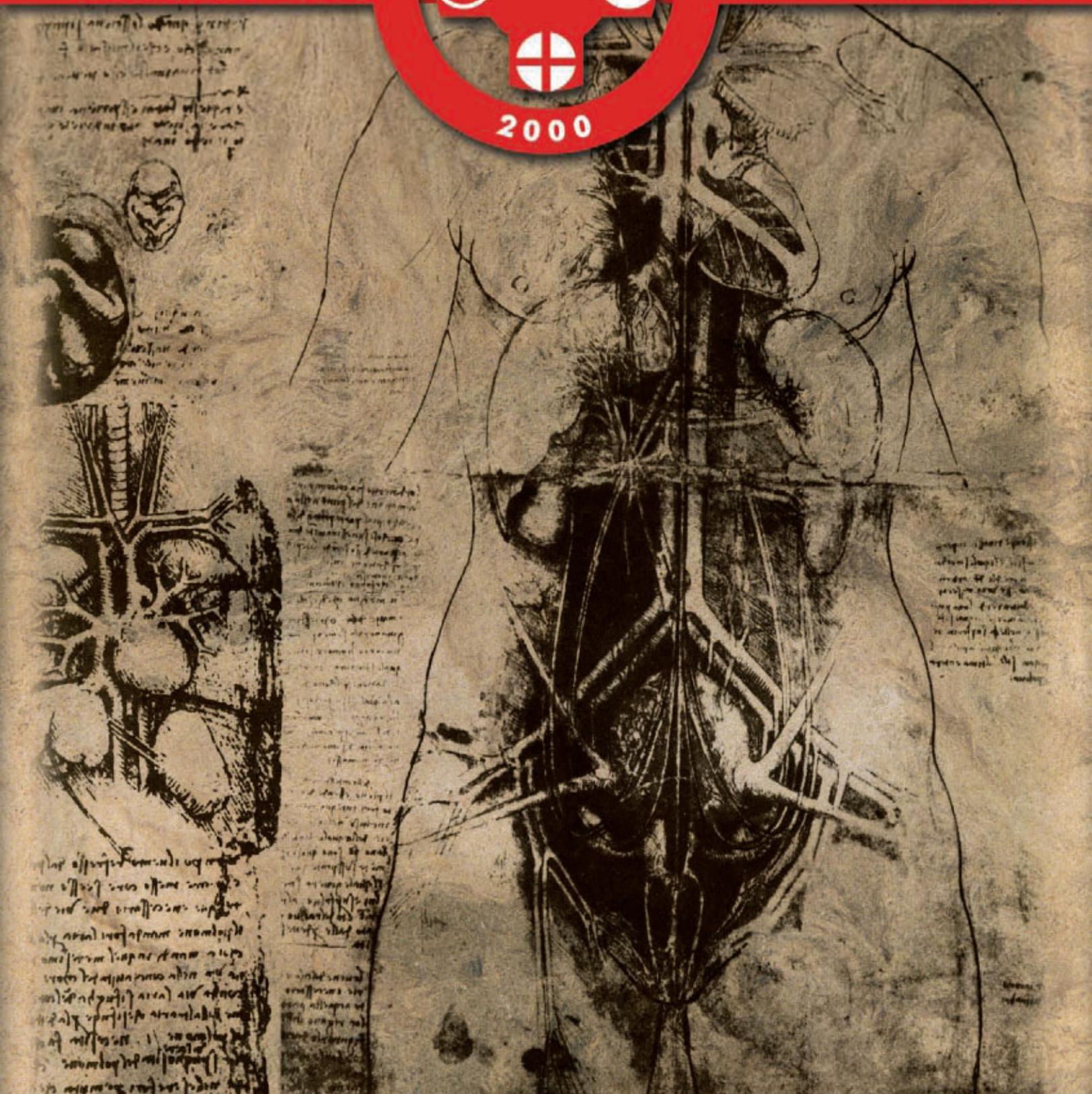


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# IMPROVING THE QUALITY OF MEDICUS (NOW SERBIAN JOURNAL OF EXPERIMENTAL AND CLINICAL RESEARCH): WHAT TO DO?



„A naturalist life would be a happy one  
if he had only to observe and never to write“  
Charles Darwin (cit. in 1)

43

Since the 17th century, scientific journals serve as primary means of communication in science. We all are witnesses that last century is marked by an exponential rise of the number of biomedical journals. Even in small countries such as Serbia, a considerable number of journals exists (2,3), some 63 being in the field of biomedicine (4). However, unlike the editors of the journals of international reputation, who have enormous submission rate and therefore very high rejection rate (5), our editors face a completely different problem: already low number of submissions (6,7) is decreasing steadily...

This phenomenon, which worries all editors of our biomedical journals, has several underlying causes. First of all, Charles Darwin was right: many scientists do not like to write. Scientific writing requires permanent improvement of one's communication skills, and the communication art has been for decades either neglected or ignored in education of our medical students\*. In addition, the poverty and moral crisis that our society has met in last twenty years, has certainly significant impact on the lack of interest for publishing results of research among our scientists.

However, all scientists know that publication of research results is a must, since the research is not finished until the results are published, and since the underpublishing is an unethical issue (9,10). The other, not less important motive is the academic advancement. Academic carrier of a scientist (either clinician, teacher or professional researcher), depends heavily on the publications – as a matter of fact, it is, or it should be, the most important criterion for academic advancement (11,12). It is very important that they publish in journals visible on international level – that is, in those indexed in databases such as PubMed/MEDLINE, Current Contents, and CABS.

Therefore, the editors' main aim is to achieve quality which would lead to their journal indexing in these databases. However, their efforts in this direction will fail unless they succeed to attract authors to submit manuscripts of quality. To help authors to improve their communication skills, editors must act as educators (13), and encourage authors to write for their journals (14,15). This implies:

- Organization of seminars on publication for young investigators – continual medical education
- Organization of seminars on peer review
- Organization of seminars on medical journal editing
- Publication of editorials, review articles and informative special articles on this topic

\* Regarding this last issue, the University of Kragujevac Medical School should be praised for being the very first medical school which introduced a mandatory course on publication in biomedicine in PhD studies (8). Later, The University of Belgrade Medical School and Dental School, and University of Niš Medical School did the same. Since the year 2004, The University of Novi Sad organizes the seminar on publication in biomedicine each year.



I am convinced that all three main actors in publishing game – authors, reviewers and editors – will benefit of such education, and that the submission rate of MEDICUS will rise in near future. Several journals in our (5,16,17) and neighboring countries did the same in the past, and efforts of some of them (J BUON, Croat Med J) were awarded in a short period - they achieved to be

covered in important databases (18-20). For example, the submission rate of J BUON rose instantly after this journal was included in PubMed/MEDLINE, so now even two or three issues can be prepared in advance (Athanasios A.E., personal communication).

Let us hope that our journal MEDICUS will soon accomplish the same goal!

Ljiljana Vučković-Dekić

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## RESISTANCE INDEX OF THE FETAL UMBILICAL ARTERY AND OXIDATIVE STRESS IN PREECLAMPSIA

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## OKSIDACIONI STRES I REZISTENTNI INDEKS UMBILIKALNE ARTERIJE U PREEKLAMPSIJI

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### ABSTRACT

Preeclampsia is a pregnancy complication with serious consequences for mother and infant. The disorder is diagnosed by hypertension and proteinuria. Several hypotheses invoke oxidative stress as a cellular process contributing to pathologic changes in preeclampsia. Literature data showed that activation and/or dysfunction of the maternal and fetal vascular endothelium may be the consequence of increased oxidative stress. Increased vasoconstriction lead to maternal hypertension and reduced uteroplacental blood flow. Increased vasoconstriction of umbilical artery can be demonstrated using Doppler velocimetry as increased resistance. Our study involved 22 healthy (control) and 20 pregnant women with mild preeclampsia (study group). The aim of this study was to investigate relationship between resistance index of the fetal umbilical artery and concentration of GSH and GSSG (indicators of oxidative stress) in maternal circulation.

**Key words:** oxidative stress, preeclampsia, fetal umbilical artery

### SAŽETAK

Preeklampsija predstavlja za trudnoću specifičan sindrom, koji je praćen povećanim morbiditetom i mortalitetom majke i fetusa. Kliničku sliku karakterišu pojava hipertenzije i značajne proteinurije u drugoj polovini trudnoće. Etiopatogenetska zbivanja tokom preeklampsije još uvek nisu dovoljno razjašnjena, ali nekoliko hipoteza pominje oksidacioni stres kao značajnu komponentu patogeneze preeklampsije. Literarni podaci ukazuju da je za disfunkciju odnosno aktivaciju endotela najverovatnije delom odgovoran i pojačani oksidacioni stres. Hipertenzija i smanjena uteroplacentalna cirkulacija su posledica vazokonstrikcije karakteristične za preeklampsiju. Primenom Doppler ultrazvuka možemo registrovati pojačanu vazokonstrikciju kroz umbilikalnu arteriju. U našoj studiji je bilo ispitano 22 zdrave trudnice (kontrola) i 20 trudnica sa umerenim oblikom preeklampsije. Cilj studije je bio da se ispita odnos između oksidacionog stresa (koncentracije u krvi GSH i GSSG) i rezistentnog indeksa (RI) u umbilikalnoj arteriji.

**Ključne reči:** oksidacioni stres, preeklampsija, umbilikalna arterija

### INTRODUCTION

Preeclampsia is human pregnancy-specific syndrome that adversely affects the mother and the fetus, with increased morbidity and mortality. The incidence of preeclampsia is between 4% and 8 % of pregnancies. Preeclampsia is diagnosed by new development of hypertension and significant proteinuria after 20 weeks of gestation. Other manifestations of preeclampsia include reduced perfusion to organs and platelet activation. After delivery, these signs remit [1]. The etiology and pathogenesis of preeclampsia remain poorly understood. Increasing evidence indicates that activation and/or dysfunction of the maternal and fetal vascular endothelium may be the consequence of increased oxidative stress. Increased vasoconstriction lead to maternal hypertension and reduced uteroplacental blood flow [2-4].

Oxidative stress is disturbance of the redox-balance, caused by increased amounts of oxidants such as reactive oxygen species – ROS (anion radical ( $O_2^-$ ), hydrogen peroxide ( $H_2O_2$ ) and hydroxyl radical (OH.) or a deficiency of antioxidants [5]. Under physiological conditions, overproduced ROS are neutralized by the activity of antioxidative defense system (AOS), which consists of enzymatic and non-enzymatic components [5].

Gluthatione (GSH) is non-enzymatic component of AOS and plays a major role in defenses against oxidative and nitrosative stress. GSH reacts with hydroxyl radical, the cytotoxic Fenton reaction product, and with  $N_2O_3$  and peroxyntirite, cytotoxic products formed by the reaction of nitric oxide (NO) with  $O_2$  and superoxide, respectively. In addition, GSH acts as a co-substrate of



GPx in the elimination of both H<sub>2</sub>O<sub>2</sub> and other organic peroxides. Each of these reactions leads directly or indirectly to the formation of glutathione disulfide (GSSG) [6]. Upon exposure to oxidants, GSH forms GSSG, thus changing the plasma concentration of GSH and GSSG, which reflects oxidative stress conditions [7]. Considering key role of placenta in initiation of oxidative stress in maternal circulation, in this study we investigated relationship between RiAU (resistance index of the fetal umbilical artery) and concentration of GSH and GSSG (indicator of oxidative stress) in maternal circulation.

## MATERIALS AND METHODS

### Chemicals

All reagents used in this study were of analytical grade and were obtained from Sigma Chemical Company, St. Louis, USA and Merck, Darmstadt, Germany.

### Patients

Ethics Committee of Clinical Centre Kragujevac approved the study protocol and all patients gave informed consent. Our study involved 22 healthy pregnant women (control group) and 20 women with mild preeclampsia (study group), attending the Obstetrics and Gynaecology Department. Preeclampsia was defined by standard criteria in accordance with the guidelines of the International Society for the Study of Hypertension in Pregnancy. Control and preeclamptic women were non-smokers and free from other disease.

