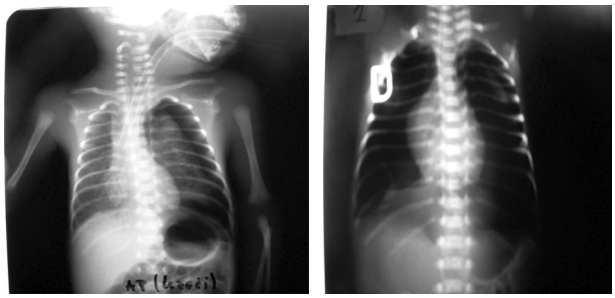

Figure 3. 3a *Neonatal pneumothorax in the left lung;* ***3b*** *Bilateral neonatal pneumothorax*

IATROGENIC PNEUMOTORAX

The leading cause of iatrogenic pneumothorax is transthoracic needle aspiration (24%), subclavian needle (22%), thoracentesis (20%), transbronchial biopsy (10%), pleural biopsy (8%) and positive-pressure ventilation (7%) (13). Other procedures associated with

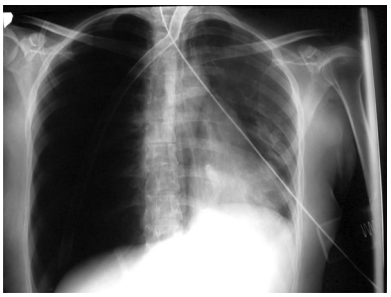

Figure 4. *Iatrogenic pneumothorax in the right lung. The rupture of membranous tracheal wall caused by reinforced tubus*

the iatrogenic pneumothorax devlopment include tracheostomy, intercostal nerve block, mediastinoscopy, liver biopsy, the insertion of nasogastric tubes, cardiopulmonary resuscitation (15). Iatrogenic pneumothorax should be suspected in any patient with respiratory distress symptoms as well as in patients who underwent some procedures (15) (Figure 4).

TRAUMATIC PNEUMOTHORAX

Traumatic pneumothorax may result from either blunt trauma or penetrating injury to the chest wall. Pneumothorax can occur at the time of the injury, immediately after the injury, or later.The incidence of severe traumatic pneumothorax is higher than 20% (22), and the incidence of chest injury is 50% (13). With non penetrating trauma, a pneumothorax may develop if the visceral pleura is lacerated secondary to a rib fracture, dislocation. Sudden chest compression abruptly increases the alveolar pressure, which may cause alveolar rupture. Blunt trauma can also cause alveolar rupture (23). With penetrating chest trauma, the wound allows air to enter the pleural space directly through the chest wall or through the visceral pleura from the tracheobronchial tree (23). Traumatic pneumothorax can also be classified as simple, open (“sucking”) and tension pneumothorax. In simple pneumothorax, the air from the injured lung enters the pleural space. There are not many symptoms of this type of pneumothorax (1). Open pneumothorax occurs when a wound on the chest is large enough to allow air to pass freely in and out of the pleural space. In this case, the atmospheric pressure is in equilibrium with intrapleural pressure, blocking the lung inflation and alveolar ventilation. The rush of air through the wound in the chest wall produces a sucking sound. In such patients the lung collapses. Traumatic open pneumothorax calls for the emergency intervention- sealing the open wound with Vaseline gauze and placing the chest tube. The wound treatment involves common surgical procedures (1, 23) (Figure 5). A tension pneumothorax is the result of the chest wall or lung injury. A one-way valve mechanism

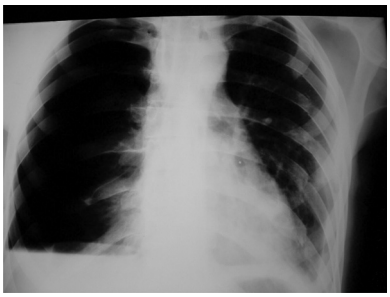

Figure 5. *Traumatic pneumothorax in the right lung (traffic accident trauma). Serial rib fractures on the right side Left pulmonary contusion*

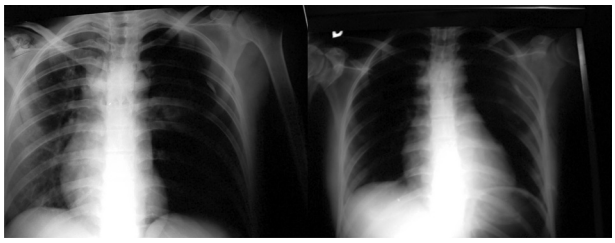

Figure 6. 6a. *Tension pneumothorax in the left lung* ***6b.*** *Condition after chest tube drainage in the left lung. Complete re-expansion of the left lung*

occurs, where the air that enters the pleural space with each inspiration is trapped and cannot be expelled durng expiration. Interthoracic pressure increases causing the lung to collapse. The collapse in the lung causes a shift in the mediastinum away from the injured side, resulting in hypoventilation, decreased venous return to the heart and potentialy in development of obstructive shock. The signs and symptoms associated with tension pneumothorax include cyanosis, dyspnea, tachypnea, tachycardia, hypotension, distended neck veins, profuse diaphoresis. A tension pneumothorax is a life-threatening injury that should be diagnosed and managed urgently. Management is perfomed by immediate needle decompression. A large bore needle is inserted in the II intercostal space, at the midclavicular line (1, 15) (Figure 6a, 6b).

