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KLINIČKI CENTAR UNIVERZITETA SARAJEVO

INSTITUT ZA NAUČNO ISTRAŽIVAČKI RAD I RAZVOJ

KLINIČKI CENTAR UNIVERZITETA SARAJEVO

U SLUŽBI VAŠEG ZDRAVLJA

Bosnia and Herzegovina was the fourth country in Europe that developed National version of HeartScore program !

Bosna i Hercegovina je bila četvrta zemlja u Evropi koja je razvila Nacionalnu verziju HeartScore programa !

Bosnia and Herzegovina version of HeartScore is developed on the languages of the people of Bosnia and Herzegovina i.e. Bosnian, Serbian and Croatian! Program is easy to use and accessible at www.heartscore.org/eu !

Verzija za Bosnu i Hercegovinu razvijena je na jezicima naroda Bosne i Hercegovine, bosanskom, srpskom i hrvatskom! Program je jednostavan za upotrebu preko web stranice www.heartscore.org/eu !

Bosnia Herzegovina	France	Russian Federation
Croatia	Germany *	Spain *
Cyprus *	Greece *	Sweden *
Czech Republic *	Poland *	Slovakia *
Estonia	Romania	Turkey

Novi Centralni medicinski blok - Klinički centar Univerziteta u Sarajevu
New Central Medical Building - Clinical Center University of Sarajevo

Novi Evropski vodič za prevenciju tromboembolizma kod A Fib

CHA_2DS_2-VASc skor za procjenu rizika od tromboembolizma kod A Fib!

Risk factor-based point-based scoring system - CHA_2DS_2 -VASc

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease*	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

*Prior myocardial infarction, peripheral artery disease, aortic plaque. Actual rates of stroke in contemporary cohorts may vary from these estimates.

Major i non-major riziko fakori za procjenu tromboembolizma kod A Fib!

Risk factors for stroke and thrombo-embolism in non-valvular AF

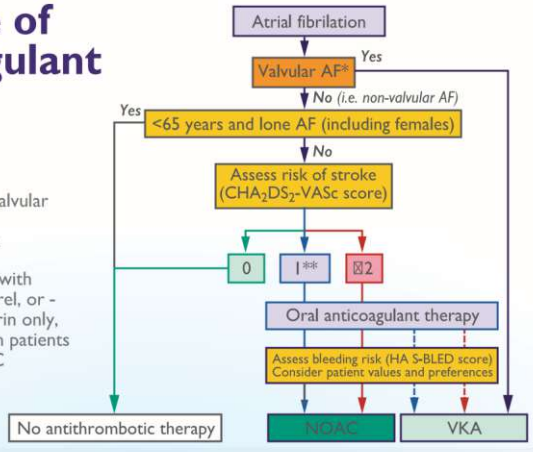
Major risk factors
Previous stroke
TIA or systemic embolism
Age ⊠75 years

Clinically relevant non-major risk factors
CHF or moderate to severe LV systolic dysfunction [e.g. LV EF ⊠ 40%]
Hypertension
Diabetes mellitus
Age 65-74 years
Female sex
Vascular disease

AF = atrial fibrilation; EF = ejection fraction (as documented by echocardiography, radio nuclide ventriculography, cardiac catheterization, cardiac magnetic resonance imaging, etc.); LV = left venticular; TIA = trasient ischaemic attack.

Algoritam antikoagulantne terapije nakon procjene CHA_2DS_2VASc i major risk faktora!

Choice of Anti-coagulant



* Includes rheumatic valvular AF, hypertrophic cardiomyopathy, etc.

** Antiplatelet therapy with aspirin plus clopidogrel, or - less effectively - aspirin only, may be considered in patients who refuse any OAC

NOAC - Novel Oral Anticoagulants, VKA - Vitamin K Antagonists

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AIMS AND SCOPE

The Medical Journal is the official quarterly journal of the Institute for Research and Development of the Clinical Center University of Sarajevo and has been published regularly since 1994. It is published in the languages of the people of Bosnia and Herzegovina i.e. Bosnian, Croatian and Serbian as well as in English.

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Evaluation of the most commonly used drugs in Neonatal Intensive Care Unit settings

Evaluacija najčešće korištenih lijekova u Jedinici intenzivne njege

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ABSTRACT

Aims: to determine which drugs from the group of Anatomical Therapeutic Chemical (ATC) Classification System are mostly used in the Neonatal Intensive Care Unit of Pediatric Clinic of the Clinical Center University of Sarajevo; to determine specific usage (drug dose, intervals between them, total daily dose, the length of therapy in days, route of administration, pharmaceutical formulation); to determine whether the drug dose and routes of administration differ in respect to the age of a patient and whether the drugs were used as recommended. Results: this research included 670 patients, 384 male (57.3%) and 286 female (42.7%). The number of mature infants was 142 (21.2%) and the number of premature infants was 528 (78.8%). The average gestation week (GA) was 33.1± 4.2, and the average birth weight was 2079.4±10.2 grams. The average number of drugs per patient was 7.5 (SD±4.3) regardless of gestational age. The most often used drugs, from each group according to ATC classification and regardless to gestational age were: probiotic drops (57.8%), vitamin K1 (81.8%), furosemide (20.6%), sildenafil (4.2%), dexamethasone (1.7%), ampicillin (97.2%), amikacin (80%), ibuprofen (3.1%), midazolam (44.6%), surfactant (14.6%), tobramycin (8.7%). There was a statistically significant difference ($p<0.05$) in the dose related to gestational age of the respondents. The results of the evaluated drugs were compared to guidelines and it was established that they were used according to guidelines applicable at the Pediatric Clinic NICU. Conclusion: this study shows that pharmacological treatment of neonatal population differs in individual dose, total daily dose and route of administration in respect to other age groups and that it is applied in accordance with the recommended guidelines.