Preeclampsia is one of indications for use of Doppler ultrasound during pregnancy. The degree of resistance in a vascular segment can be ascertained. This information is used to determine the condition of the fetus, especially in the third trimester. In preeclampsia, there is reduction in placental perfusion, which could be detected by Doppler measurements as increased resistance to blood flow through feto-placental vessels [8]. The Doppler ultrasound investigation was performed on ALOKA Pro Sound 3500 SSD. We measured index of resistance to blood flow through umbilical artery.

### Blood sampling and analytical methods

Blood samples were taken by venepuncture from pregnant women in third trimester of pregnancy. The blood was collected in sterile tubes with preservative-free sterile heparin (40 U/ml) and centrifuged 10 min at 5000 rpm. After blood centrifugation plasma of healthy and preeclamptic women were used for extraction and determination of the next parameters: concentrations of reduced glutathione (GSH) and oxidized glutathione (GSSG). Extract of GSH and GSSG were stored at -80°C until further biochemical analysis. Levels of GSH was determined on the basis of GSH oxidation with 5,5-dithio-bis-6,2-nitrobenzoic acid [9]. Concentration of GSSG was enzymatically determined by glutathione reductase [10] after inhibition of GSH oxi-

dation by N-ethylmaleimide. Concentration of GSH and GSSG were expressed in nmol/ml of plasma.

### Statistical analysis

The data are expressed as mean  $\pm$  S.E.M. The data were analyzed by SPSS (version 10.0) for Windows. Paired samples t-test was used for comparison of the data. Correlation coefficient (*r*) was determined by Pearson correlation. For comparisons and correlation *p* < 0.05 was considered as significant.

## RESULTS

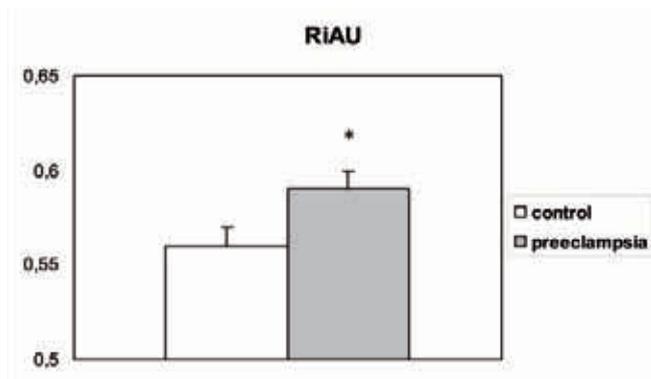
Clinical data of pregnant women are summarized in Table 1. Maternal age and parity were not significantly different between the groups. As anticipated from the defined criteria, MAP (mean arterial pressure) and proteinuria were significantly higher in the preeclamptic group than in the control group. Gestational ages at delivery and infant birth weights were significantly lower in the preeclamptic group than in the control group. Apgar score was not different between the groups.

**Table 1.** Clinical characteristics of healthy (control) and preeclamptic pregnant women

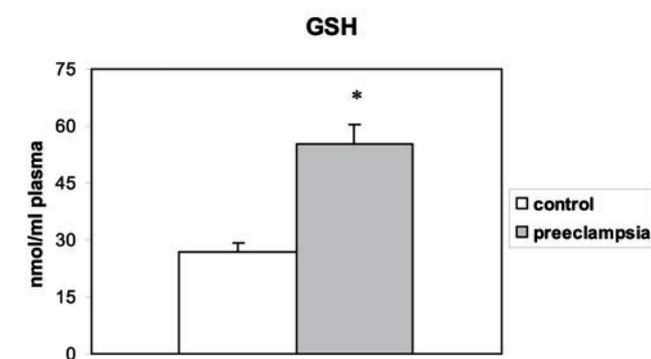
Characteristic	Control (n = 22)	Preeclampsia (n = 20)
Maternal age (years)	26.9 $\pm$ 4.5	28.1 $\pm$ 5.5
Parity	1.4 $\pm$ 0.2	1.5 $\pm$ 0.2
Gestational age at delivery (w)	40.36 $\pm$ 0.53	38.52 $\pm$ 0.90*
MAP (mean arterial pressure) (mmHg)	91.08 $\pm$ 1.99	109.54 $\pm$ 1.66*
Proteinuria	0.00 $\pm$ 0.00	0.54 $\pm$ 0.035*
Infant birth weight (g)	3736 $\pm$ 0.08	3259 $\pm$ 0.11*
Apgar score	8.78 $\pm$ 0.14	8.82 $\pm$ 0.16

Values are means  $\pm$  SEM. \**p* < 0.05 preeclampsia versus control

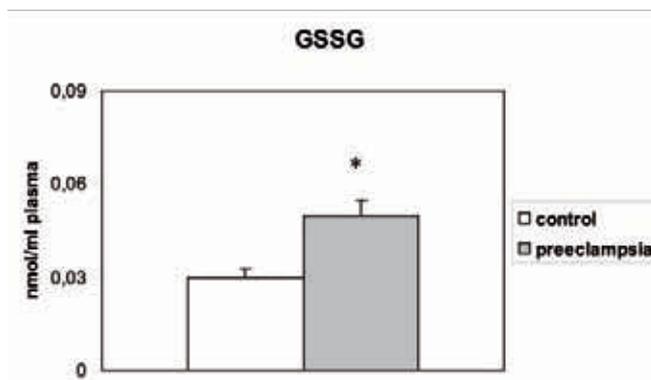
The resistance index of the fetal umbilical artery is presented in Fig. 1. Results of this study showed that RiAU was significantly higher in preeclampsia in comparison to healthy pregnant women. Concentrations of GSH and GSSG are present in Fig. 2 and Fig. 3. Our results showed significantly higher concentrations of GSH and GSSG in plasma of preeclamptic women in comparison to healthy pregnant women. The results of this study show that RiAU was significantly negatively correlated with concentration of GSH in plasma of preeclamptic women (*r* = - 0.847, *p* < 0.0001). Negatively correlation between RiAU and concentration of GSSG was not significant in preeclampsia.



**Figure 1.** RIAU in women with preeclampsia and in healthy women. Values represent means  $\pm$  SEM. \* $p < 0.05$ , preeclampsia versus control.



**Figure 2.** The concentrations of GSH in women with preeclampsia and in healthy women. Values represent means  $\pm$  SEM. \* $p < 0.05$ , preeclampsia versus control.



**Figure 3.** The concentrations of GSSG in women with preeclampsia and in healthy women. Values represent means  $\pm$  SEM. \* $p < 0.05$ , preeclampsia versus control.

## DISCUSSION

Oxidative stress is the link between the poor placental perfusion and the impaired maternal endothelial function occurring in preeclampsia [1, 4]. Placental ischemia may promote the release of a variety of biologically active factors, including cytokines such as tumor necrosis

factor-alpha (TNF- $\alpha$ ), which induce neutrophils to discharge reactive oxygen species. Threshold increases in the plasma levels of placental factors may lead to endothelial cell dysfunction [11-14]. The release of factors from hypoxic placenta may also increase the release of or the vascular reactivity to endothelium-derived contracting factors such as endothelin (ET-1), thromboxane, and ANG II [15].

Production of free radical is relatively low in normal conditions due to active antioxidative defense systems, including GSH. Reduced glutathione is an endogenous scavenger of free radicals and peroxides because it maintains the redox potential and is very protective against oxidative stress [6, 7]. The changes in plasma concentration of GSH suggest increased oxidative stress [4, 5]. In this study, we showed higher concentration of GSH in plasma of preeclamptic women in comparison to healthy pregnant women. Literature data show that TNF- $\alpha$  increases hepatocellular GSH levels, mediated by transcriptional regulation of the GCS-HS gene, which attenuates the generation of hydrogen peroxide and lipid peroxidation [16]. Scalera et al. [17] showed that higher concentration of ET-1 also increases the intracellular concentration of GSH. Glutathione efflux from liver by TNF- $\alpha$  resulted in significant elevation of the plasma GSH concentration [18]. Increase of plasma GSH represent an additional protective mechanism to control the consequences of oxidative stress induced by inflammatory cytokines in preeclampsia.

While deactivating reactive oxygen species, the reduced form of glutathione is oxidized, thereby changing the ratio of free and oxidized glutathione [5]. The results of this work show that concentration of GSSG was significantly higher in plasma of women with preeclampsia, while ratio GSH/GSSG is not different between the study groups. Because preeclampsia is characterized by oxidative stress, we anticipated that ratio of GSH and GSSG would be lower in women with preeclampsia. No change in GSH/GSSG ratio may be result of rapidly reduced GSSG by glutathione reductase, thereby consuming nicotinamide adenine dinucleotide phosphate. In addition, when increasing oxidized glutathione, some of the GSSG undergo renal degradation by gammaglutamyl transpeptidase, resulting in an irreversible loss of GSSG [19]. Because of one or both of these mechanisms, the ratio of GSH and GSSG remained unchanged.

Okatani et al. [20] showed that H<sub>2</sub>O<sub>2</sub> is potent vascular tension in human umbilical arteries. General vasoconstriction in preeclampsia, mediated by oxidative stress, results with high flow resistance in the capillaries of the terminal villi, and with a low end-diastolic velocity in the umbilical artery and consequent hypoxia [2, 4]. Because of the prolonged fetal hypoxia, circulatory adaptation occurs in the form of cerebral vasodilatation, resulting in the redistribution of the cardiac output to provide an adequate oxygen supply to the brain. These changes, which help fetus to adapt to a hostile environment, may correlate with fetal neonatal health [21].



Because GSH acts as a co-substrate of GPx in the elimination of  $H_2O_2$ , we investigated correlation between RiAU and concentration of maternal GSH in plasma. On the basis of our results, RiAU increases and is negatively correlated with GSH in preeclampsia. This suggests that increased concentration of GSH in maternal plasma is protective mechanism against oxidative injury in human umbilical arteries.

## ACKNOWLEDGMENTS

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# INFLUENCE OF VISCOELASTICS ON EYE PRESSURE CHANGES FOLLOWING THE CATARACT SURGERY

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## UTICAJ VISKOELASTIKA NA PROMENU OČNOG PRITISKA POSLE OPERACIJE KATARATE

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### ABSTRACT

**Introduction.** Due to a series of significant characteristics, viscoelastic substances are regularly used during the cataract surgery. However, viscoelastic matrix also aids fibrin polymerization and physically stuffs fibrin and inflammatory products into the structures of the chamber angle. It results in decreased fluid outflow from the anterior chamber throughout the trabeculum, leading to rise of eye pressure after surgery.

**Aim.** To explore influence of different viscoelastics used during the phacoemulsification on the postoperative eye pressure.

**Methods.** Influence of two dispersive viscoelastics on 40 normotensive patients was examined. Hydroxypropyl methylcellulose 2% was used on 20 patients, and sodium chondroitin sulphate 4% – sodium hyaluronate 3% on 20 others. The pressure was measured by Goldmann's applanation tonometer before surgery, as well as 6 and 24 hours, and a week after surgery.

**Results.** In the sixth hour after surgery middle intraocular pressure (IOP) was increased by 4,6 mmHg in hydroxypropyl methylcellulose 2% group ( $p < 0,001$ ), and by 8,6 mmHg in sodium chondroitin sulphate 4% – sodium hyaluronate 3% group ( $p < 0,001$ ). This increase in sodium chondroitin sulphate 4% – sodium hyaluronate 3% group was significantly higher than that in u hydroxypropyl methylcellulose 2% group ( $p = 0,004$ ).

**Conclusion.** Our study suggests that in the early postoperative period after phacoemulsification, sodium chondroitin sulphate 4% – sodium hyaluronate 3% is associated with significantly higher increase in IOP than hydroxypropyl methylcellulose 2%.

**Key words:** viscoelastic, phacoemulsification, eye pressure

### KRATAK SADRŽAJ

**Uvod.** Zbog čitavog niza značajnih karakteristika viskoelastične supstance imaju stalno mesto u operativnom toku hirurgije katarakte. Međutim, viskoelastični matriks takođe potpomaže fibrinsku polimerizaciju i fizički nabija fibrin i inflamatorne produkte u strukture komornog ugla, tako da unutar trabekuluma postoji otežano oticanje očne vođice iz prednje komore, što dovodi do postoperativnog skoka očnog pritiska.