DIAGNOSIS OF PNEUMOTHORAX

The diagnosis of pneumothorax is established from the patients' history and physical examination findings that reveal decreased movement of the hemithorax, decreased or absent fremitus, hyper sonority on percussion and decreased or absent breath sounds on the affected side. Radiography of the chest in the upright position and PA projection of the chest are the most common methods of diagnosing pneumothorax. The main feature of a pneumothorax on a chest radiograph is a white visceral pleural line, which is separated from the parietal pleura by a collection of gas (15). Radiographs that are obtained in the lateral decubitus position can be useful in cases of clinically suspected pneumothorax, while PA radiograph is normal. CT scan of the chest is used to differentiate large bulla from pneumothorax (24). When PA radiograph reveals abnormalities, it is possible to calculate the actual pneumothorax size by using the Light index: PTX% = 100 [1-diameter lung /diameter hemitorax^3], and it may be useful for research purposes (15). To calculate the size of a pneumothorax: is to measure the distance between the pleural surface and the lung edge (at the level of the hilum). If this is 2 cm or more, it represents a large pneumothorax and if it is < 2 cm it is considered to be a small pneumothorax (24).

COMPLICATIONS OF PNEUMOTHORAX

These complications include tension pneumothorax, hemopneumothorax, bronchopleural fistula, pneumomedistanium,chronic pneumothorax (failure of the lung to re-expand).

Spontaneous hemopneumothorax

The incidence of pleural effusion is 15 to 20% in patients with hydropneumothorax.

Approximately 5% of patients with pneumothorax will have concomitant haemothorax with an amount of blood in the pleural space. The mechanisms of bleeding described in SHP are bleeding either of a torn apical vascular adhesion between the parietal and visceral pleura or of torn congenital aberrant vessels between the parietal pleura and the bulla as the lung collapses or due to rupture of vascularized bullae. Manifestations depend on the amount of blood lost during this disorder. Treatment of SHP includes tube thoracostomy for drainage of the haemothorax and re-expansion of the lung. If the re-expansion of the lung does not stop the bleeding, thoracotomy is needed to stop the bleeding (15) (Figure 7).

Bronchopleural fistula

A bronchopleural fistula may occur in patients with primary spontaneous pneumothorax (3% to 4%),

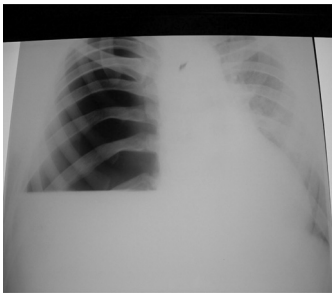

Figure 7. *Spontaneous hemopneumothorax in the right lung. Upright radiography*

though it is more common in patients with secondary spontaneous pneumothorax or traumatic pneumothorax. Persistent air leakage occurring after thoracic drainage for pneumothorax is the early clinical sign of this complication. It can be managed by thoracotomy, closng the fistula and pleurodesis (15).

Pneumomediastinum

Pneumomediastinum is a rare complication of pneumothorax (< 1%). It is the presence of free air within the mediastinum. Subcutaneous emphysema is often associated with pneumomediastinum.This entity is without significant clinical importance. Pneumomediastinum has rarely been reported to cause some serious complications (esophageal injuries and injuries in the large airways) (1).

Chronic pneumothorax (failure of the lung to re-expand)

Chest tubes are used for pneumothorax to promote lung re-expansion. But in some cases, this procedure fails.The thickened cortex on the visceral pleura prevents the re-expansion of the lung. Medical procedures for this condition is thoracotomy and decortication (1).

TREATMENT

The objective in treating a pneumothorax is to eliminate the air from the pleural space, to allow lung to re-expand, and to prevent recurrences. The best method for achieving this depends on the severity of the lung collapse, the type of pneumothorax, patient's overall health and on the risk of complications.There are many therapeutic possibilities in clinical practice.