Key words: neonates, drugs, doses, routes of administration, pharmaceutical formulation

SAŽETAK

Ciljevi: utvrditi koji su lijekovi iz grupa lijekova prema Anatomsko terapijsko hemijskoj klasifikaciji (ATC), najčešće korišteni na odjelu neonatalne intenzivne njege (NICU) Pedijatrijske klinike Kliničkog centra Univerziteta u Sarajevu (KCUS), te utvrditi specifičnosti primjene tih lijekova (pojedinačnu dozu, interval između dvije doze, ukupnu dnevnu dozu, dužinu trajanja terapije u danima, načine aplikacije, te farmaceutske oblike), utvrditi da li se način aplikacije i farmaceutski oblici razlikuju u odnosu na stariju djecu i odrasle i da li su lijekovi primijenjeni u skladu sa preporučenim smjernicama. Rezultati: Istraživanjem je obuhvaćeno 670 ispitanika od kojih je 384 (57,3%) bilo muškog, a 286 (42,7%) ženskog spola. Broj terminske novorođenčadi je 142 (21,2 %), a preterminske 528 (78,8%). Prosječna dob u nedjeljama gestacije (NG) kod ispitanika iznosila je 33,1±4,2 NG, a prosječna porođajna težina je iznosila 2073,4±910,2 grama. U provedenoj studiji, prosječan broj lijekova po ispitaniku je 7,5 (SD±4,3) bez obzira na gestacionu dob. Najčešće korišteni lijekovi, iz svake grupe prema ATC klasifikaciji, kod svih ispitanika, bez obzira na gestacionu dob su: probiotičke kapi kod 57,8%, K1 vitamin kod 81,8%, furosemid kod 20,6%, sildenafil kod 4,2%, deksametazon kod 1,7%, ampicilin kod 97,2%, amikacin 80%, ibuprofen kod 3,1%, midazolam kod 44,6%, surfaktant kod 14,6%, tobramicin kod 8,7% ispitanika. Utvrđena je statistički signifikantna razlika ($p<0,05$) u odnosu na primjenjivanu dozi i dob ispitanika. Dobijeni rezultati evaluiranih lijekova su komparirani sa preporučenim smjernicama, te je utvrđeno da su u skladu sa smjernicama koje se koriste na NICU Pedijatrijske klinike KCUS-a. Zaključak: Farmakološke mjere u liječenju neonatalne populacije na NICU Pedijatrijske klinike KCUS razlikuju u odnosu na pojedinačnu dozu i način aplikacije prema ostalim dobnim skupinama i slijede preporučene smjernice.

Ključne riječi: novorođenče, lijekovi, doze, načini aplikacije, farmaceutski oblik lijeka

INTRODUCTION

According to the World Health Organization's (WHO)

definition, newborns are babies from birth to 28 days of age. They represent the most vulnerable part of the population. Specific neonatal diseases, pharmacological therapy and therapeutic procedures have led to the creation of neonatal intensive care units (NICU) worldwide (1). Pharmacological therapy has immensely improved the survival rate and the quality of life of the newborns (2). This therapy often includes a large amount of different medications. The average number of medicines used by newborns in NICU has been increasing steadily over the past 40 years. The use of drugs in neonatal intensive care units is characterized by a high variability in the treatment of various diseases, and this is a widespread phenomenon both within and between different countries (3). Unfortunately, there are still no universally accepted and standardized guidelines related to rational prescribing and individualization of drugs at NICU. All newborns, especially those born prematurely, are the most vulnerable part of the population. Also, there are still no universal guidelines for the use of drugs at this age (2). In treating this population, as with other age groups, the goal is to achieve therapeutic effect without, or with minor side effects.

Aims of the this study were to determine which drugs from the group of Anatomical Therapeutic Chemical (ATC) Classification System are mostly used in the NICU of Pediatric Clinic of the Clinical Center University of Sarajevo (CCUS) from April 2015 to April 2017; to determine the most common routes of administration at NICU during the study period; to determine the most common pharmaceutical formulations at NICU during the study period; to determine specific usage (drug dose, intervals between them, total daily dose, the length of therapy in days, route of administration, pharmaceutical formulation); to determine whether the drug dose and routes of administration differ in respect to the age of a patient, and whether the drugs were used as recommended; to determine which drugs used by newborns during the study period had different indications for newborns in relation to the adult population; to determine that the medicines used during the period of study were exclusively used in the neonatal period; and finally to determine whether the most commonly used drugs were applied in accordance with the guidelines used at the Pediatric Clinic NICU.

MATERIALS AND METHODS

This retrospective-prospective analytic study included 670 patients of both gender and different gestational age hospitalized at NICU of Pediatric Clinic of the CCUS from April 2015 to April 2017. Patients were aged between 21 and 42 of gestational age (GA), and the average gestation age was 33.1 ± 4.2. Their body weight was from 500 to 5175 g, and the average birth weight was 2073.4 ± 910.2 grams. Based on the gestational age they were divided into premature (<37 GA) and terminal newborns (≥37 GA). The results of the analysis are shown in tables and figures in percentages, arithmetic mean (X) with standard deviation (SD), standard error (SEM) and range of values (min-max). Testing of differences between the age groups was performed using Wilcoxon's signed rank test and one-way variance analysis (ANOVA) at a significance level of $p<0.05$, which was considered statistically significant. The analysis was carried out using the IBM Statistical Statistics SPSS v 21.0 statistical package.

S. Loga-Zec

RESULTS

Gender and age structure of patients

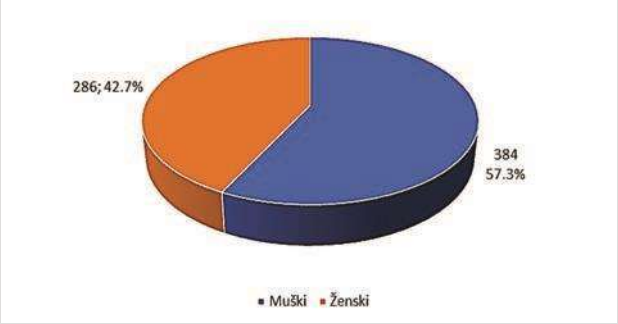

Figure 1 Gender structure of patients.