**Cilj.** Utvrditi uticaj različitih vrsta viskoelastika korišćenih tokom fakoemulzifikacije na postoperativne vrednosti očnog pritiska.

**Metod rada.** Ispitivan je uticaj dva disperzivna viskoelastika kod 40 normotenzivnih pacijenata. Kod 20 pacijenata je tokom operacije korišćena hydroxypropyl methylcellulosa 2%, a kod drugih 20 sodium chondroitin sulphat 4% – sodium hyaluronat 3%. Pritisak je meren Goldmann-ovim aplanacijonim tonometrom, preoperativno, kao i 6 sati, 24 sata i jednu nedelju posle operacije.

**Rezultati.** U 6. satu posle operacije srednji IOP je povećan za 4,6 mmHg u hydroxypropyl methylcellulosa 2% grupi ( $p < 0,001$ ), a za 8,6 mmHg u sodium chondroitin sulphat 4% – sodium hyaluronat 3% grupi ( $p < 0,001$ ). Ovo povećanje u sodium chondroitin sulphat 4% – sodium hyaluronat 3% grupi je u odnosu na povećanje u hydroxypropyl methylcellulosa 2% grupi bilo značajno veće ( $p = 0,004$ ).

**Zaključak.** Može se reći, da u ranom postoperativnom periodu posle fakoemulzifikacije, sodium chondroitin sulphat 4% – sodium hyaluronat 3% pokazuje značajno veće povećanje IOP-a nego hydroxypropyl methylcellulosa 2%.

**Ključne reči:** Viskoelastik; fakoemulzifikacija; očni pritisak

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### INTRODUCTION

Viscoelastic substances have the following rheological characteristics [1]: viscosity – the measure of its resistance to moving; viscoelasticity – elasticity – the ability of the material to return to its initial position after stretching or compression; pseudoplasticity – sliding; coatibility – ability to coat; tenacity – the degree to which particles

of material stick to each other, as the result of mutual action of molecule weight and elasticity.

The characteristics listed enable viscoelastics to enter all eye segments and maintain their shape and volume, coat all the surfaces of sensitive tissues and thus protect them. They also protect corneal endothelium cell lay-



ers, iris, lens and retina from mechanical damage of other tissues, implants and instruments; compensate eye liquid and stabilize the depth of anterior chamber during the surgery; they also push back iris and vitreous, which facilitates work on the anterior segment during surgery. Viscoelastic reduces the possibility of postoperative growth of tissue by separating tissues surfaces. It can also replace vitreous and push back the lifted retina.

Hydroxypropyl methylcellulosis 2% and sodium chondroitin sulphate 4% - sodium hyaluronate 3% are dispersive viscoelastics with low viscosity. The dispersive nature enables better adherence of viscoelastics to corneal endothelium [2], probably resulting in better protection of cornea from turbulence of liquid and lens fragments during the phacoemulsification.

Apart from the range of characteristics important for cataract surgery, viscoelastic matrix aids fibrin polymerization and physically sticks fibrin and inflammatory products into the structures of chamber angle, so that viscoelastic itself, fibrin and cell structures inside the trabeculum decrease the outflow of eye liquid from the anterior chamber, thus leading to the postoperative rise in eye pressure.[3]

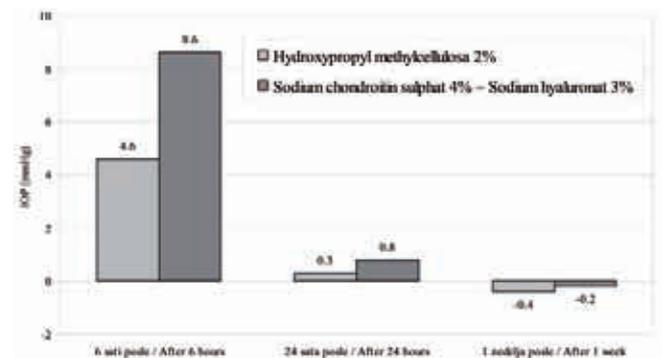
## METHODS

The type and the degree of influence of viscoelastics used during the phacoemulsification (PHACO) on the postoperative values of eye pressure (IOP) was studied. Two dispersive viscoelastics were used on patients with normal eye hydrodynamics, without local risk factors, with no previous surgeries, without eye hypertension (IOP from 22 mmHg) and presence of primary or secondary glaukoma. Twenty-seven patients were women, 13 of them were men. Average age was 75,9 (SD 9,3 interval 54-92) years. Patients were divided into two groups and reactions observed in one-week study. Operation method: corneal tunnel is made on 12h by 3,2 mm wide keratome (triangular knife). Anterior chamber was filled up by viscoelastic substance (the type differed depending on the group of the patients observed). After that, continuous circular capsulorhexis was made. Phacoemulsification was used to remove lens nucleus after hydrodissection; the remaining cortical material was removed by irrigation and aspiration. After cortical aspiration was done, keratome was used for widening of the incision up to 6 mm. Filling up of the anterior and the posterior chamber by viscoelastic substance preceded placing of polymethylmetacrylate non foldable intraocular lens of 5,5 mm diameter into the posterior eye chamber. Viscoelastic was then aspirated and the incision closed by "one x" extended stitch with 10,0 Nylon monofilament suture. In the end subconjunctival injection (Sol. Dexason + Sol.Gentamicin) was given. During the surgery hydroxypropyl methylcellulose 2%, was used on 20 patients during the surgery, and sodium chondroitin

sulphate 4% – sodium hyaluronate 3% on 20 others. The pressure was measured by Goldmann's Applanation Tonometer preoperatively and 6 hours, 24 hours and a week after surgery. T test was used for the group comparison of the preoperative and the postoperative eye pressure. T test was also used for the mean preoperative IOP values compared to the values measured 6 hours, 24 hours and a week after surgery.  $\chi^2$  test was used for the comparison of the groups of patients with IOP of 30 mmHg or more.

## RESULTS

A significant difference in IOP among groups after surgery did not exist. In the sixth hour after surgery the average IOP was increased by 4,6 mmHg in the hydroxypropyl methylcellulose 2% group ( $p < 0,001$ ), and by 8,6 mmHg in the sodium chondroitin sulphate 4%- sodium hyaluronate 3% group ( $p < 0,001$ ). (Graph 1) This increase in the sodium chondroitin sulphate 4%- sodium hyaluronate 3% group related to the increase in the hydroxypropyl methylcellulose 2% group was significantly higher ( $p = 0,004$ ). In the first group, and in the second group too, 24 hours after surgery eye pressure values were almost equal to those before surgery, while the decreases in IOP measured a week later were not statistically significant ( $p = 0,084$ ;  $p = 0,075$ ) (Table 1, Table 2). Twenty-four hours and a week after surgery the difference in the average IOP among the groups was not statistically significant ( $p = 0,662$  and  $p = 0,650$ ).



**Graph 1.** Changes of eye pressure measured before and after surgery.

**Table 1.** Values of eye pressure in the group on which hydroxypropyl methylcellulose 2% was used.

The group which received hydroxypropyl methylcellulosa 2%					
Time of measurement		Before operation	After 6 hours	After 1 day	After 2 days
Average value		14	18.6	14	13.5
Standard deviation		2.8	6	3.5	2.7
Interval of variation	Min	8	9	8	9
	Max	20	39	24	20



**Table 2.** Values of eye pressure in the group on which sodium chondroitin sulphate 4 % – sodium hyaluronate 3% was used.

The group which received sodium chondroitin sulphate 4% – sodium hyaluronate 3%				
Time of measurement	Before operation	After 6 hours	After 1 day	After 2 days
Average value	14.1	22.7	14.7	13.8
Standard deviation	2.8	8.7	4	2.9
Variation interval	Min	8	12	9
	Max	19	48	24

IOP of 11 of total 40 patients on whom the surgery was performed from both groups (27%) was more than 30 mmHg in the sixth hour after surgery. There was significantly larger number of eyes in the sodium chondroitin sulphate 4%- sodium hyaluronate 3% group with this high rise in IOP than in the hydroxypropyl methylcellulose 2% group ( $p=0,023$ ). Among nine patients in the second group the highest IOP value was 48 mmHg,(Table 2) while with only two patients in the hydroxypropyl methylcellulose 2% group that rise was 39 mmHg.(Table 1)

## DISCUSSION

The rise in IOP of 30 mmHg and more immediately after surgery can appear with pain, corneal epithelium edema and damage of optic disc, especially in patients with glaucoma. This can be important, considering the number of cataract patients that undergo surgery in the world today according to the principle of a single day surgery, and are discharged from the hospitals right after surgery. The main causes of the rise in IOP after surgery are residuals of viscoelastic substance used, which cause mechanical obstruction of trabeculum. [4]

The mechanism of rise in IOP after surgery is still not clear. The main cause could be the residue of a certain amount of viscoelastic, which mechanically obstructs trabeculum and thus decreases outflow of aqueous.[4] This is why it is of the utmost importance to remove as much of viscoelastic as possible in order to avoid the rise in IOP

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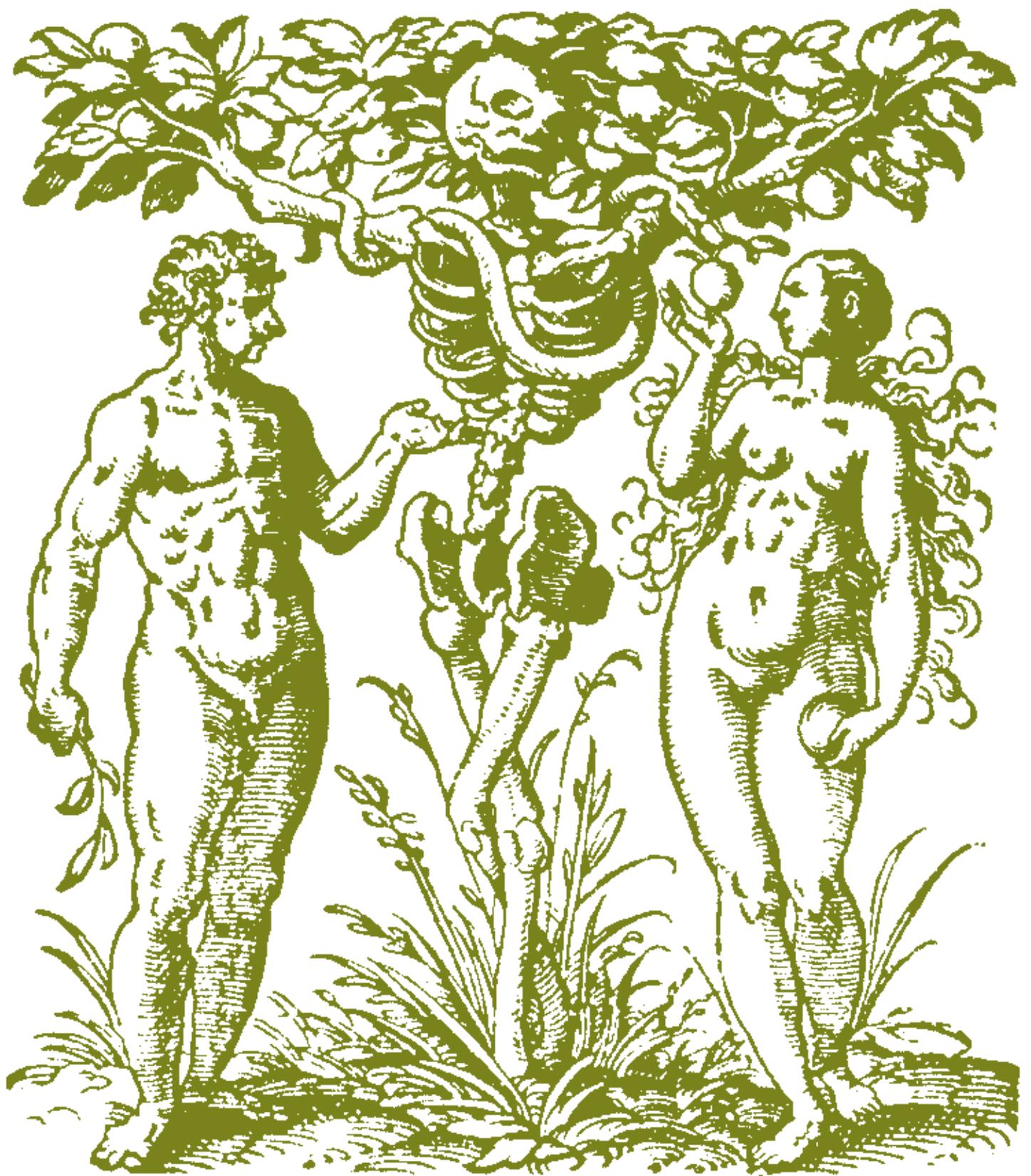
after surgery. There are numerous techniques for the removal of viscoelastic substance, especially that behind the lens, [5,6,7], but complete protection from the rise in IOP could not be achieved by any of these techniques.