Observation

Observation is recommended for patients with PSP occupying less than 15% of the hemithorax. As with these patients, observation remains the first-line treatment in patients with pneumothoraces of less than 1 cm depth or isolated apical pneumothoraces (24). The rate of air absorption is 1, 25% every 24 hours. Supplemental oxygen can be administered to increase the rate of pleural air absorption. A small number of patients is treated this way (15).

Aspiration- exsufflation

Aspiration may be the initial treatment for the patients with primary pneumothorax. It may also be considered for patients younger than 50 with secondary pneumothorax of moderate size (air rim 1–2 cm). Percutaneous needle aspiration results in complete lung re-expansion in 59 to 83% patients with PSP and in 33 to 67% patients with SSP. Recurrence rate of pneumothorax after the exsufflation is almost the same as the one after the chest tube drainage (24).

Tube thoracostomy

Tube thoracostomy is the most commonly perfo-rmed surgical procedure in thoracic surgery.

Thoracostomy tube placement is indicated for the PSP and symptomatic patients, as well as for the symptomatic SSP, iatrogenic and traumatic pneumothorax (24).

The overall objestive of chest-tube therapy is to promote lung reexpansion. The chest tube is inserted via an incision at the 4th or 5th intercostals space in the anterior axillary or mid-axillary line. It can also be inserted via 2nd midclavicular intercostal space (Figure 8). It is inserted near the upper border of the rib. There are three techniques most commonly used to place a chest tube: using the trocar, associated with a higher rate of intrathoracic organ injury, blunt dissection after skin incision (less comfortable but with lower risk of complications) (Figure 9), or Seldinger technique in which a guide wire is inserted through the introducer needle and a chest tube is inserted into the pleural space. Once the chest tube has been inserted, it must be

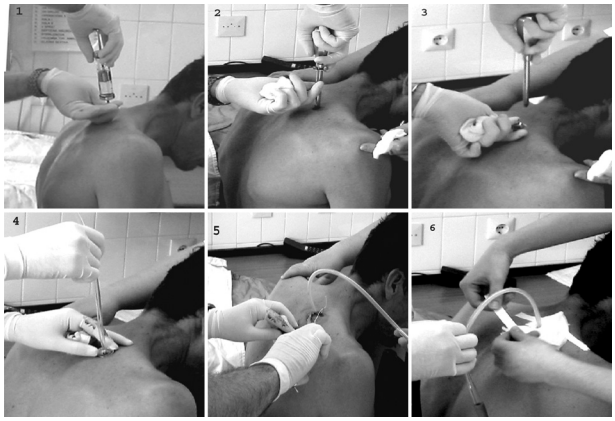

Figure 8. *Thoracic trocar drainage in the right lung*

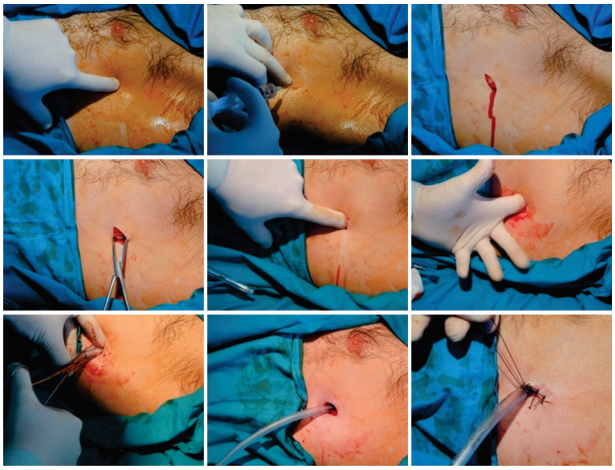

Figure 9. *Tube thoracostomy drainage*

connected to either suction or an apparatus to allow unidirectional drainage (water seal without suction or a Heimlich valve). If the adequate expansion is achieved, the catheter can be removed (after 5 to 7 days). The instillation of sclerosing agents (talc) through chest tubes can help prevent recurrences of pneumothorax (1).

SURGICAL MANAGEMENT AND PREVENTION OF RECURRENT PNEUMOTHORACES

Chemical pleurodesis

Chemical pleurodesis is a procedure to achieve symphysis between the two layers of pleura by sclerosing agents. These agents can be introduced into the pleural space. The therapeutic action of the agent (tetracycline or talc) instilled into the pleural cavity through a chest drain is thought to result from induction of an inflammatory reaction (24).