Figure 1 shows that out of the total of 670 patients there were 384 (57.3%) male, and 286 (42.7%) female patients.

Table 1 Average number of drugs per patient.

Gestational age (GA)	N	$\bar{X}$	SD	SEM	Min.	Max.
<28	59	10.15	3.67	0.48	3.00	20.00
28-30	106	9.62	3.45	0.33	1.00	22.00
31-32	154	6.42	2.83	0.23	1.00	20.00
34-36	209	5.77	3.94	0.27	2.00	24.00
≥ 37	142	8.37	5.41	0.45	1.00	25.00
Total	670	7.47	4.31	0.17	1.00	25.00

N - number of patients; $\bar{X}$-arithmetic mean; SD - standard deviation; SEM - standard error; Min. -minimal value; Max. - maximum value

According to Table 1, an average of 7.5 ± 4.3 drugs were administered per patient. There was at least one and a maximum of 25 drugs prescribed per patient during their stay at NICU. There is a statistically significant difference ($p=0.0001$) in the number of drugs per patient and the age of patients. Younger patients received more drugs.

Table 2 Individual dose (mg/kg) of ampicillin.

Gestational age (GA)	N	$\bar{X}$	SD	SG	Min.	Max.
<28	58	79.87	22.95	3.01	45.45	170.45
28-30	103	75.79	23.20	2.29	31.58	184.78
31-33	150	72.56	20.33	1.66	41.18	122.64
34-36	200	71.27	19.35	1.37	47.24	110.24
≥37	139	71.59	21.67	1.84	9.40	106.38
Total	650	73.12	21.15	0.83	9.40	184.78

N - number of patients; $\bar{X}$-arithmetic mean; SD - standard deviation; SEM - standard error; Min. -minimal value; Max. - maximum value

According to Table 2, ampicillin was used in 650 patients. The average individual drug dose (mg/kg) was 73.12 ± 21.15. The lowest administered individual drug dose of ampicillin was 9.40 and the highest was 184.78. In 58 patients <28 GA, the average individual drug dose (mg/kg) was 79.87 ± 22.95. Ampicillin was given to 200 patients aged 34-36 GA and the average individual drug dose (mg/kg) was 71.27±19.35. There was a statistically significant difference (p=0.041) between individual doses and gestational age of patients.

Table 3 Duration of therapy with ampicillin.

Gestational age (GA)	N	$\bar{X}$	SD	SEM	Min.	Max.
<28	58	5.43	2.88	0.38	1	12
28-30	103	5.25	1.99	0.20	1	11
31-33	150	5.35	1.90	0.16	1	12
34-36	200	5.41	2.37	0.17	1	19
≥37	139	6.07	2.55	0.22	1	13
Total	650	5.51	2.32	0.09	1	19

N - number of patients; $\bar{X}$-arithmetic mean; SD - standard deviation; SEM - standard error; Min. -minimal value; Max. - maximum value

Table 4 Individual dose (mg/kg) of amikacin.

Gestational age (GA)	N	$\bar{X}$	SD	SEM	Min.	Max.
<28	49	17.09	1.65	0.24	13.64	21.82
28-30	89	16.73	2.43	0.26	9.74	30.00
31-33	120	17.09	1.94	0.18	11.58	28.30
34-36	169	16.30	2.82	0.22	8.89	33.76
≥37	109	14.52	1.35	0.13	8.98	20.11
Total	536	16.26	2.41	0.10	8.89	33.76

N - number of patients; $\bar{X}$-arithmetic mean; SD - standard deviation; SEM - standard error; Min. -minimal value; Max. - maximum value

Table 5 Duration of therapy with amikacin.

Gestational age (GA)	N	$\bar{X}$	SD	SEM	Min.	Max.
<28	49	5.37	2.88	0.41	1	12
28-30	89	5.27	2.12	0.22	1	11
31-33	120	5.43	1.91	0.18	1	12
34-36	169	5.47	2.20	0.17	1	12
≥37	109	6.39	2.58	0.25	1	15
Total	536	5.61	2.31	0.10	1	15

N - number of patients; $\bar{X}$-arithmetic mean; SD - standard deviation; SEM - standard error; Min. - minimal value; Max. - maximum value

Table 6 Individual dose (mg/kg) of ibuprofen.

Gestational age (GA)	N	$\bar{X}$	SD	SEM	Min.	Max.
<28	9	6.86	2.73	0.91	3.90	10.00
28-30	9	8.93	1.51	0.50	5.59	10.00
34-36	2	4.69	0.11	0.08	4.61	4.76
≥37	1	2.40	.	.	2.40	2.40
Total	21	7.33	2.66	0.58	2.40	10.00

N - number of patients; $\bar{X}$-arithmetic mean; SD - standard deviation; SEM - standard error; Min. -minimal value; Max. - maximum value

The average duration of therapy was 5.51 ± 2.32 days. The

shortest ampicillin administration was 1 day and the maximum was 19 days. There was a statistically significant difference (p=0.030) in the duration of therapy between patients of different gestational age (Table 3).

According to Table 4 amikacin was used in 536 patients. The average individual drug dose (mg/kg) was 16.26±2.41. The lowest administered individual drug dose was 8.89 and the highest was 33.76. In 49 patients <28 GA the average individual drug dose (mg/kg) was 17.09±1.65. Amikacin was used in 169 respondents aged 34-36 GA and the average individual drug dose (mg/kg) was 16.30 ± 2.82. There was a statistically significant difference (p=0.0001) between the individual dose and the gestational age of patients.