In our study, hydroxypropyl methylcellulose 2% and sodium chondroitin sulphate 4%- sodium hyaluronate 3%, as viscoelastics used during the phacoemulsification, were equally carefully removed from the anterior chamber, as well as behind the lens. However, it is almost impossible to remove the viscoelastic completely without damaging endothelium or other vulnerable eye structures.

Considering the fact that the remaining quantity of both viscoelastic substances in our study was the same, the difference in IOP after surgery between the two kinds of viscoelastics could be explained by the difference in their biophysical characteristics. It is believed that outflow of viscoelastics through trabeculum depends on the viscosity and the molecule weight of the used substance. [8] Theoretically, lower viscosity and molecule weight of a viscoelastic substance enables its easier flow through trabeculum. In accordance with this theory, in our study hydroxypropyl methcelulose 2%, which has lower molecule weight and viscosity than chondroitin sulphate 4%- sodium hyaluronate 3%, caused lower increase in IOP. Lower viscosity of hydroxypropyl methylcellulose 2% could, however, lead to less efficient protection of corneal endothelium.

Viscoelastic substances used in the cataract surgery are the main cause of the early postoperative eye pressure rise.

Our study showed that in the early postoperative period after phacoemulsification, sodium chondroitin sulphate 4% – sodium hyaluronate 3% was associated with significantly higher rise in IOP than hydroxypropyl methylcellulose 2%. Although both viscoelastics were adequately removed, significant rise in IOP compared to the values before surgery was observed with both preparations. This is why supervision of the patients after phacoemulsification is necessary, and use of drugs for lowering IOP is recommendable, especially with the patients with the endangered optic disc.



# CORRELATION BETWEEN REPLICATION OF HEPATITIS B VIRUS AND DEMOGRAPHIC CHARACTERISTICS AND DIFFICULTIES OF PATIENTS WITH CHRONIC HEPATITIS B

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## KORELACIJA REPLIKACIJE VIRUSA HEPATITISA B SA DEMOGRAFSKIM KARAKTERISTIKAMA I TEGOBAMA OBOLJELIH OD HRONIČNOG HEPATITISA B

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### ABSTRACT

Hepatitis B virus infects more than 2 billion people in the world, and 300 million of them developed chronic infection, that is as long as life lasts, and puts them at risk of developing cancer or cirrhosis of the liver. The aim of the work is to show correlation between Hepatitis B virus replication and demographic characteristics and difficulties in persons with chronic Hepatitis B.

Study sample involved all persons with Hepatitis B in whom diagnosis was made based on epidemiological, clinical, biological and pathohistological parameters in the period from January 2002 to January 2008. In the study sample, out of 30 persons with chronic hepatitis B, 23 (77%) were men and 7 (23%) were women. Replication of hepatitis B virus was found in higher percentage in men (78%). Examinees were from all age groups, and most of them were adults (between 20-59 years of age), 24 patients (80%). Virus replication was found in all groups without statistically significant difference. Difficulties in patients with chronic hepatitis B were fatigue and nausea, and in 54,5% cases virus replication is mainly found in men of all age groups, with different level of education.

Chronic infection caused by this virus with "mute" clinical picture followed by virus replication accelerates developing of cirrhosis and hepatocellular carcinoma

**Key words:** Hepatitis B, replication, gender, age group, difficulties

### SAŽETAK

Dvije milijarde ljudi širom svijeta inficirano je virusom hepatitisa B od kojih više od 300 miliona ima hroničnu infekciju a koja traje cio život i koja ih izlaže riziku da obolevanja od raka ili ciroze jetre. Cilj rada je prikazati povezanost replikacije virusa hepatitisa B sa demografskim karakteristikama i tegobama oboljelih od hroničnog hepatitisa B.

Isiraživački uzorak čine svi oboljeli od hroničnog hepatitisa B kod kojih je dijagnoza postavljena na osnovu epidemioloških, kliničkih virusoloških i patohistoloških parametara u vremenskom periodu od januara 2002. do januara 2008. god.. U istraživačkom uzorku od 30 oboljelih od hroničnog hepatitisa B bila su 23 (77%) muškaraca i 7 (23%) žena. Replikacija virusa hepatitisa B je bila više prisutna kod oboljelih muškog pola. (78,2%). Oboljeli ispitanici pripadali su svim starosnim grupama a većina njih činila je grupu odraslih bolesnika (između 20 i 59 godina), tj 24 bolesnika (80%). Replikacija virusa bila je prisutna u svim grupama bez statistički značajne razlike. Tegobe kod oboljelih od hroničnog hepatitisa B su se najčeće manifestovale kroz zamor i mučninu a njih 54.5% imalo je i prisutnu replikaciju virusa.. Hronični hepatitis B sa prisutnom replikacijom virusa je bolest većinom muškaraca, svih uzrasta, različitog obrazovanja. Hronična infekcija ovim virusom uz prisustvo replikacije virusa uz nijemu kliničku sliku brže vodi kacirozi i hepatocelularnom karcinomu

**Ključne riječi:** hepatitis B, replikacija, pol, uzrast, tegobe

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### INTRODUCTION

In the last decades of XX century the significant improvement in diagnosis and therapy of liver diseases has been achieved. Many dilemmas related to etiology of viral hepatitis, its pathogenesis, morphological picture and therapy have not yet been resolved detailly. It is especially from the reason that these diseases can be asymptomatic for a long period and they are recognized at the moment of occurrence of irreversible damage of the liver. (1) World Health Organization estimates that Hepatitis B virus infects more than 2 billion people in

the world, and 300 million people of them developed chronic infection lasting whole life and which puts them at risk at developing cancer or cirrhosis of the liver. High percentage of Hepatitis B virus is found in many developing countries (2). Transmission results from exposure to infectious blood or body fluids containing blood. Possible forms of transmission include (but are not limited to) unprotected sexual contact, blood transfusions, re-use of contaminated needles, syringes, and vertical transmission from mother to child during childbirth. Without interven-



tion, a mother who is positive for the hepatitis B surface antigen confers a 20% risk of passing the infection to her offspring at the time of birth. This risk is as high as 90% if the mother is also positive for the hepatitis B e antigen. HBV can be transmitted between family members within households, possibly by contact of nonintact skin or mucous membrane with secretions or saliva containing HBV.(3) However, at least 30% of reported hepatitis B among adults cannot be associated with an identifiable risk factor.(4,5)Chronic infection with Hepatitis B virus may be either asymptomatic or may be associated with a chronic inflammation of the liver (chronic hepatitis), leading to cirrhosis over a period of several years. This type of infection dramatically increases the incidence of liver cancer. Chronic carriers are encouraged to avoid consuming alcohol as it increases their risk for cirrhosis and liver cancer. Hepatitis B virus has been linked to the development of Membranous glomerulonephritis (6) The hepatitis B surface antigen (HBsAg) is most frequently used to screen for the presence of this infection. It is the first detectable viral antigen to appear during infection. However, early in an infection, this antigen may not be present and it may be undetectable later in the infection as it is being cleared by the host. The infectious virion contains an inner "core particle" enclosing viral genome. The icosahedral core particle is made of 180 or 240 copies of core protein, alternatively known as hepatitis B core antigen, or HBcAg. During this 'window' in which the host remains infected but is successfully clearing the virus, IgM antibodies to the hepatitis B core antigen (anti-HBc IgM) may be the only serological evidence of disease.(7)Shortly after the appearance of the HBsAg, another antigen named as the hepatitis B e antigen (HBeAg) will appear. Traditionally, the presence of HBeAg in a host's serum is associated with much higher rates of viral replication and enhanced infectivity; however, variants of the hepatitis B virus do not produce the 'e' antigen, so this rule does not always hold true. During the natural course of an infection, the HBeAg may be cleared, and antibodies to the 'e' antigen (anti-HBe) will arise immediately afterwards. (8)This conversion is usually associated with a dramatic decline in viral replication. More recently, PCR tests have been developed to detect and measure the amount of viral nucleic acid in clinical specimens. These tests are called viral loads and are used to assess a person's infection status and to monitor treatment.(9).

The life cycle of Hepatitis B virus is complex. Hepatitis B is one of a few known non-retroviral viruses that use reverse transcription as a part of its replication process. The virus gains entry into the cell by binding to a receptor on the surface of the cell and enters it by endocytosis. Because the virus multiplies via RNA made by a host enzyme, the viral genomic DNA has to be transferred to the cell nucleus by host proteins called chaperones. The partially double stranded viral DNA is then made fully double stranded and transformed into closed circu-

lar supercoiled DNA (cccDNA) that serves as a template for transcription of four viral mRNAs. The largest mRNA, (which is longer than the viral genome), is used to make the new copies of the genome and to make the capsid core protein and the viral DNA polymerase. These four viral transcripts undergo additional processing and go on to form progeny virions which are released from the cell or returned to the nucleus and re-cycled to produce even more copies.(10,11) The long mRNA is then transported back to the cytoplasm where the virion P protein synthesizes DNA via its reverse transcriptase activity.

Presence of active form of chronic hepatitis B supports faster progression from hepatitis B viral infection to cirrhosis and hepatocellular carcinoma. In our conditions through carefully selected group of patients with chronic hepatitis B where other causes of chronic hepatitis were excluded based on virologic and immunologic tests, the demographic characteristics and presence of active disease can be observed. Majority of population has regular vaccination status but also the portion of population with risky behavior without regular vaccination status for hepatitis B viral infection is significantly high. In the last ten years in our country the cases of making diagnosis of hepatitis B viral infection in the stadium of decomposed cirrhosis and hepatocellular carcinoma have not been rarely reported.

## AIM

The aim of study was to present correlation between Hepatitis B virus replication and demographic characteristics and difficulties of people with chronic hepatitis B.

## MATERIAL AND METHODS

Sample size involving 30 patients was epidemiologically processed at the Institute of Public Health Podgorica and diagnosis and treatment was done at the Clinic for Infectious diseases, Clinical Center of Montenegro and the Institute for Infectious and Tropical Diseases, Clinical Center Serbia, in the period from January 2002 to January 2008.

Epidemiological processing was done by conducting survey in patients using questionnaire specially designed for this purpose, in the Center for Disease Control and Prevention, Institute of Public Health, Podgorica.

Markers of Hepatitis B viral infection: HbgAg, HbeAg, anti HbcAg, anti Hbe, anti HBs were detected by enzymeimmunoassay (ELISA) at the Institute of Public Health of Montenegro and the Center for Blood Transfusion, Clinical Center of Montenegro.

Presence of HBV DNA in serum was detected by using PCR commercial tests in laboratory for virology, In-



stitute for Infectious and Tropical Diseases in Belgrade and the Institute for nuclear researches in Vinca.

Presence of hepatitis B virus replication was defined through presence of replication markers in serum of patients: HbeAg, HBVDNK, IgM, anti HBc. For this study we used data on Hepatitis B markers before initiating therapy treatment. Pathohistological analyzing of liver tissue was done at the Institute for Pathology, Clinical Center of Montenegro, after sampling by blind aspiration or target biopsy of liver during surgical remove of gall-bladder.

After electronic processing in statistical package SPSS for Windows (version 10) results have been presented in tables.