Surgical management and mechanical pleurodesis

Surgical management is the common method for pneumothoraces with persistent air leak (5 to 7 days of thoracic drainage), the failure of the lung to expand, recurrence of pneumothorax (ipsilateral or contralateral), bilateral sponatenous pneumothorax, hemothorax, high risk professions (air craft personnel, scuba divers). The objective of surgical management of pneumothorax is to remove air from the pleural cavity (resection of blebs) and to prevent recurrence (obliteration of pleural space). Small posterolateral thoracotomy, transaxillary mini thoracotomy, minimally invasive endoscopic surgery (VATS- Video-assisted thoracoscopic surgery) are the most common surgical procedures (24) (Figure 10). Bullae can be treated with different surgerical procedures- lung resection, stapled excision, electrocoagulation, suture ligature. To prevent the recurrence of pneumothorax, resection is combined with some of the procedures for obliteration of pleural space. This procedure may be parietal pleurectomy (partial-apical or total), parietal pleural abrasion (mechanical pleurodesis), chemical pleurodesis (application of sclerosing agents). Parietal pleurectomy produces adhesion between visceral pleura and endothoracic fascia; pleural abrasion produces adhesions between visceral and parietal pleura while anatomic layers are preserved, reducing the risk of thoracoscopy (24). Open thoracotomy with bullectomy plus pleural abrasion or pleurectomy is effective in diminishig the rate of recurrence (1%). The rate of mortality after the procedure is low (3,7%). Compared to VATS, after this treatment the lung function is compromised and the

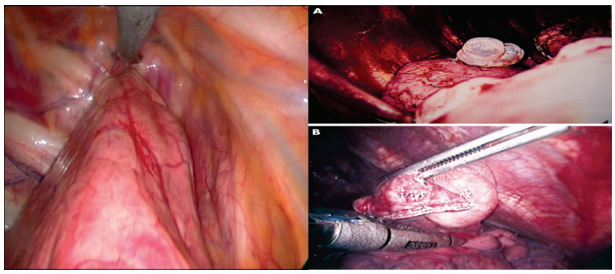

Figure 10. *VATS resection of right-sided bullae*

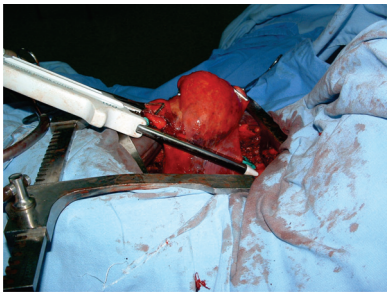

Figure 11. *Primary spontaneous pneumothorax. Excision of the bulla using stapler*

hospitalization period is longer. In minimally invasive surgery not all blebs may be detected, and the recurrence rate is higher (5-10%), while hospitalization period is shorter, post-surgical pulmonary gas exchange is better and post-surgical pain is not so severe (240 (Figure 11).

CONCLUSION

Pneumothorax is defined as the presence of air in the pleural space. It is caused by a rupture in visceral or the parietal pleura.Pnemothoraces can be divided into spontaneous pneumothoraces and traumatic pneumothoraces. Spontaneous pneumothoraces are further divided into primary and secondary spontaneous pneumothoraces. Traumatic pneumothorax may result from either blunt trauma or penetrating injury to the chest wall.It may also be caused by iatrogenic injuries resulting from diagnostic or therapeutic procedures.

The diagnosis of pneumothorax can be established from the patients' history, physical examination findings and the chest X-ray. Pneumothorax can be managed conservatively (rest and observation), exsufflation, and chest tube thoracotomy. Recurrent pneumothorax and complications are managed through surgical procedures (thoracotomy or VATS).

Abbreviations

PaO2 — partial pressure of arterial oxygen
PSP — Primary spontaneous pneumothorax
SSP — Secondary spontaneous pneumothorax
COPD — Chronic obstructive pulmonary disease
PCP — Pneumocystis carinii
SHP — Spontaneous hemopneumothorax
VATS — Video-assisted thoracoscopic surgery

Sažetak

PNEUMOTORAKS — DIJAGNOSTIKA I LEČENJE

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Uvod: Pneumotoraks predstavlja prisustvo vazduha u pleuralnom prostoru, odnosno prisustvo vazduha između pluća i zida grudnog koša. U zavisnosti od etiologije pneumotoraks se klasifikuje na spontani i traumatski. Spontani pneumotoraks se dalje deli na primarni i sekundarni. Traumatski pneumotoraks nastaje kao posledica tupih ili penetrantnih povreda grudnog koša, ili nakon jatrogenih povreda. Recidivantni pneumotoraks se javlja kao ponovljeni spontani pneumotoraks.

Cilj rada: Prikaz savremene dijagnostike i načina hirurškog lečenja kod pacijenata sa pneumotoraksom.

Metodologija: Ovo je pregledni članak. Korišćena je literatura uvidom u bazu medicinskih podataka Medline i Pubmed.

Zaključak: Pneumotoraks, bilo spontani bilo traumatski predstavlja hitno stanje u medicini i zahteva brzu i neodložnu intervenciju lekara, kako bi se funkcija pluća što pre normalizovala i očuvao život vitalno ugroženom pacijentu.