The average duration of therapy was 5.61 ± 2.31 days. The shortest administration of amikacin was 1 day and the maximum was 15 days. There was a statistically significant difference (p=0.002) in the duration of therapy between patients of different gestational age (Table 5).

The ibuprofen was used in 21 patients. The average individual drug dose (mg/kg) was 7.33 ± 2.66. The lowest administered individual drug dose (mg/kg) was 2.40 and the highest was 10.0. In 9 patients <28 GA the average individual drug dose (mg/kg) was 6.86 ± 2.73. Ibuprofen was used in 9 patients aged 28-30 GA and the average individual drug dose (mg/kg) was 8.93 ± 1.51. There was a statistically significant difference (p=0.015) between individual doses and gestational age of patients (Table 6).

DISCUSSION

In the conducted study, the average number of drugs per patient was 7.5 (SD ± 4.3) regardless of gestational age. There was a statistically significant difference (p=0.0001) in the number of drugs per patient and the age of patients. Younger patients received more drugs. The obtained results are similar to the results of previously conducted studies, according to which the average number of drugs varies between 3.7 and 11.1 per respondent (4). The difference in the average number of drugs per patient varies because of different drugs included in different studies and there is no single method of choice for medication. Accordingly, it is obvious that the results differ and therefore may not be directly comparable (5). On the other hand, it is impossible not to notice that the number of drugs per patient is significant, especially if we take into account the population in question. The number of newborns has increased steadily over the past 40 years. Consequently, newborns exposed to a large number of drugs have a higher risk of adverse effects (1).

The usage of drugs in newborns represents a significant challenge. The choice of the route of administration depends on chemical and physical properties of the drug, the therapeutic effects of the drug, as well as of the response of a patient and patient's population (2). Newborns received at NICU, either preterm or term, have different clinical problems. In this population, with various clinical problems, a range of drugs is big and drugs are applied in different ways to get specific therapeutic outcomes. The most commonly used method of application in all patients from the study, regardless of their gestational age, was intravenous (75%). Other methods have rarely been used. Also, this was the most commonly used method of application (78.7%) in newborns in a multicenter study in Italy (6), and 57.7% in the performed prospective observation study (7).

During the drug administration, regardless to the method of

administration, the basic goal is a safe, proper, therapeutically effective and least painful application. In older children and adults, who can swallow and are not life-threatening, the most common method is oral administration. During oral administration in infants, interactions between milk and drug components are possible, and if a newborn does not drink the whole meal with which the drug is mixed, it can only receive a partial dose. There is also a risk of inconsistent dosing resulting in inadequate, usually very low doses, and the problems are also caused by excipients added to oral medicaments which may be potentially or already known to be harmful to the newborn. In addition, since the neonatal period is the period of intense growth and development there are significant pharmacokinetic (increased stomach pH, reduced stomach discharge time, variable intestinal mobility, decreased bile acid synthesis, variable amount of bacteria in the intestine, reduced blood flow, immaturity of the enzyme, decreased number of binding proteins) and pharmacodynamic differences in newborns as compared to older children and adults affecting the ultimate outcome of orally administered drugs (8). Due to all above mentioned regarding this population, drugs are most commonly administered intravenously.

The most frequently used group of drugs in all patients, regardless of gestational age, are anti-infective drugs (5,6).

The most frequently used anti-infective drugs in the study were antibiotics, ampicillin and amikacin (9). Differences in the use of individual drugs are explained by the fact that empirical antibiotic treatment varies between different country NICUs as there are no generally accepted guidelines for choice of empirical antibiotics (10).

Ampicillin was used in 650 (97.2%) out of 670 patients. It was used in cases of newborns in existing or suspected early-onset sepsis and meningitis caused by Group B streptococci, Lysterimonocytogenes and susceptible E.coli strains. Ampicillin was mainly used in combination with some aminoglycoside. According to the guidelines, the recommended dose is 25 to 50 mg/kg/dose in suspected or proven infection every 12 hours and for meningitis the recommended dose is 200 to 300 mg/kg/day divided every 8 hours (11). Therapy should last at least 2 weeks in the case of meningitis, and the recommended duration of treatment for infections is 7 to 10 days. According to the recommendations, the interval between two doses is 12 hours, and the route of administration implies i.v. or i.m. application. In all respondents, the interval was 12 hours, and ampicillin was administered i.v. The average length of therapy in the study was 5.51 (SD ± 2.32) days. According to the guidelines, empirical therapy lasts for 48 hours while waiting for microbiological examinations and if the culture is negative, therapy should be discontinued. If the culture is positive, it is necessary to continue with the same therapy if the agent is susceptible to the given therapy, and if not, appropriate antibiotic therapy (11) should be ordered. In 350 (53.8%) respondents from the study, for which the therapy lasted for up to 5 days, ampicillin was used empirically. In 281 (43.2%) patients, ampicillin was used over 6 to 10 days, for the treatment of infections. In 19 (2.9%) patients, the duration of the therapy was over 10 days, with the maximum duration of 19 days. Ampicillin used in the study was packed as a powder in 0.5g concentration vials. Ampicillin was applied according to the guidelines.

Amikacin is used in the treatment of infections caused by gram negative bacteria, resistant to other aminoglycosides. It is mainly used in combination with beta lactam antibiotics in the treatment of suspicious or proven late neonatal sepsis. According to the guidelines, for patients <29 GA the recommended dose is 18 mg and the interval between the two doses is 48 hours. In patients of 30-34 GA the recommended dose is 18 mg at intervals of 36 hours. In patients >35 GA the recommended dose is 15 mg in 24-hour intervals (7,12).

S. Loga-Zec

CONCLUSION

In the conducted study, the average number of drugs per patient was 7.5 (SD ± 4.3) regardless of their gestational age, and the most commonly used route of administration in all patients, regardless of gestational age, was intravenous. The most commonly used pharmaceutical form was a solution for infusion/injection. The most commonly used group of drugs in all patients, regardless of gestational age, were anti-infective drugs. All medications used at the Pediatric Clinics NICU (CCUS) were applied in accordance with the recommended guidelines.