## RESULTS

During epidemiological survey conducted in the period from 2002-2008 patients with chronic Hepatitis B indicated different possible modes of infection by hepatitis B virus.. In the survey examinees have been selected into two groups depending on mode of transmission and presence of Hepatitis B virus replication (Table 1).

**Table 1.** Exposure to risk and presence of Hepatitis B virus replication in relation to risk

Risk	N		Virus replication	
	N	%	N	%
Risky sexual contact	10	33,3	8	80
Transfusion of blood and blood derivates	5	16,6	3	60
Surgical interventions	5	16,6	3	60
Narcotics	6	20	4	66
Tran placental	2	6,7	2	100
Accidental- injury with needle	2	6,7	2	100
<b>Total</b>	<b>30</b>	<b>100%</b>	<b>22</b>	<b>73,3%</b>

Data presented in the table show that during epidemiological survey the most of the examinees indicated the risky sexual contact as a possible mode of transmission of infection - 33,3% and the same percent of examinees indicated the exposure to infection via blood and surgical interventions.

In the study sample of 30 patients with chronic hepatitis B there were 23 (77%) men and 7 (23%) women. Hepatitis B virus replication was found in higher percentage in men (78,2%) in relation to total number of diseased with replication (83% 18/22). Table 2

**Table 2.** Hepatitis B virus replication in relation to gender

Gender	Positive replication		Negative replication		Total	
	No	%	No	%	No	%
Male	18	(78,2%)	5	(21,8%)	23	100%
Female	4	(57,1 %)	3	(42,9%)	7	100%
<b>Total:</b>	<b>22</b>		<b>8</b>		<b>30</b>	<b>100%</b>

Analysis of obtained results showed that male patients were dominant with 77% in relation to female patients 23% and Hepatitis B virus replication was more frequently found in male patients (78,2%) than in female patients (57,1%).

Hepatitis B is present in all age groups. The least number of case was reported in under 10 age group - 0,6% and over 60 age group - 0,3%. The highest number of cases was reported in the age group between 20-50 years -19 (63%) cases. There were 5 patients in the age group between 50-60 years (1,7%). Table 3

**Table 3.** Hepatitis B virus replication in relation to age groups

Age groups	Replication	%	Without replication	%	Total
0-9	1	50%	1	50%	2
10-19	3	100%	0	-	3
20-29	2	50%	2	50%	4
30-39	6	74%	3	26%	9
40-49	4	66%	2	34%	6
50-59	5	100%	0	-	5
60-69	1	100%	0	-	1
<b>Total</b>	<b>22</b>		<b>8</b>		<b>30</b>

Analysis of results showed that viral replication was found in all age groups of examinees without statistically significant difference  $p > 0,05$  in relation to number of diseased in certain age groups. The highest number of cases with replication was registered in age group between 30-50 years - 10 (33%) which was statistically significant difference in relation to number of examinees without replication in the same age group (10/15,66%,  $p < 0,05$ )

Within demographic characteristics of patients with chronic Hepatitis B the level of education was also considered. The most of examinees had with higher school education 13 (43,4%) but without statistically significant difference in relation to those with elementary school education - 26% and secondary school education - 30%. Table 4



**Table 4.** Level of education of patients with hepatitis B and the presence of viral replication

Education	No.	%	Viral replication	%
Elementary school education	8	26,6	6	75%
Secondary school education	9	30	7	77,7
Higher school education	13	43,4	9	69%
Total	30	100%	22	73%

The most of patients were in the group with higher school education - 43,4% and the least number of patients were in the group with elementary school education - 26,6%, while the highest percentage of viral replication was found in the group with secondary school education.

Difficulties of patients with chronic Hepatitis B were mild but they existed and they manifested through fatigue, nausea and pain under right rib edge. Total number of patients who had some of mentioned difficulties was 8 (40%). Hepatitis B virus replication was more frequently present in the group of patients who had difficulties but without statistically significant difference in relation to patients without difficulties (18/12, 60%v.s.40%,  $p>0,05$ ). Table5.

**Table 5.** Presence of viral replication in relation to difficulties in patients with chronic Hepatitis B

Presence of difficulties	Replication	Without replication	Total
With difficulties	12(54,5%)	6 (45,5%)	18(60%)
Without difficulties	10 (83,3%)	2 (16,7)	12 (40%)
<b>Total:</b>	<b>22(73,3%)</b>	<b>8 (26,7)</b>	<b>30(100%)</b>

Analysis results showed that most of patients had coincidental viral replication regardless to the presence of difficulties (60%v.s 40%).

## DISCUSSION

Viral hepatitis has significant portion in causing of liver diseases. According to frequency they are placed directly after alcohol diseases depending on geographical distribution of viruses that have ability to persist, causing chronic liver disease.

WHO estimates that Hepatitis B virus infects more than 2 billion people in the world, and 300 million people of them developed chronic infection, that is as long as life lasts, and puts them at risk of developing cancer

or cirrhosis of the liver. High percentage of Hepatitis B virus is found in many developing countries (2). Today it is possible to exclude other etiology of chronic liver disease, by using contemporary, commercial, rapid and effective tests for detecting virologic, immunologic and inheritably diseases.

Based on epidemiological survey 33% of our patients reported risky sexual contact as a most common exposure to infection by hepatitis B virus; then exposure to infection via blood transfusion, blood donors and surgical interventions, 16,6 %. Virus replication was found in all groups of patients with highest incidence of 80 % in patients who reported risky sexual contact as a most common mode of hepatitis B virus infection.

Regular follow up of Alfa fetoprotein as a glikoprotein, because its level increase in serum can be significant for liver disease progression to hepatocellular carcinoma, did not show increase in people with chronic hepatitis B regardless to replication. Injected drug use is common mode of hepatitis B virus transmission (1,2). In our study 20 % of patients reported intravenous drug injection as a possible mode of infection. Hepatitis B virus replication in injected drug users was found in 66 % of cases.

Analysis of demographic characteristics in 30 patients with chronic hepatitis B showed that majority of diseased was men-77 %. Higher percent of infected among men can be explained by epidemiological characteristics, mode of transmission and risky behavior which is more common in male population. Hepatitis B virus replication was 78.2 % in men, and 57,1 % in women. More frequent presence of replication in men than in women indicates possible influence of sexual hormones to glucocorticoid receptor in genome of hepatitis B, which accelerate virus replication (12,13).

Analysis of age distribution showed presence of disease in all age groups with highest incidence between 20 and 50 years of age, which can be explained by highest exposure to risks in that period of life (surgical interventions, drug use, blood transfusion and sexual activity) as well as unimplemented vaccination against hepatitis B virus. Viral replication in chronic hepatitis B is found in 63 % of cases in the age group between 20-50 years of age in which the number of diseased was the highest. In regard to total number of patients with viral replication in relation to age distribution selected by age groups there was not significant difference.

This finding could indicate that virus replication is not influenced by age group of a host..(14,15)

There was not significant difference in the number of patients with chronic hepatitis B in regard to level of education (elementary, secondary and higher school education).

Number of patients with higher school education was inconsiderably higher -13 (43,4%) but with the group of patients with secondary school education – 9 (30%) it is not statistically significant. Chronic hepatitis B is significantly more often reported in people with certain level of



education and better economic life conditions. Hepatitis B is common in people who travel abroad often, drug users and in people who often change partners of both genders (16,17).

It is generally accepted that people with chronic hepatitis B who have not developed the cirrhosis of the liver and its complications do not have characteristic difficulties.(18).

In our study sample 60% of examinees had difficulties. Analysis of difficulties in our examinees showed that the more common were fatigue and nausea. Viral

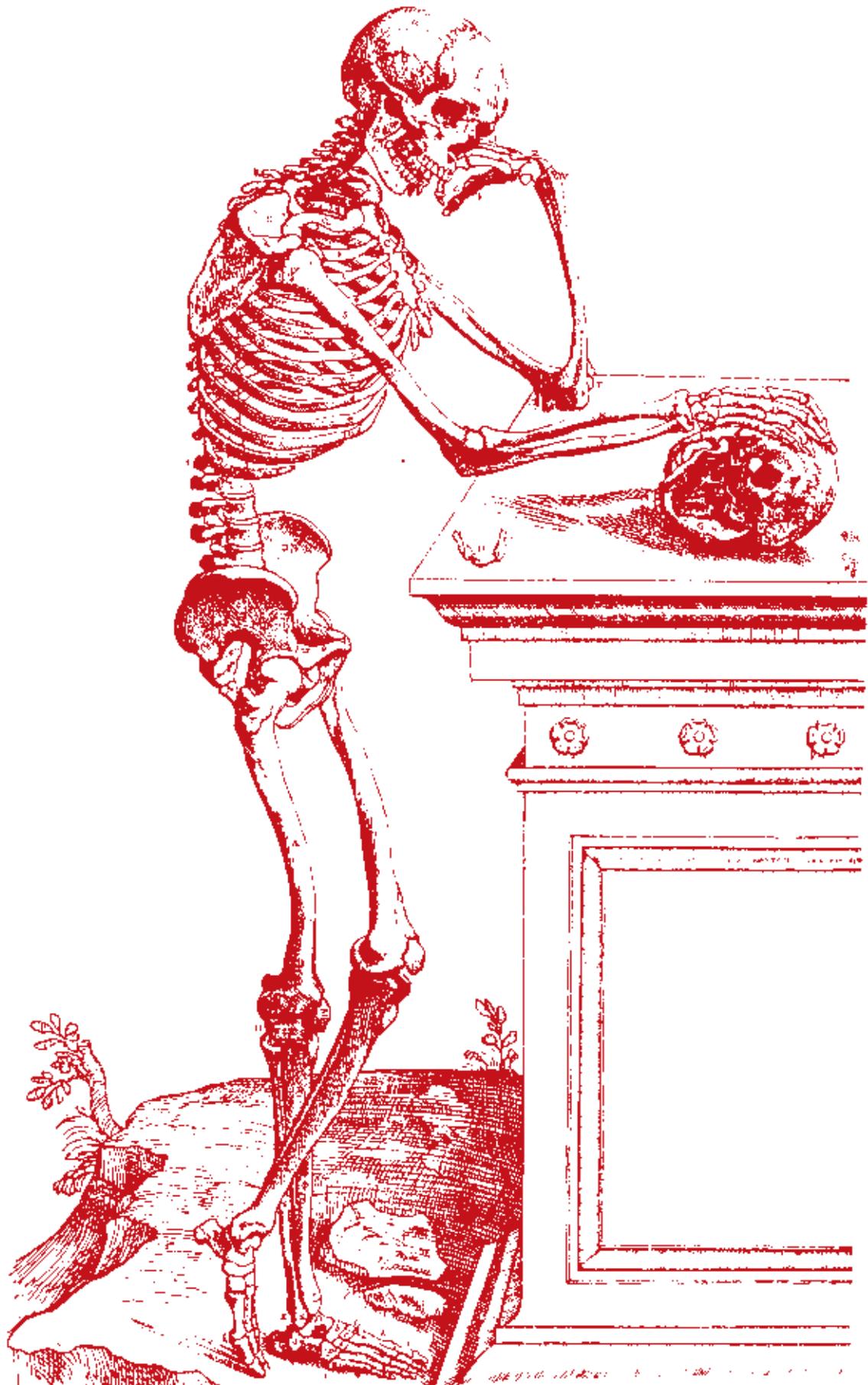
replication is not associated with presence of difficulties in patients as the patients without manifested difficulties had statistically significant presence of viral replication - 83%, $p < 0,05$ .

Vaccination against hepatitis B virus is mandatory but the number of people with hepatitis B is not insignificant especially in men in their most productive period of life and regardless to level of education. Chronic infection with "mute" clinical picture followed by virus replication accelerates developing of cirrhosis and hepatocellular carcinoma.

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# GIGANTIC BENIGN TUMOR OF THE RIGHT UPPER LEG

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# GIGANTSKI BENIGNI TUMOR DONJIH EKSTREMITETA

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## ABSTRACT

**Introduction:** Deep vein insufficiency of the lower extremities can cause many serious symptoms and severe disability. It is more intensive when it is complicated by a gigantic benign tumor.