Ključne reči: pneumotoraks, grudna drenaža, torakotomija.

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Review article

LASER CORRELATION SPECTROSCOPY (LCS) AND ITS CLINICAL PERSPECTIVES IN OPHTHALMOLOGY

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Abstract: The method of laser correlation spectroscopy (LCS) is based on the analysis of the spectrum of quasielastic light scatter during coherent monochromatic laser irradiation of micro-particles in biological fluids (blood serum, urine, oropharyngeal washout fluid, tear fluid etc.). Spectrum provides information on dynamic processes in the analyzed system: translation motion of scattering particles and their orientation and conformation dynamics. Special procedures of cluster analysis make it possible to find out to which linkage group a particular spectrum belongs. LCS allows evaluation of sub-fractional composition of biological fluids in a wide range of molecular sizes (from 1 to 10,000 nm), which determines principal novelty of this approach in ophthalmology.

Key words: laser correlation spectroscopy, tear fluid, contact lenses, the cornea, PRK, Trans PRK.

INTRODUCTION

The analysis of tear fluid is a simple, safe and minimally invasive method of investigation. Method of quantitative analysis of tears fluid and functional tests of the tear secretion is used traditionally and mostly long ago (1). In many works of various authors changes of composition of the plaintive liquid (PL) at pathology of the plaintive device were described and scientifically proved generally, and also local metabolic and immune changes of an organ of vision (2). Most of the work is devoted to a comparative analysis of trace element of tear fluid for various common diseases of the body, such as diabetes, eye diseases in general (diabetic retinopathy, primary open-angle glaucoma), as well as after surgery (photorefractive keratoektomiya and laser in-situ keratomileusis, cataract extraction). Changes of sub-fractional compound of tear fluid after these processes as a result of a variety of local tissue and intracellular processes (3). However, the analysis of these changes was conducted by various methods, which proved to be technically difficult to achieve, or not sufficiently express, or because of low sensitivity. But with laser correlation spectroscopy (LCS) it is possible to record objectively the nature and extent of these changes.

Laser correlation spectroscopy (LCS) (analogs: spectroscopy of quasi-elastic light scatter, optical mixing spectroscopy, photon-correlation spectroscopy) consists of measurement of spectral characteristics of light scattered in quasi-elastic mode from the spectrum of fluctuation intensity of the recorded light (4-9). Two schemes of measurements can be used: homodyne (selective recording of the light scattered by the system) and heterodyne (recording of beats between the scattered light and reference fixed high-intensity light). The spectrum of light intensity fluctuations is a Fourier-transform of a correlation function of intensity fluctuations of the recorded field. In the device used by us, a heterodyne scheme (Figure 1) is applied (5). Helium-neon laser serves as a source of light (2).

Laser beam is divided by a plate (3) and about 0.1% light beam (S) is separated from the main beam,

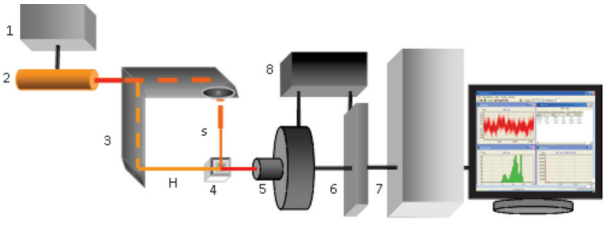

Figure 1. *Scheme of laser correlation spectroscope*

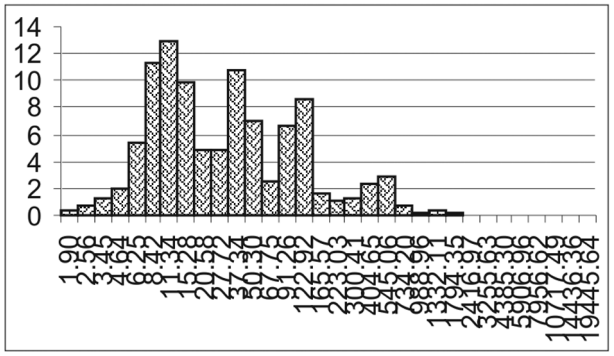

Figure 2. *Histogram of size distribution of particles. Ordinate – contribution of particles of the corresponding zone into light scattering (%). Abscissa – particle size (nm)*

is transmitted to a photo recorder (5), and is mixed with the scattered portion. Not the spectrum of light scattered by the studied system, but the spectrum of photoelectric fluctuations at the photo recorder (5) output is directly recorded in LCS. This spectrum represents a result of mutual beats of electromagnetic filed harmonics and is located in a low-frequency band.