Conflict of interest: none declared.

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Embryonic development disorders and adverse pregnancy outcomes in the area of Zenica-Doboj Canton - analysis of possible causes

Poremećaj embrionalnog razvoja i nepovoljan ishod trudnoće na području Zeničko-dobojskog kantona - analiza mogućih uzroka

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ABSTRACT

Introduction: according to the World Health Organization 2-7% of all pregnancies have a negative outcome. In this study, we observed pregnancies with disorders in embryonic development and adverse outcome in the form of miscarriage, stillbirth and birth of a child with abnormalities. Aim: to find the cause of these adverse pregnancy outcomes. Materials and Methods: this was a retrospective, analytical and anamnesticdescriptive analysis of pregnancies based on an Annual report on births, abortions and neonatology in the Zenica-Doboj Canton in 2015. Results: all registered pregnancies were observed, total of 2,941 of which 2,463 were successfully completed. Out of 478 pregnancies with an adverse outcome, 439 were completed in miscarriage, 18 in a stillbirth, and 21 children were born with abnormalities. The study showed that the average age of these mothers was 26.74 years. Only 12.5% of these women had regular control examinations during pregnancy (and irregularly), and only 16 amniocentesis was performed out of 145 required. Previous miscarriages were recorded in a total of 230 (36.7%) cases, of which 8% habitual. Among the observed pregnant women, 4.3% of them previously had a stillbirth, and 1.4% gave birth to a child with anomaly. Discussion: in similar studies which partly correspond to our research major differences of fetal and neonatal mortality were established, depending on the country where the study was conducted. Conclusion: the small number of pregnant women (12.5%) did not have regular pregnancy controls, which resulted in a small number of amniocentesis.

Key words: embryonic development, adverse pregnancy outcomes

SAŽETAK

Uvod: prema Svjetskoj zdravstvenoj organizaciji 2-7% svih trudnoća ima negativan ishod. U ovom istraživanju su posmatrane trudnoće s poremećajem u embrionalnom razvoju i nepovoljnim ishodom u vidu spontanog pobačaja, mrtvorođenja, rođenja djeteta s anomalijama. Ciljevi: pronaći uzroke nastanka tih nepovoljnih ishoda trudnoća. Materijal i metode: rad je retrospektivna, anamnestičko-deskriptivna analiza trudnoća urađena na temelju godišnjih izvještaja o porođajima, pobačajima i neonatologije u Zeničko-dobojskom kantonu u 2015. godini. Rezultati rada: obrađene su sve evidentirane trudnoće, ukupno 2941, od kojih su 2463 uspješno završene. Od 478 trudnoća s nepovoljnim ishodom, 439 je završeno kao pobačaj, 18 kao mrtvorođenje te je 21 dijete rođeno s anomalijama. Istraživanje je pokazalo da je prosječna starost ovih majki 26.74 godina. Samo 12.5% ovih žena je dolazilo na kontrolne preglede u toku trudnoće (i to neredovno), a urađeno je samo 16 amniocenteza, od potrebnih 145. Prethodni spontani pobačaji su evidentirani u ukupno 230 (36.7%) slučajeva, od toga 8% habitualnih. Među posmatranim trudnicama, njih 4.3% je ranije imalo mrtvorođenje, a 1.4% je rodilo dijete s anomalijom. Diskusija: u sličnim istraživanjima, koja donekle korespondiraju našem istraživanju ustanovljene su velike razlike fetalnog i neonatalnog mortaliteta, ovisno o zemlji u kojoj je studija rađena. Zaključak: mali broj trudnica (12.5%) su neredovno kontrolirale trudnoću, što je rezultiralo i malim brojem urađenih amniocenteza.

Ključne riječi: embrionalni razvoj, nepovoljan ishod trudnoće

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INTRODUCTION

Adverse pregnancy outcome means death of the fetus at any stage of intrauterine development, or spontaneous abortion and/or stillbirth. The frequency of adverse pregnancy outcomes in the world population varies, depending on the observed sample, between 2 and 7% of clinically diagnosed cases of pregnancy. Abortions make up by far the largest part of various forms of adverse pregnancy outcomes (1). During embryonic development of the fetus some changes which disrupt the normal development may occur, which can lead to miscarriage (there are even 30% of them).

Miscarriages, particularly habitual, in a history of pregnant

women present biological markers of risk pregnancies which have the greatest practical importance (2,3,4), and they are classified into the group of markers from the mother (immune factors, hormonal, developmental anomaly of the genital tract, mother's diseases) and those during embryonic development of the fetus (5,6). Frequent causes also relate to: cardiovascular disorders, diabetes, lupus, psychological trauma, smoking, alcohol and genital infections (3,7,8). Fetal mortality or stillbirth indicates fetal deaths during pregnancy from the 28th week of age weighing more than 1.000 grams.

It is believed that in half of the cases the main cause of fetal death is fetal hypoxia. It can be caused by bleeding during pregnancy, infections and conditions that compromise the fetoplacental circulation, and diseases and anomalies of both mother and fetus. In many cases, the etiology of fetal death remains unknown (9,10).

Deviations from the average, which are located outside the boundaries of normal variability, are called disturbances in embryonic development, congenital abnormalities or congenital anomalies (11,12,13).

Congenital defect is an anomaly of morphological, structural, functional and molecular development which is present at birth or which occurs later in the development (9).

"Pathological" genes are generally less expressiveness of "normal", while in phenotype can manifest itself only with the participation of environmental factors, to raise their expressiveness (10,11,12).

Goal

To examine the causes of unsuccessful pregnancies and discover reasons for the occurrence of spontaneous abortions, stillbirths and birth of a child with anomalies.