**Case Notes:** The 63-year-old patient visited a doctor because of the pain in her lower legs. She had trouble walking and difficulties on urination. In the case history she stated many accompanying conditions which were usually related to insufficiency of venous circulation. The main cause of her difficulties was a gigantic tumor of the right upper leg. The change was present there for three years and made micturition difficult for the last ten months. Clinical examination set the indication for surgical treatment. During the routine preoperative preparation it was established that the patient also suffered from a serious insufficiency of deep veins. She was treated preoperatively for ten days with adequate anti-coagulant therapy. She was operated under the spinal anesthesia. During the intervention, saphenous vein was prepared carefully. The saphenous vein was about 1.40 meters long, curved a lot and with thickened walls. Tumor, fibrolipoma, of 3350 grams was removed.

**Conclusion:** The problem of the patient was solved with radical operation. Because of the insufficiency of the deep veins, saphenous vein was saved. It was lengthened a lot because of long-lasting process and the size of the tumor, so the preparation lasted for a few hours. The patient dealt with the intervention well, so she was discharged and advised to continue her treatment by a phlebologist.

**Key Words:** Gigantic benign tumor, fibrolipoma, vein insufficiency, anti-coagulants.

## SAŽETAK

**Uvod:** Insuficijencija dubokih vena donjih ekstremiteta može dovesti do niza ozbiljnih simptoma, a u krajnjem slučaju i do teškog invaliditeta. Sve ovo je naročito izraženo kada je komplikovano gigantskim benignim tumorom.

**Prikaz pacijenta:** Reč je o pacijentkinji staroj 63 godine koja se javlja lekaru zbog bolova u donjim ekstremitetima, otežanog hoda i problema sa mokrenjem. U anamnezi ona navodi veliki broj komorbidnih stanja kod kojih je najčešće u osnovi – insuficijencija venske cirkulacije. Osnovni uzrok sadašnjih tegoba je gigantski benigni tumor desne nadkolenice, nastao pre tri godine, dok u poslednjih nekoliko meseci onemogućava normalnu mikciju. Nakon kliničkog pregleda postavljena je indikacija za operativno lečenje. Tokom rutinske preoperativne pripreme dijagnostikovana je teška insuficijencija dubokih vena. Nekoliko dana je preoperativno tretirana odgovarajućom anti-coagulantnom terapijom. Hirurški zahvat je izvršen u spinalnoj anesteziji. U toku intervencije je detaljno ispreparisana VSM koja dostiže duzinu od oko 1,40m i koja je jako izvijana i zadebljalih zidova. Uklonjen je i tumor mase 3350gr (fibrolipoma).

**Zaključak:** Problem sa kojim se pacijentkinja javila hirurgu je rešen radikalnom operacijom. Zbog insuficijencije dubokih vena, sačuvana je VSM koja je zbog dugotrajnosti procesa i veličine tumora, jako izdužena pa je preparacija trajala nekoliko sati. Pacijentkinja je dobro podnela intervenciju i otpuštena kući sa savetom da se dalje leči kod flebologa.

**Ključne Reči:** Gigantski benigni tumor, venska insuficijencija, anti-coagulansi

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## INTRODUCTION

Gigantic benign tumors, although benign in their nature, can cause great troubles to the patients (5)(by their size, pressure on the surrounding structures, closing the natural openings, causing hypertension in natural cavities, etc.), so it was said that they were malignant by their localization. To the patient who came to us, benign tumor of fat tissue that was located on her right upper leg prac-

tically disabled normal micturition by its size. This additionally complicated the patient's underlying disease as well (insufficiency of deep veins of the lower extremities). All of the things previously mentioned can also cause a severe disability.



## CASE NOTES:

A female patient, 63 years old (Figure 1), visited the doctor because of her micturition difficulties, troubled walking and pains in her lower extremities. General practitioner referred her to a surgeon. In the case-history the patient said that she noticed a "swelling" of her right upper leg three years ago. She didn't have any difficulties at the beginning but the swelling grew gradually, so her troubles with walking started a few months ago, and the other complications later on. She has been treated because of vascular problems for a long time.



Figure 1

The patient's first symptoms started after a traffic accident, when she was hurt as a pedestrian. She was brought unconscious to the Emergency Centre as an urgent case. During the diagnostics it was confirmed that there was a serious injury of her pelvis with the opening of her pelvic ring. There was also a serial fracture of ribs on the left side (from the third to the seventh) as well as numerous blood boils and grazes on the body. There was a slight hemi paresis of the left side. She was treated conservatively and she was set into the "swing" after her neurological condition had been stabilized. Thrombosis of deep iliac vein developed, regardless of anti-coagulant therapy. During the hospitalization, acute holecys-

titis appeared with gradual development of the acute abdomen. She was then operated urgently and holecystectomy was done. Soon after the surgery, a lung micro-embolization occurred. Gradual recovery ensued, due to intensive and anti-coagulant therapy.

The patient was referred to physical therapy after several months of hospitalization. During the therapy thrombosis of deep veins persisted. When the therapy ended, the patient's health became stable and she was released from the hospital.

She was operated because of incarcerated umbilical hernia six years ago, when the intensive anti-coagulant therapy was administered again to prevent the deep veins thrombosis.

She was hospitalized as an urgent case five years ago because of thrombosis of deep veins and cellulitis of both legs.

Two years later she was hospitalized again as an urgent case because of left leg swelling and redness, with the signs of cellulitis as well. She was then treated conservatively, with anticoagulants and high doses of antibiotics.

The patient had extra systoles among the concomitant diseases, and she was taking drugs for it regularly.

Inspection showed that the tumor mass of the right upper leg was as big as a watermelon and it practically completely closed her vagina, not letting the patient to put her legs together. Palpation confirmed that it was a tumor of soft consistency; it was lightly sensitive to the pressure, movable and lightly fixed for the surface.

At the admission to Surgery Clinic, complete laboratory blood and urine examinations were done: Gly-6,7, Urea-5,1, Creatinine-76, Total proteins-72, Albumin-39, Cholesterol-5,73, Tryglicerides-2,28, AST-11, ALT-16, Amylase-23, CK-52, LDH-336, Globulins-33, SE-54/87, Er-4,0, Le-6,1, Hb-121, INR-3,37, APTT-27,8. Hematologist and cardiologist were consulted. A low molecular heparin in prophylactic doses was introduced preoperatively. Color duplex scan of leg veins was also done preoperatively. Iliac and femoral veins were reciprocally compressive, their walls were thickened, and their spontaneous phasic flow was due to fresh thrombotic masses. The walls of popliteal veins were thickened with echoic masses along the wall of the blood vessel. The walls of tibial veins were thickened with echoic masses along the wall of the blood vessel.

After the intensive preoperative preparation, the patient was operated under the spinal anesthesia. Large amount of serous liquid was leaking out the tumor all the time during the operation. Surgical intervention lasted for five hours. The saphenous vein was with thickened walls, its lumen was largely expanded and it was lengthened a lot, so it often changed its direction unpredictably and it practically filled the whole tumor. After the attentive preparation, saphenous vein was isolated, about 1.40 meters in length. Tumor was sent to a histological verification and the wound was drained, and



closed with the isolated stitches. During the postoperative period, low-molecular heparin was continued and APTT and INR were measured daily. Antibiotic therapy was used, followed by the daily check-ups by the cardiologist. Histological diagnosis, based on the extirpated material was: fibrolipoma. The total weight of that material was 3,750 grams with some skin above the tumor 740 millimeters long (Figure 2) (taken without large amount of serous liquid which was oozing from the tumor during the operation, and which was not measured).



**Figure 2**

The patient was gradually switched to oral anticoagulant therapy, and she was discharged twelve days after the operation. Her general health condition was well; she was not febrile, did not feel any pain, and the vital parameters were within the normal values.

## DISCUSSION

A patient with gigantic tumor of the right upper leg was admitted to the Surgery Clinic (4, 6). In spite of a high risk, a surgical intervention had to be done since the complications would have occurred if the tumor hadn't been removed. Its further growth would have completely disabled spontaneous urination and it would have

caused complete distal obstruction of deep veins (1, 3). During the intervention the strategy was to save saphenous vein as a collateral pathway, to partly enable normal venous drainage. Long-lasting growth of the tumor led to the lengthening of saphenous vein and its unpredictable flow, so its preparation was extremely difficult. In spite of the long-lasting surgical intervention, and the risky general health condition as well, she took the operation well and she recovered successfully without any complications that had occurred during her previous surgical interventions. Searching the expert literature we did not find tumors of such size (5) and complications like these ones, mostly because the health culture in developed countries doesn't allow the developing of similar lesions.

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## PERITONEAL CATHETER EXPULSION AS A COMPLICATION OF VENTRICULO-PERITONEAL SHUNT AFTER AN OPERATION OF HYDROCEPHALUS IN ADULT PATIENTS

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## EKSPULZIJA PERITONEALNOG KATETERA KAO KOMPLIKACIJA VENTRIKULOPERITONEALNOG ŠANTA NAKON OPERACIJE NORMOTENZIVNOG HIDROCEFALUSA KOD ODRASLIH

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### ABSTRACT

The aim of this study is to show a rare complication of the drainage system insufficiency in hydrocephalus in adult patients. This study presents 3 patients who had different causes of hydrocephalus (tumor of the cerebello-pontine angle, spontaneous subarachnoid hemorrhage after rupture of an aneurysm at the anterior communicating artery and unknown cause). All three patients were operated and V-P shunt with Hakim valve was implanted. Due to the system insufficiency, all three patients were re-operated. All three patients had, as the final complication, expulsion (expelling) of the peritoneal catheter from the peritoneal cavity into the abdominal wall where a pseudo cyst appeared. The cause of the expulsion in two patients was an infection, one being caused by a direct catheter contamination with *Staphylococcus aureus*, and the second by secondary system contamination as an accompanying occurrence of the sepsis caused by *Proteus mirabilis*, (the intrusion spots were decubitus ulcers). In the third case, the expulsion and pseudo cyst were caused by ascites due to the heart failure. In the case of system contamination and pseudocyst, attempts of the peritoneal catheter re-implantation did not have sustainable effect. The only possible solution was system extirpation followed by the appropriate antibiotic therapy. The third case was solved by peritoneal catheter implantation and administration of diuretics.

**Key words:** hydrocephalus, V-P shunt, complications

### SAŽETAK

Cilj ovog rada je da se prikaže retka komplikacija insuficijencije drenažnog sistema kod normotenzivnog hidrocefalusa kod odraslih. U radu su prikazana 3 bolesnika koji su imali različite uzroke hidrocefalusa (tumor pontocerebralnog ugla, spontana subarahnoidna hemoragija nakon rupture aneurizme na prednjoj komunikantnoj arteriji i nepoznat uzrok). Svo troje su operisani tako što im je ugrađen V-P šant po Hakimu. Zbog insuficijencije sistema kod svo troje je više puta rađena reintervencija. Kao krajnja komplikacija kod sva tri bolesnika javila se ekspulzija (spontano izbacivanje) peritonealnog katetera iz peritonealne šupljine u trbušni zid gde je nastala pseudocista. Uzrok ove pojave kod dva bolesnika bila je infekcija, jedna izazvana direktnom kontaminacijom katetera *Staphylococcus aureus*-om, a druga sekundarna kontaminacija sistema u sklopu sepse *Proteus mirabilis*-om, a ulazna mesta su bili dekubitusne rane. U trećem slučaju ekspulzija i pseudocista uzrokovani su ascitesom usled srčane dekompenzacije. Kod pojave kontaminacije sistema i nastanka pseudociste pokušaji reimplantacije peritonealnog katetera nisu dali trajni efekat. Jedini mogući način rešavanja je ekstirpacija sistema uz odgovarajuću antibiotsku terapiju. Treći slučaj rešen reimplantacijom peritonealnog katetera i uvođenjem diuretika.