A histogram of typical size distribution is presented in Figure 2. The size scale is discrete and consists of 32 points.

The distribution histograms in biological fluid provide qualitative information on the mean particle sizes and their relative content. Strict correspondence of certain fragments of the spectrum to biological nature of serum components can be determined after additional studies.

For example, in degenerative and catabolic processes increased activity of hydrolases in interstitial fluid appears low-molecular weight molecules. The recorded spectrum of tear fluid will contribute to increased light scatter low-molecular ingredients - from 10 to 200 nm (mainly albumin and globulins). When processes are associated with modification of cellular metabolism and the growth of different nature toxicity contribution to light scattering is increasing from 200 to 600 nm (glycoproteins) (10).

Assessment of the severity of the postoperative period and possible complications (including concomitant diseases)

Analysis of tear fluid was conducted in patients after cataract extraction followed by IOL (intraocular lens) and in patients after refractive surgery. With an increase in subjective symptoms, inflammation in the eye was revealed after cataract extraction with IOL implantation in the experimental spectrum of the growing contribution to light scattering high-molecular ingredients (from 400 to 600 nm) - a type of heavy glycoprotein complex. It is typical to the processes accompanying the increase of inflammatory intoxication. Also, increasing the contribution of high and very high-molecular fractions range (600 - 1200 nm or more), which is associated with the formation of increased numbers of immune complexes (11). In patients after refractive surgery there was marked prevalence in washouts of tear fluid albumin and globulins, which suggested a tendency to catabolic processes which can be caused by increased activity of hydrolases and due to chronic traumatization of the contact lens (CL) and the damaging influence of the laser directly on the collagen fibres of the cornea, destroyed during ablation, small fragments that give this prevalence in the spectrum of the tear fluid. In the early postoperative period showed an increase in the number of small particles that can be caused by the presence of protein ingredients such as albumins, globulins, growth factors and cytokines protein nature, including transforming growth factor-β (TRF-beta), and may also indicate about the growth of the inflammatory response of different nature, including the endogenous nature, which may be due to undergoing surgery and reparative processes occurring after the ablation of the cornea. In the future, the results of this study can be used for screening for monitoring and forecasting process in the postoperative corneal surface ablation (12, 13).

Assessment of consequences of wearing soft lenses

The method of laser correlation spectroscopy has been used to analyze the tear fluid in patients using soft contact lenses (CL) to different wearing experience (5 years and 5 years and more). For the possibility of extending the maximum safe wearing CL, requires an objective assessment of the status of local eyes of these patients. The results of analysis of laser-correlation spectrum revealed that patients using soft contact lenses as a contact lens, dominates presence in the tear fluid glyco-lipoprotein complexes and a relatively high content of immune complexes in comparison with the control group, indicating that the build-up of the inflammatory intoxication of various natures including endogenous character. Many authors have described various disadvantages of the use of contact lenses, such as hypoxia, oedema, corneal epithelial damage, superficial keratitis, micro-cysts, erosion, corneal ulcer, neovascularization, toxic and allergic reactions, infectious eye disease, a syndrome of “dry eye”. These complications of the use of the CL lead to various changes in the composition of tear fluid (14, 15). In addition to influence on the qualitative composition corneal membrane, contact lenses reduce the supply of oxygen to the corneal epithelium, thus reducing the metabolic rate

therein. Analysis of the samples between the groups of patients differing in duration of use CL showed that patients with many years of application of this type of contact lens, there was a slight prevalence of middle and low molecular weight components compared to patients using contact lens less than 5 years. People who use CL leads to the predominance in the tear fluid glyco-lipoprotein complexes and a relatively higher content of immune complexes, compared with patients who did not use the contact correction that says about the growth of the local inflammatory intoxication of different nature, including the endogenous nature. These changes may be related to chronic traumatization of the eye surface structures of soft contact lenses (16, 17).

It is worth noting that in the study, patients were taken without concomitant ophthalmopathology not instilled in the conjunctive cavity preparations. In addition, patients were used soft contact lenses of planned replacement for a period of wearing 2 weeks. So, what kind of extended wear contact lenses the patient chooses, of course, it will affect the structure of sub-fractional structure of tear fluid and reflect on the results of further research.

The prospects further research (correlation with clinical data and analysis, comparing the effects of different types of transactions, etc.)