MATERIALS AND METHODS

This was a retrospective, analytical and anamnestic-descriptive analysis of pregnancies with adverse outcome in the Zenica-Doboj Canton in 2015. The analysis used regular statistical reports from the Department of Obstetrics, Neonatology and Perinatology of the Cantonal Hospital in Zenica and the Public Health Institute of ZenicaDoboj Canton such as: annual birth reports and annual abortion and neonatology reports.

We observed pregnancies with disorders in embryonic development and adverse outcome in 2015. They included:

a) all abortions (spontaneous and intentional),
b) stillbirths,
c) birth of a child with one or more anomalies.

For all these needs, we created data which included the following parameters:

- Mother's age;
- Social factors (education, employment);
- Pregnancy – control;
- The outcome of the controlled and previous pregnancies;
- Mother's personal history - previous diseases;
- Family history (genetic malformations in the family, age of the father of the child, ABO and Rh factor).

Statistical analysis was done in MS Excel and the results were presented in tables by number of cases, percentage, mean (X) with a standard deviation (SD) and standard error of arithmetic mean (AS), median and range of values.

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RESULTS

The total sample included 2941 pregnancies in 2015, of which 2.463 (83.75%) were completed in successful birth, and 478 (16.25%) as pregnancy with adverse outcome (Table 1).

Table 1 Overview of pregnancy outcomes in 2015.

Pregnancy outcome		2015.	
		Nr.	%
Successful births		2.463	83,75
unsuccessful pregnancies	Abortions overall	439	14,93
	Stillbirths	18	0,61
	Children with anomalies	21	0,71
Total		2941	100,0

In the observed period 18 children were stillborn, and 21 children were born with abnormalities (Table 1,2).

Table 2 Diagnosed malformations of children in 2015.

Diagnose	2015	
	Nr.	%
Sy. L. Down	7	33.3
Malformatio multiplex	3	14.3
Hydrocephalus	4	19.2
Sy. Edwards	1	4.7
Cheilognathopalatoschisis	1	4.7
Vitium cordis congenitum	5	23.8
Total	21	100.0

The average age of women who had spontaneous abortion was 28.74 ± 6.66 years (Table 3). From the recorded spontaneous abortions, 69.66% were registered in women aged 31 and over, and 30.33% in women aged 20-30.

Table 3 The age of women with adverse pregnancy outcomes.

Age groups	2015	
	Nr.	%
under 20	6	1.2
20-25	189	39.5
26-30	138	28.9
31-35	83	17.4
36-40	61	12.8
41 and over	1	0.2
Total	478	100
The average age of women a.s.	26. 4	
s.d.	±5. 18	

There were only 16 amniocentesis, and in only two cases some pathological changes were recorded. Women who needed amniocentesis included those over 35 years of age and with previously unsuccessful pregnancies.

Table 4 Amniocentesis in 2015.

	Number of women
Required amniocentesis	145
Performed amniocentesis	16

Table 5 Educational status of women with adverse pregnancy outcomes in 2015.

Level of education	Number	%
Without any education	4	0.8
Primary school	151	31.6
High school	283	59.3
Upper high school	17	3.5
University	23	4.8
Total	478	100.0

Table 6 Number of previous births.

	Number	%
Without any birth	157	25.0
One	235	37.5
Two	209	33.3
Three or more	26	4.2
Total	627	100.0

Table 7 Number of previous miscarriages.

	Number	%
No abortion	396	63.3
One	180	28.7
Two	33	5.3
Three or more	17	2.7
Total	626	100.0

The largest number of women with an adverse outcome

pregnancy completed primary or secondary school (Table 5), and most of them were housewives (90.9%) or unemployed (82.5%).

Only small number of women used to come to control examinations during pregnancy, only 78 (12.5%), and those controls were recorded as "irregular" in the anamnesis list.

Before the last pregnancy, women had an average of 1.17% of deliveries (Table 6), and 2.72% of abortions (Table 7).

Previous miscarriages were recorded in a total of 230 (36.7%) cases, of which 8% related to recurrent (repeated) miscarriages. Out of the total number of women whose pregnancies ended unsuccessfully, 4.3% of them (27) previously had a stillborn baby, and 1.4% (9) gave birth to a baby with abnormality. Nine mothers had hypertension, and four of them had diabetes mellitus.

Gynecological disorders or abnormalities of the uterus were not recorded in this sample, considering that only 12.5% of patients used to have control examinations during pregnancy.

According to the ABO blood group system, the majority of mothers with unsuccessful pregnancies (Table 8) had blood type 0 (51.46%), and 12.5% were Rh negative.

Table 8 Blood groups of mothers with unsuccessful pregnancy in 2015.

ABO	Number	%
„0"	246	51.46
„A"	132	27.63
„B"	57	11.92
„AB"	43	8.99
Total	478	100.0

DISCUSSION

Similar research from 2015 included twelve European countries. The research observed a relationship between fetal and neonatal mortality depending on the mother's age and parity. Depending on the country where the study was conducted we have found significant differences from 3.3 to 7.1 and from 2.0 to 6.0 per 1000 live births. The results showed that in mothers over 35 years old representation of mortality was 7.0 to 22%. The connection between age of the mother and fetal mortality decreases as the prevalence of older mothers in the total population increases (14,15).

Out of the total of 83 women up to 35 years of age and 62 women aged 36 and more only 16 amniocenteses were done. This random but particular group of women shows that especially large number of women should be indicated amniocentesis because of previous pregnancy outcomes, perhaps the stress in the life as a reflection of unemployment and other problems. This year, 21 children were born with malformations. This low number of performed amniocentesis and the number of children with congenital malformations in this case is explained by the lack of supervision of gynecologists and genetic counseling.

Pregnancies with an adverse outcome in 2015 were observed in relation to biological markers (risk factors) which were taken from the history of the pregnant woman.

The average age of women who had a pregnancy with adverse outcome was 26.74 ± 5.98 years. It is easy to notice that a very small number of pregnant women from this group who were under the supervision of gynecologists. Only 78 of them (12.5%) used to come to control examinations, which were recorded as "irregular" in the anamnestic list, and that included only one or rarely two controls.