**Ključne reči:** hidrocefalus, V-P šant, komplikacije

### INTRODUCTION

Diagnosed internal hydrocephalus in adults sets two tasks to the clinicians: determining of the cause of hydrocephalus and defining of appropriate, the best treatment option. The cause of hydrocephalus could be found at three levels: at the level of liquor production, the level of liquor circulation pathway and the level of liquor absorption. Increased liquor production has been the rarest cause of hydrocephalus and it appears in tumors of plexus chorioideus. An obstacle in the liquor circulation can be caused by tumors and pseudotumors of the cerebral

ventricles, brain stem, hemispheres of the cerebrum and cerebellum, the pineal region, cerebello-pontine angles or by the obstruction of the aqueduct of Sylvius due to adhesions after infections or hemorrhage. Non-obstructive hydrocephalus where liquor absorption is compromised becomes most frequently the consequence of inflammatory processes or subarachnoid hemorrhage.

The recognition of hydrocephalus causes in adults makes the causal treatment of hydrocephalus possible. If the causal treatment does not give the total effect in

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curing of hydrocephalus or if it is not possible at all, the only solution is some of drainage operations. Another problem of hydrocephalus in adults is the fact that normotensive hydrocephalus has been the most common, which eliminates a significant number of operative solutions. In the first place, intra cranial liquor drainage (ventriculocisternostomy) is impossible because there is no pressure gradient between the ventricles and basilar cisterns. From this, we can conclude that the method of choice should be some of the extra cranial drainages: ventriculoatrial (V-A) or ventriculoperitoneal (V-P) shunt. V-A and V-P shunt with Pudenz or Hakim valve with modifications are used in practice most commonly. Regarding normotensive hydrocephalus, the systems for average, moderately low and low pressure are used in practice. In our institution, we apply the systems with programmable valve that enable changing of the postoperative system efficacy by external pressure regulation. Correctly set indication and appropriate kind of drainage operation are a prerequisite of the positive outcome. After adequate drainage operation, the triad of symptoms (dementia, incontinency and difficulties in walking) vanishes.

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Although a high standard has been reached in drainage operations, everyday practice and numerous references speak of a significant number of complications. On one side, there are the complications which are not associated with the adequately chosen system, as an infection and rarely, allergy to silicone material, and on the other side, there are the complications associated with the system, like ventricular catheter obstructions, inadequate valve function, distal catheter obstruction or its migration into natural orifices, hollow organs and the outer environment. The dilemma whether to drain the liquor into the venous system or peritoneal cavity regarding the aspect of possible complications is not justified. The percentage of complications on distal catheter is approximately the same in V-A as well as in V-P shunt. V-P shunt is more suitable because it is simple for implantation and the complications are easy to solve (1).

Dysfunction of the peritoneal catheter due to appearance of pseudo cysts around it as well as ascites, has been described in literature. Pseudo cysts are manifested by signs of the system insufficiency and are most frequently the consequence of infection. On the other hand, the appearance of ascites is the consequence of reduced resorption capacity of the peritoneal liquor because of the venous stasis in heart failure, liver cirrhosis and similar conditions and this is manifested by abdominal symptoms. The biochemical structure of liquor is by rule transudate. When a pseudo cyst is in question, it can be cured by reimplantation into other parts of the peritoneal cavity. When the cause of the system dysfunction is ascites, an adequate reintervention is implantation of the distal catheter into the venous system (2).

Publications which deal with this problem, describe a series of complications at the peritoneal catheter level such as its migration into abdominal organs through

natural and made orifices, into other cavities or into the outer environment through umbilicus (3), through the gastrostomy orifice (4), through the colon and anus into the scrotum (5), into the thoracic cavity (6). Frazier and his associates (7) describe a rare complication such as migration of the peritoneal catheter through a damaged jugular vein into the right heart. In fact, while pulling the peritoneal catheter, damage of the jugular vein occurred through which the peritoneal catheter migrated later.

The aim of this study was to show three cases of irregular complication of V-P shunt in hydrocephalus such as retroauricular expulsion of the peritoneal catheter into the abdominal wall and subcutaneous tissue.

## CASES

Three adult patients were operated: the first patient with hydrocephalus as a consequence of the cerebello-pontine angle neurinoma, the second after subarachnoid hemorrhage, and the third due to an unknown cause.

### *The first patient*

The patient, 74 years old, had hydrocephalus caused by the left cerebello-pontine angle neurinoma and was hospitalized in another neurosurgical institution. Because of the age and poor somatic status, he was not radically operated but the drainage operation was done (V-P shunt sec. Hakim-Cordis, medium pressure). Eight months after his release from the Clinic, the infection signs appeared around the peritoneal catheter on the thoracic wall. Incisions were made and *Staphylococcus aureus* was isolated. After administration of the antibiotic therapy, the condition became stable. After a year, a painless swelling on the spot of a surgical incision on the front abdominal wall with the diameter around 10 cm was found. A pseudo cyst filled with liquor was detected by the ultrasound examination. A revision was done in total endotracheal anesthesia, the pseudo cyst was found below the fascia in the muscular layer and it was filled with clear liquor, having the whole distal end of the peritoneal catheter in it. The operation was completed by the catheter reimplantation into the peritoneal cavity. Pathological germs were not found in the cyst structure and *Staphylococcus aureus* was isolated in the blood. Antibiotics were prescribed according to the antibiogram. The wound healed up, the sutures were taken off and the patient was released in a good shape from the hospital. After 11 months, he came again with the painful swelling behind the right ear, about the size of a child fist. Clear liquor was obtained by puncture but again, pathological germs were not found. By native radiography of the tumor, wrapped and retracted peritoneal catheter was noticed and its top was found subcutaneously on the front wall of the rib cage. The catheter was re-implanted into the abdominal cavity by another



operation. In spite of negative bacteriological results in the catheter swab and pseudocyst structure, the antibiotics according to the antibiogram for blood culture were prescribed and the patient was released home in a good shape. After 3 months, inflammation signs along the whole peritoneal catheter were noticed so that the whole drainage system was surgically removed and *Neisseria* species were isolated in the swab from the catheter channel. After administration of appropriate antibiotics, the condition became stable. After a year, the patient is well without the signs of intracranial hypertension (normotensive hydrocephalus) and no other surgical interventions were considered necessary.

### **The second patient**

The patient, 45 years old, had spontaneous subarachnoid hemorrhage because of the aneurysm rupture of the anterior communicating artery. After the re-rupture and long lasting treatment with physical therapy, during a prolonged vegetative condition after 8 months, a large internal hydrocephalus with a liquor perfusion into the periventricular area was noticed on the control CT scan. Drainage operation (V-A shunt) with Hakim valve for the average low blood pressure was performed. Due to the system dysfunction, it was converted into V-P shunt. After a month, the system insufficiency was diagnosed with the ventricles still widened, so valve was replaced with the valve for low blood pressure. General condition of the female patient was slightly improved and moderate decrease in the size of hydrocephalus was verified on the control CT scan. In the meantime, an infection of decubital ulcers appeared on both gluteus regions which was followed by sepsis (*Proteus mirabilis* had been isolated in the blood culture). The antibiotics were prescribed, but a pseudo cyst on the anterior abdominal wall was found on the spot of catheter implantation into the peritoneal cavity. By native radiological and ultrasound examinations, it was detected that the end of the peritoneal catheter had been in the cyst. The revision was done and turbid cerebrospinal fluid in the cyst was found. The cyst was rinsed, the cavity obliterated, and the catheter re-implanted into the abdominal cavity through a new laparotomy procedure. During the next period, septicemia lasted and on the spot of laparotomy wound, the signs of local inflammation appeared so the system was totally removed. Infections were treated by the antibiotics according to the results of microbial sensitivity tests. The CT findings of the brain on control examination showed the dilated ventricular system, without flow of cerebrospinal fluid (normotensive hydrocephalus). The patient remained in prolonged vegetative state and no other surgical interventions were considered necessary.

### **The third patient**

The patient, 50 years old, was hospitalized because of a headache; during hospitalization disturbed, imbalanced walk was observed and a three-chamber hydrocephalus

of an unknown cause was verified. Namely, the patient had mild-to-moderate hearing failure for years. Drainage operation (V-P shunt) by Hakim for the average low blood pressure was performed. After 3 months, the control examination was performed, the symptoms were present and it was found that hydrocephalus was not reduced on the CT scan. The ventricular catheter was slightly longer, so after a reintervention the catheter was shortened. After a year, signs of the system insufficiency were found such as imbalanced walk and incontinency. On the spot of laparotomy on the abdominal wall, a pseudo cyst about the size of male fist was found, and by native radiography and ultrasound, the peritoneal catheter end in the cyst was noticed. The revision was done, clear cerebrospinal fluid in the cyst was found, and clear liquor was leaking from the canal by which the cyst communicated with the peritoneal cavity– the fibrous canal created around the catheter while it was in the peritoneal cavity. Otherwise, the system functioned regularly. The cyst was obliterated by the stitches, and the catheter was implanted into the peritoneal cavity through a new laparotomy opening. During the next period, the physical condition was better, with occasional incontinency, and by CT, the dilated chamber system was noticed. After 6 months, since the condition was stable, a revision was done so that the valve was replaced with the programmable valve. In the next period, the patient's condition was stable, but after 2 months, the cyst was again found on the anterior abdominal wall, being filled with clear liquor from the peritoneal catheter which migrated out of the peritoneal cavity. The catheter was re-implanted into the abdominal cavity through a new laparotomy opening. By laboratory examinations, the possibility of local as well as general infection was excluded. After that period, the patient felt fairly well and diuretics were introduced along with the other therapy for cardiovascular diseases.

## **DISCUSSION**

This study deals with three patients with drainage operations. All three were operated several times and all had similar complications. In the first patient, just after the operation, the contamination of the system and its peritoneal catheter was found and the conservative treatment by antibiotics led to control of local infection. After that, expulsion of the system from the peritoneal cavity into the abdominal wall was found, and later on, along its canal even to the retroauricular region. The same causative agent that was isolated beside the catheter at the beginning was now found in the blood culture. An infection of the central nervous system and infection of the peritoneal cavity were not found in the patient. The condition was improved after the extirpation of the whole drainage system and the antibiotic therapy according to the antibiogram. In the second patient, hydrocephalus appeared as a consequence of spontaneous subarachnoid hem-



orrhage and the patient was re-operated several times, because of insufficient function of the drainage system and, finally, implantation of the adequate system for low pressure resulted in improvement of the general condition of the patient. Worsening of the patient condition was caused by sepsis, starting from decubital ulcers. This resulted with the system contamination and expulsion of the peritoneal catheter from the peritoneal cavity into the anterior abdominal wall, where a purulent pseudocyst was found. The complication was solved by the extirpation of the whole system and the antibiotic therapy according to the culture results. In the third patient, hydrocephalus of an unknown cause was solved with drainage operation; signs of insufficient function of the system at the beginning were caused by an inadequate drainage system, and later because of the heart failure and insufficient resorption capacity of the peritoneum. The ascites developed and the peritoneal catheter migration into the front abdominal wall with a pseudo cyst was found. The case was solved by the catheter re-implantation and introduction of diuretic therapy

All three patients had hydrocephalus of different genesis. The hydrocephalus in all three cases was cured by V-P shunt. In all three, several re-interventions were done because of the system failure. All three patients had the same complications at the end, that is, expulsion of the peritoneal catheter from the peritoneal cavity into the abdominal wall. In the first two patients, the complication caused the infection, in the first case through the primary system contamination and in the second case, as a part of the sepsis. In the third patient, the system expulsion ensued because of the ascites caused by the heart failure. All attempts to save the system in the patients where the infection appeared were unsuccessful and the only adequate solution was extirpation of the whole system. The surgical methods performed in the first and in the second patient were similar to previous published experience (1, 5). On the other side, for the third patient we did not convert V-P into V-A shunt as it was recommended by other authors. That patient had congestive heart failure, reduced absorption capacity of the peritoneal liquor because of the venous stasis. The administration of a diuretic, furosemide, normalized the pressure of the cerebrospinal liquor. In the patient with ascites, although it is recommended in literature that drainage should be converted by some other method, the authors have chosen re-implantation along with the diuretic therapy.