Conducting photorefractive surgery is accompanied by metabolic and immunological changes of eye tissues, which persist for a long time (18). These changes may have a significant impact on the sub fractional composition of the tear fluid. Analysis of samples of tear fluid was conducted in patients undergoing several types of photo refractive surgery: photorefractive keratectomy and trans-epithelial photorefractive keratectomy. In the run-off from the groups of patients on the day after surgery epithelialization it was noted an increase in the number of albumin and globulin fractions, with difference between the groups. In the samples of Tear fluid patients after PRK slightly predominated small-molecule when it was compared with samples of patients after Trans PRK (13% and 10%, respectively), which may be associated with a higher precision calculation of the ablation zone during the second type of operation. The presence of middle fractions (glyco-lipoprotein particles) it is possible to assume a tendency to catabolic processes which could be caused by the damaging effects of the laser directly on the collagen fibres of the cornea, destroyed during ablation, small fragments that give this prevalence in the spectra of tear fluid. In the period of 3 months after surgery there was showed an increase in the number of fine particles of tear fluid compared to the control group, which may be due to the presence of protein ingredients, such as albumin, globulin, growth factors, interleukins and cytokines protein nature, including those described actively produced after excimer laser ablation of corneal transforming growth factor-β (TRF-beta). The presence of these factions during the early postoperative period and in the period of 3 months after the operation was expected to characterize the activity of reparative processes after corneal ablation.

Excimer laser photorefractive keratectomy and trans-epithelial photorefractive keratectomy have a direct impact on surface structures of the eye, which leads to similar long-life use that we have described the characteristic changes in the composition of the tear fluid sub-fractional (18).

By using enzyme immunoassay method it was analysed pro-inflammatory and anti-inflammatory cytokines in patients undergoing these operations. The results showed a significant increase in the concentration of IL-10 and significant predominance of IL-4 in samples of tear fluid patients postoperatively Trans PRK compared with of PRK, which can be indicative of the suppression of inflammatory reactions during Trans PRK. In two groups the cconcentration of pro-inflammatory cytokines was about the same, except peak group Trans PRK concentration IF-γ. However, it should be noted that this analysis was conducted on a small group of patients and more significant research in this area is planned for the near future.

The laser correlation spectroscopy is an original technique by means of which it is possible to diagnose initial changes in a forward piece of an eye when objective complications still aren't present on early terms. Besides, further results of the real researches can be used for screening monitoring and forecasting of a course of postoperative process at superficial ablation of a cornea. In addition, by means of this method at early stages, it is possible to correct the mode of carrying soft contact lenses, to appoint trophic therapy with the purpose to exclude and delay complications.

Conclusion

Based on the results of our study we can conclude that LCS - is express analysis, with which we can diagnose and observe the initial changes in local metabolism in the anterior segment of the eye, when the objective breaches have not seen yet. The observed changes in the direction of metabolic shifts maybe are stochastic and reflect either adaptive or non-adaptive responses of the organism to therapeutic or surgical intervention. More numerous sample and broader range of ef-

fects in combination with traditional research methods are required for deciphering of the real significance of the detected relationships. Visual analysis of histograms is low-effective for clinical studies; special classification programs are required to enable analysis of data bulk over a short time. The algorithm of classification analysis may be based on methods of the theory of groups. Metabolic deviations, measured by LCS, are due to different external influences. Thus we can suppose the LCS can be an integrative method, useful for experimental and clinical ophthalmological research.

DECLARATION OF INTEREST. None

Abbreviations

CL — contact lens
IF-γ — interferon - γ
IL — interleukin
IOL — intraocular lens
LCS — laser correlation spectroscopy
PL — plaintive liquid
PRK — photorefractive keratectomy
TRF-beta — transforming growth factor-β
Trans PRK — trans-epithelial photorefractive keratectomy

Sažetak

LASERSKA KORELACIONA SPEKTROSKOPIJA (LCS) I NJENA KLINIČKA PERSPEKTIVA U OFTALMOLOGIJI

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Metoda laserske korelacione spektroskopije je bazirana na analizi spektra kvazielastičnog rasipanja svetlosti tokom koherentnog monohromatskog laserskog zračenja mikročestica u biološkim fluidima (krvni serum, urin, orofaringealni ispljuvak, suze, itd.). Spektar pruža informacije o dinamskim procesima u ispitivanom sistemu: kretanje rasutih čestica i dinamika njihove orijentacije i građe. Specijalne procedure klaster analize omogućavaju da se otkrije kojoj povezanoj grupi pripada posebni spektar. LCS omogućava evaluaciju sub-frakcionalnog sastava bioloških fluida u okviru širokog spektra veličine molekula (od 1 do 10 000 nm), što određuje glavnu novinu ovog pristupa u oftalmologiji.

Ključne reči: laserska korelaciona spektroskopije, suze, kontaktna sočiva, rožnjača, PRK, Trans PRK.

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Pregled iz literature čine: uvod, odgovarajući podnaslovi, zaključak, literatura.