Therefore, there is no genetic counseling which should be recommended by a competent gynecologist after mentioning possible anamnestic risk factors. For the same reason, there is no detection of ultrasound and biochemical markers of pathological pregnancies.

Most of the patients were housewives (45%) or unemployed (38.5%), with low education level. The strikingly low socio-economic status is reflected in the lack of perinatal care.

Diseases of pregnant women were registered in 16.4% of cases with adverse pregnancy outcomes. 12.4% of them had hypertensive disease.

The study observed that mother's disease had the most impact on fetal death. A pregnant woman who had diabetes mellitus gave birth to a stillborn child with polyhidramnion and other multiple malformations. Disorders in the development of the embryo in the mother who had diabetes were significantly more frequent (16.7%) than in the general population. They usually occur in the eighth week of gestation.

Although the exact cause is not known yet, it is clear that they are

associated with hyperglycemia during the period of organogenesis.

Cardiovascular and CNS malformations are particularly frequent, as well as those connected with skeleton and urogenital tract. Prophylaxis of malformations is to control a level of glucose before conception and in early pregnancy.

Hypertension in pregnancy is very significant problem and occurs in 6-10% of pregnant women. It increases the morbidity and mortality of the mother, fetus and newborn. A direct consequence of hypertension is a change in the blood vessels of the placenta which reduces its nutritional and oxygen role. This condition can also cause a perinatal death (3,1). Before the last pregnancy, these women had an average of 1.17% births and 2.72% miscarriages.

Out of the total number of pregnant women who had abortions, 25% related to those who were pregnant for the first time. Previously, 36.7% of them had abortions, of which 8% had repeated (habitual) abortion. Extensive research of the population of pregnant women in Keiser's Health Plan in North Carolina lead to the conclusion that the risk of miscarriage increases with the serial number of pregnancy, that is, regardless of the age of pregnant women (15,16).

Results of the study on recurrent miscarriages (Steinburg 2013) are: risk for women with a first pregnancy loss rate is 15%. For those who have already had an abortion it is 12-24%, after two consecutive miscarriages 19-35%, and after three consecutive miscarriages it is 25-46%. Although the risk of miscarriage increases with maternal age, women aged 20-24 years have a risk of 9%, and those of 45 years have a risk of 75%. As the age of expectant mothers in recent decades is growing, consequently, it could be expected to increase the number of abortions (17). Single study says, if a woman had one or more children, the risk of miscarriage in the next pregnancy is significantly higher in those with normal caryogram of previously aborted fetus (24.3%) compared to those with pathological caryogram (7.3%). This study also shows that the prognosis for the next pregnancy is better in patients whose fetus had pathological caryogram, because in the next pregnancy 14% of women had a miscarriage compared to 26% of spontaneous abortions in the group whose previous embryo had a normal caryogram (15,18).

Out of the total number of women whose pregnancy ended successfully, 4.3% previously had a stillborn child, and 1.4% gave birth to a baby with anomalies.

This study registered the highest number of spontaneous abortions among women aged 25-40 years. The largest number of pregnancies occured in this age group. Observing the socio-economic status and low level of education, and thus the lack of antenatal care of these pregnant women in the Zenica-Doboj Canton, all these factors lead to pathological conditions in pregnancy that can result in miscarriage. If abortion is performed in the earlier weeks of pregnancy, especially if there was no embryo or was macerated with longer retention, the cause was probably abnormal caryogram given that chromosomal abnormalities (trisomy) occur more often in older mothers.

A study carried out in India showed a chromosome analysis at 742 pairs (1,484 individuals) who had at least two miscarriages or stillbirths or birth of a child with malformations in the 2003-2013 period, as well as those who have had repeated miscarriages (>3) with normal life problems. This study estimated the contribution of chromosomal anomalies in repeated miscarriages. In this group, chromosomal aberrations were found in 31 persons (2%). These abnormalities in 22 (2.9%) persons were structural, and in 9 (1.2%) persons numerical. In all of these abnormalities 21 (3.2%) different chromosomal variants were found. It is concluded that the analysis of chromosomal abnormalities is important in finding the etiological causes in couples with repeated miscarriages because it helps in genetic counseling and decision-making about further reproductive options (20). The risk of repeated miscarriage is about 20% and the habitual over 30% (1,4,7).

In this sample, fathers are usually older than their wives, but the differences between the ages of parents are not large and are approximately equal in cases of pregnancies with an adverse outcome as well as in successful pregnancies and range from 2-5 years.

On the whole, the average age of the father in this study was 31 ± 6.22 years which shows no correlation with the frequency of pregnancies with an adverse outcome. There is no doubt that male gametes (sperm) can be a cause of non development of the fetus, or unsuccessful pregnancy.

Considering the fact that male sex cells continuously produce in the body (up to termination due to age of the person, or due to a pathological cause), the probability of mutant sperm occurrence increases with age, whether it is a genetic or chromosomal mutations. Therefore, the rule is that the probability of miscarriage increases with the age of the father. Some researches suggest that there is around 2.7% annual increase in risk that is associated with the age of the father, regardless of the age of the mother and one parity. It is also known that an unsuccessful pregnancy can occur as a result of poor quality of sperm. As a man gets older, his sperm gets different quality (15). In this group of women who had a pregnancy with an adverse outcome, 12.4% were smokers. None of them have consumed alcohol or drugs.

A Norwegian study examined changes in smoking habits from the beginning until the end of pregnancy in the period from 2004 to 2014. The aim was to examine whether there is a general decline in smoking in pregnant women. Among daily smokers reduced incidence from 17.3% to 13.2% was observed. The highest prevalence of smoking was found among underage mothers, single women and women with lower education. Quitting smoking highly depends on the social polarization and education of the woman.