We recommend that, in case of catheter expulsion caused by infection, whole system should be removed with administration of antibiotics until blood and cerebrospinal fluid cultures become sterile. Additional therapy could include diuretics (in the case of sustainable high pressure of cerebrospinal fluid) as well as temporary external drainage. In the case of system expulsion due to ascites and heart failure, it is necessary to administer appropriate drug therapy in consultation with cardiologist. Another option is to convert V-P into V-A shunt.



**Figure 1.** Peritoneal catheter in retro-auricular soft tissue.



**Figure 2.** The top of retracted peritoneal catheter in the same patient.



**Figure 3.** Peritoneal catheter in the pseudocyst in the front abdominal wall



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**THE SEVENTH/THIRTEEN CONGRESS OF ASSOCIATION OF SERBIAN NEUROLOGISTS WITH INTERNATIONAL PARTICIPATION  
THE FOURTH CONGRESS OF SERBIAN ASSOCIATION OF NEUROSCIENCES WITH INTERNATIONAL PARTICIPATION  
THE FIRST SYMPOSIUM OF NEUROLOGICAL NURSES-TECHNICIANS WITH INTERNATIONAL PARTICIPATION**

(September 11-14, 2008, Kragujevac, Serbia)

The Seventh/Thirteen Congress of Association of Serbian Neurologists (the Thirteen Congress in former Yugoslavia), the Fourth Congress of Serbian Association of Neuroscience, and the First Symposium of Neurological Nurses and Technicians were held between September 11-14, 2008 at hotel "Sumarice" and hotel "Kragujevac" in Kragujevac.

This congress was organized by Association of Serbian Neurologists and has been supported by Serbian Association of Neurosciences, Faculty of Medicine University of Kragujevac and Clinic of Neurology Clinical Center Kragujevac.

The total number of participants was more than 600 from Serbia, Montenegro, Bosnia and Hercegovina, Macedonia, Slovenia, Croatia, Hungary and Germany.

Scientific work was presented in six invited lectures, 21 scientific symposia and 260 poster presentations in two sessions. Thirty abstracts were rejected on the base of the ad hoc scientific committee evaluation. Abstract book was published and regularly CIP indexed.

Invited speakers were Prof Vécsei László (University of Szeged, Hungary), Csiba László (Debrecin University, Hungary), Academician Vladimir Kostic (Institute of Neurology, Clinical Center of Serbia, Belgrade), Prof Slobodan Apostolski (Institute of Neurology, Clinical Center of Serbia, Belgrade), Academician Ljubisa Rakic (Serbian Academy of Sciences and Arts, Belgrade) and Prof Miroslav Samardzic (Institute of Neurosurgery, Clinical Center of Serbia, Belgrade).

Scientific symposia included all fields of Neurology and Neuroscience: How early we have recognized Parkinson's disease, Ictal video EEG (old words, new contents), SETIS (Serbian Experience with Thrombolysis in Ischemic Stroke), Advance in treatment of Neuromuscular Diseases, Stroke, Heterogeneous factors in develop-

ment of Multiple Sclerosis, Dementias, Methods in Neurology, Neuroinjury, Young neurologists, Neurological Units of Critical Care, Medicaments Overuse Headache, Neurosurgery, Child Neurology, Evolution and Ageing, Neurodegeneration and Neuroprotection, Autoimmune Diseases of nervous system, Neurotoxicity and Apoptosis, Stress and Nervous System, Neurophysiology and Behavior, Experimental Models in CNS Plasticity.

Attractive social programs and events added to the overall positive impression about congress.

Gordana Tončev



# REPORT FROM THE SECOND EUROPEAN SYMPOSIUM OF IMMUNOLOGISTS

The Medical Faculty in Kragujevac in cooperation with the European Federation of the Society of Immunologists organised the Second European Symposium of Immunologists named "EFIS/EJI Belgrade Symposium / Postgraduate Course – Inflammation at the Interface of Innate and Acquired Immunity" during the period from September 7th to September 10th 2008 in the Hyatt Regency Hotel in Belgrade.

While preparing this symposium, a large number of people was engaged to realise this meeting, including doctors, administrators, staff in the domain of publishing, technical staff, designers and students. The agency HRG from Belgrade was selected to prepare the symposium and coordinate the organisation with the hotels. Considering the anticipated number of visitors, five halls were used in the Hyatt Regency Hotel in Belgrade. The hall Belgrade-Budva was used to hold sessions, the hall Kopaonik was used for stall exhibitions and the hall Boardroom for registering the participants.

200 participants were present at the symposium, including widely-recognised immunologists from almost all countries around the world, such as prof. dr Peter Doherty, a Nobel Prize winner for medicine, as well as a large number of domestic researchers who live abroad.

The opening ceremony was held on September 7th 2008 at 5 o'clock in the afternoon in the hall of National Assembly of Serbia. Prof. dr Miodrag Lukic opened this scientific meeting and the visitors were also greeted by prof. dr Slavica Djukic-Dejanovic, the president of the National Assembly of Serbia.

During the four days of the Symposium the participants had an opportunity to hear more than 35 oral presentations, and to observe more than 10 poster presentations.

Our faculty presented one oral and three poster presentations:

- Miodrag Lukic - Galectin-3 in autoimmunity
- Nemanja Zdravkovic, Aleksandar Djukic, Ivan Jovanovic, Nebojsa Arsenijevic, Miodrag Lukic - Regulatory mechanisms in low dose streptozotocin diabetes induction
- Marina Stojanovic, Ivanka Zelen, Ivana Nikolic, Dejan Baskic - A novel role for ST2 as an inhibitory regulator of apoptosis and inflammation in CON-A induced hepatitis
- I.Tanaskovic, T.Kastratovic, N.Arsenijevic, S.Arsenijevic, A.Mladenovic-Mihailovic, B.Stankovic, B.Todorovic, B.Lackovic - The role of smooth muscle cells and vascular dendritic cells in the inflammatory response in atherosclerosis

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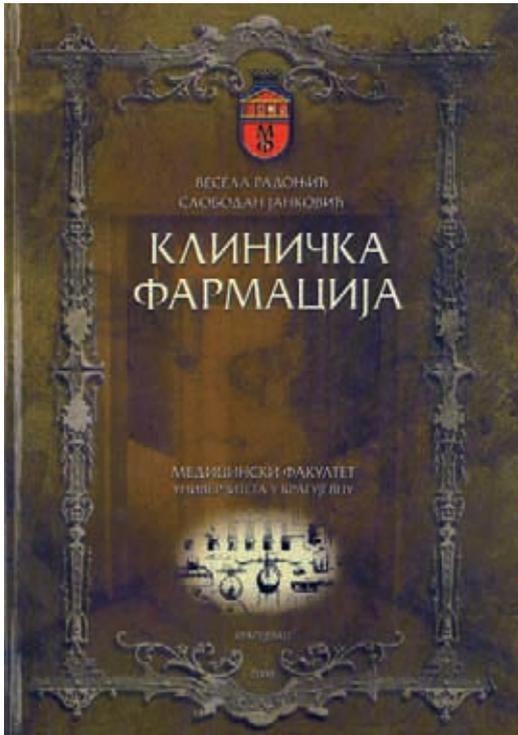


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## CLINICAL PHARMACY

By Vesela Radonjic and Slobodan Jankovic



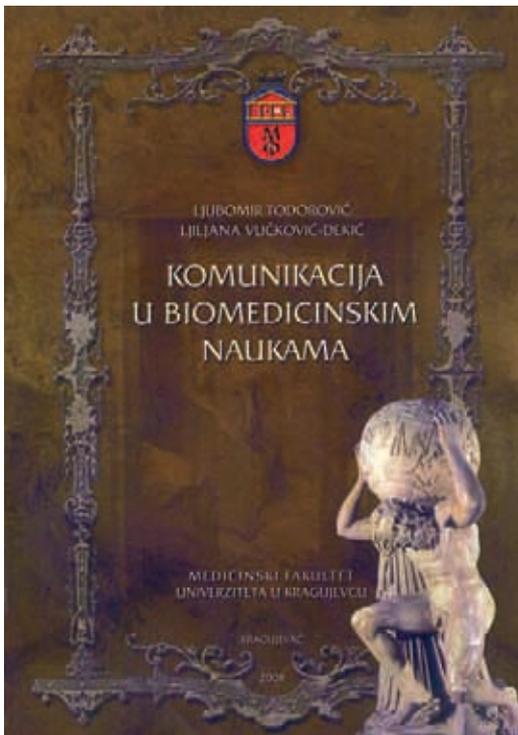
After tremendous efforts of the two authors, the first Serbian textbook of clinical pharmacy appeared at daylight. Written in modern style, and yet clear and comprehensive, this book covers all major topics of clinical pharmacy. After long period of concentration to drug production only, pharmacy is now open towards patients and their needs. Clinical pharmacy deals primarily with hospitalized patients, helping to clinicians to administer drugs, and follow their positive and adverse effects. Students of pharmacy will find in this book a lot of necessary facts and tips about drug administration in elderly, in children, and in patients with renal or hepatic insufficiency. Therapeutic drug monitoring, medicine management, evidence-based pharmacy, pharmaceutical calculations and many other topics are also well described and explained in this book. It could be used both by students of pharmacy for preparation of exams and by graduated pharmacists as a handbook in their everyday work. We gladly recommend this book to all profiles

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Milica Prostran, MD, PhD, and Zoran Todorovic, MD, PhD, Professors of pharmacology, toxicology and clinical pharmacology,

## COMMUNICATION IN BIOMEDICAL SCIENCE

By Ljubomir Todorovic and Ljiljana Vuckovic Dekic



This valuable book is practical guideline for design and conduct of biomedical research, as well as for presenting research results at scientific gatherings or in scientific journals. It is well designed, systematically composed, written by clear language and with good style. Not only PhD students, but also many senior researchers will benefit from this book, learning how to present their results more efficiently. The book is composed of seven chapters: Scientific Communication, Creation of a scientific work, Presentations at Gatherings, Publication of Articles, Ethical questions, Appendices and Recommended Literature. The book was edited as textbook for PhD students, and is one of a few of its kind in Serbian scientific literature. Both Medical Faculty as an editor, and the readers themselves, will be honored to have and use this book.

Nebojsa Arsenijevic, MD, PhD, Professor of microbiology, immunology, and oncology, and Snezana Zivancevic Simonovic, MD, PhD, Professor of pathophysiology



## ELECTROMAGNETIC FIELD AND BIOLOGICAL SYSTEMS

By Tanja Zecevic Lukovic and Milan Radovanovic

This monograph is devoted to biological effects of electromagnetic field, especially in humans. Throughout five chapters (History of electromagnetic field use, Characteristics of electromagnetic field, Physiological effects of electromagnetic field, Effects on organs and Adverse effects), the authors highlighted all aspects of electromagnetic field, and of its effects on living organisms. The electromagnetic field is widely used in physical medicine, and may cure certain conditions. The authors used over 300 references, and wrote clear and comprehensive text, which could be used by both researchers and PhD students. From the text, one can understand that the authors had incorporated their large clinical experience in the book, which gives special value to it. This book also filled a gap in national medical literature concerning this topic, contributing to better treatment of Serbian patients.

Milorad Jevtic, MD, PhD, Professor of physical medicine, Mirko Rosic, MD, PhD, Professor of physiology and Miodrag Veljkovic, MD, PhD, Associated Professor of physical medicine

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# INSTRUCTION TO AUTHORS FOR MANUSCRIPT PREPARATION

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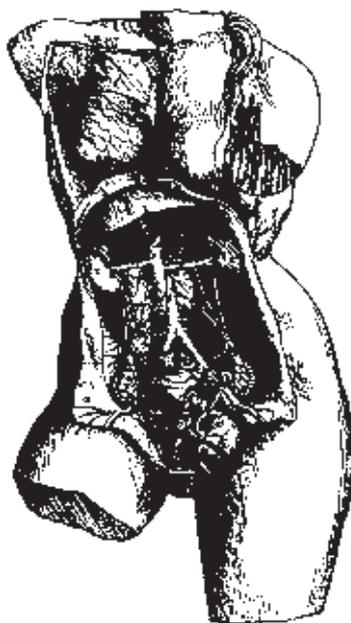
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