Bolesnici i metode/materijal i metode. Treba opisati izbor bolesnika ili eksperimentalnih životinja, uključujući kontrolu. Imena bolesnika i brojeve istorija ne treba koristiti.

Metode rada treba opisati sa dovoljno detalja kako bi drugi istraživači mogli proceniti i ponoviti rad.

Kada se piše o eksperimentima na ljudima, treba priložiti pismenu izjavu u kojoj se tvrdi da su eksperimenti obavljeni u skladu sa moralnim standardima Komiteta za eksperimente na ljudima institucije u kojoj su autori radili, kao i prema uslovima Helsinške deklaracije. Rizične procedure ili hemikalije koje su upotrebljene se moraju opisati do detalja, uključujući sve mere predostrožnosti. Takođe, ako je rađeno na životinjama, treba priložiti izjavu da se sa njima postupalo u skladu sa prihvaćenim standardima.

Treba navesti statističke metode koje su korišćene u obradi rezultata.

Rezultati. Rezultati treba da budu jasni i sažeti, sa minimalnim brojem tabela i slika neophodnih za dobru prezentaciju.

Diskusija. Ne treba činiti obiman pregled literature. Treba diskutovati glavne rezultate u vezi sa rezultatima objavljenim u drugim radovima. Pokušati da se objasne razlike između dobijenih rezultata i rezultata drugih autora. Hipoteze i spekulativne zaključke treba jasno izdvojiti. Diskusija ne treba da bude ponovo iznošenje zaključaka.

Literatura. Reference numerisati rednim arapskim brojevima prema redosledu navođenja u tekstu. Broj referenci ne bi trebalo da bude veći od 30, osim u pregledu literature, u kojem je dozvoljeno da ih bude do 50.

Izbegavati korišćenje apstrakta kao reference, a apstrakte starije od dve godine ne citirati.

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Primeri:

1. **Članak:** (svi autori se navode ako ih je šest i manje, ako ih je više navode se samo prva tri i dodaje se *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg 2003; 29: 650–652.

2. **Knjiga:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Poglavlje ili članak u knjizi:**

Latković Z. Tumori očnih kapaka. U: Litričin O i sar. Tumori oka. 1. izd. Beograd: Zavod za udžbenike i nastavna sredstva, 1998: 18–23.

Tabele. Tabele se označavaju arapskim brojevima po redosledu navođenja u tekstu, sa nazivom tabele iznad. Svaku tabelu odštampati na posebnom listu papira i dostaviti po jedan primerak uz svaku kopiju rada.

Slike. Sve ilustracije (fotografije, grafici, crteži) se smatraju slikama i označavaju se arapskim brojevima u tekstu i na legendama, prema redosledu pojavljivanja. Treba koristiti minimalni broj slika koje su zaista neophodne za razumevanje rada. Slike nemaju nazive. Slova, brojevi i simboli moraju biti jasni, proporcionalni, i dovoljno veliki da se mogu reprodukovati. Pri izboru veličine grafika treba voditi računa da prilikom njihovog smanjivanja na širinu jednog stupca teksta neće doći do gubitka čitljivosti. Legende za slike se moraju dati na posebnim listovima, nikako na samoj slici.

Ako je uveličanje značajno (fotomikrografije) ono treba da bude naznačeno kalibracionom linijom na samoj slici. Dužina kalibracione linije se unosi u legendu slike.

Treba poslati dva kompleta slika, u dva odvojena koverta, zaštićene tvrdim kartonom. Na pozadini slika treba napisati običnom olovkom prezime prvog autora, broj slike i strelicu koja pokazuje vrh slike.

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The manuscript should be arranged as following: title page, abstract, key words, introduction, patients and methods/material and methods, results, discussion, conclusion, references, tables, figure legends and figures.

Each manuscript component (title page, etc.) begins on a separate page. All pages are numbered consecutively beginning with the title page. The first author's last name is typed at the top right corner of each page.

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Original work should have the following headings: introduction, aim, methods, results, discussion, conclusion, references.

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Review of the literature include: an introduction, subheadings, conclusion, references.

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Statistical methods used, are outlined.

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Discussion. An exhaustive review of literature is not necessary. The major findings should be discussed in relation to other published works. Attempts should be made to explain differences between results of the present study and those of the others. The hypothesis and speculative statements should be clearly identified. The discussion section should not be a restatement of results, and new results should not be introduced in the discussion.

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1. **Article:** (all authors are listed if there are six or fewer, otherwise only the first three are listed followed by *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg 2003; 29: 650–652.

2. **Book:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Chapter or article in a book:**

Trier JJ. Celiac sprue. In: Sleisenger MH, Fordtran J5, eds. Gastro-intestinal disease. 4 th ed. Philadelphia: WB Saunders Co, 1989: 1134–52.

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