The study concludes that special attention should be given to minors, single women and women with lower education, because of the risk of smoking on pregnancy outcome (2,8,18,21).

A case-control study carried out in a district of northern Italy, which gathered a large number of women who were occupationally exposed to organic waste, and worked in 400 factories showed a significant association between risks such as smoking, drinking coffee and alcohol with a miscarriage. Thereafter, a campaign on health education had been done. Also, they wanted to raise awareness of the risk factors for pregnancy. The effects of this campaign were estimated by number of abortions before and after that were recorded in local hospitals. Smoking, drinking coffee and alcohol were reduced, but exposure to solvents remained the same. The results showed that campaigns on health education can reduce exposure to maternal risk factors for miscarriage (22).

Smoking greatly increases the risk of miscarriage. The use of cocaine and alcohol is also one of the possible causes. Smoking can

change the immune response during pregnancy. However, in the analysis of these causes it is difficult to say that they are really the main causes of spontaneous abortion, since they are usually associated with low standards, malnutrition, certain habits and ethnic factors. Usually, it is a combination of several factors (7,19).

From the women with adverse pregnancy outcomes in 2015, 51.46% had blood group "O", and 12.5% were RhD negative. Approximately 15% of the population in BiH is RhD negative. The risk of maternal isoimmunization is 4-8% during the first pregnancy, or about 13-17% during the second pregnancy. It is well known that Rh isoimmunization is not developing in all pregnancies of Rh negative mothers who carry the Rh positive fetus. It is believed that only 5% of mothers develop aloimmunization, so it is a very rare phenomenon. The main reason why the sensitization rarely develops lies in ABO incompatibility of the fetus and the mother, because maternal anti-A and anti-B agglutinins very quickly (within a few days) lead to hemolysis of fetal red blood cells in the mother's bloodstream, so immunocompetent cells do not have time to register Rh antigene. ABO sensitization occurs in about 20% of all pregnancies, but fetal hemolysis occurs in less than 2% of cases. It occurs in A or B blood group of the fetus and the "O" blood of the mother with "A" and "B" from the group of IgG antibodies that cross the placenta. For mothers who are "A" or "B" blood type there are only IgM antibodies which do not pass placental barrier. In subsequent pregnancies there is no progression of the disease (23).

CONCLUSION

This research shows that pregnant women must be regularly monitored by gynecologist. She should also be consulted through genetic counseling. Education and socioeconomic status are essential for prenatal care because they result in raising awareness of the importance of control and behavior during pregnancy. The probability of an adverse pregnancy outcome increases in the case when the previous pregnancy ended in miscarriage, stillbirth and birth of a child with anomalies. In this study, only a small number of pregnant women used to control their pregnancies, and the reasons were in the extremely low socioeconomic status, which was reflected in the lack of perinatal care.

Conflict of interest: none declared

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Issues in the use of clinical inventory PAI for the purpose of staff selection

Korišćenje PAI kliničkog inventara u procesu selekcije kadrova

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ABSTRACT

PAI is a psychological instrument primarily intended for clinical assessment of psychopathological phenomenon. However, simultaneously it proved to be a good instrument for the selection of personnel for risk professions (police, army, fire brigade). In this paper we discuss the strengths and weaknesses of the use of clinical instrument for selection purposes. Presented a study where in Montenegro on a sample of 207 respondents who are on the labor market and job seekers applied PAI questionnaire. The results show a significant deviation selection of the sample of the general population. It discusses how the pattern of jobseekers, especially important to analyze the validity scales and setting the norm for the selection of certain purposes (context which uses questionnaire, type of profession for which the selection is made).

Key words: PAI, selection, personality assessment

SAŽETAK

PAI je psihološki instrument koji je primarno namenjen kliničkoj proceni psihopatoloških fenomena. Međutim, istovremeno se pokazao kao dobar instrument za selekciju kadrova za profesije koje uključuju rizik (policajci, vojnici, vatrogasci). U radu razmatramo prednosti i slabosti korišćenja kliničkih instrumenata u svrhu selekcije kadrova. Prezentovani su rezultati istraživanja u Crnoj Gori, gde je PAI upitnik primenjen na 207 ispitanika koji se nalaze na tržištu rada. Rezultati pokazuju značajno odstupanje rezultata na ovom uzorku od rezultata u opštoj populaciji. Diskutuju se specifičnosti ispitanika koji traže posao, značaj skala validnosti i formiranja specifičnih normi PAI upitnika (zavisno od konteksta u kome se sprovodi istraživanje, specifičnosti određenih profesija za koje se vrši selekcija).

Ključne reči: PAI, selekcija kadrova, procena ličnosti

INTRODUCTION

Personality Assessment Inventory - PAI was established in 1991, and belongs to a group of self-report questionnaires of the new generation (1). The PAI is designed to assess a wide range of psychopathology in adults and there are already numerous articles about its application in clinical and forensic psychology (2). The PAI inventory is now considered one of the most commonly used instruments in the selection of public safety jobs, especially in the selection of jobs that entail much more responsibility and risk: police officers, pilots, firefighters, ambulance technicians, nuclear reactor operators, prison officers and prison educators (3). The aim is to recognize people who have psychopathological problems which are opposite to the job requirements or who exhibit character traits that negatively affect their work performances.

The question is how much it is justified to use clinical inventories to test normal people applying for a job. The thesis that was dominant for a very long period of time is that in the staff selection process for many jobs was not indicated the use of patocentric questionnaires, especially the use of the norms obtained from a clinical sample. There is an argument in favor of the above thesis that in employees selection we usually deal with the mentally healthy people and we do not expect them to show any kind of psychological problems, and we should have in mind that the PAI inventory gives a large number of false positive estimation in normal subjects. There are many limitations in the use of questionnaires in personnel selection context: candidates are generally healthy people who score below the average in a small range thus the distinctiveness of these questionnaires is decreased. Candidates with high score do not get a job so they are not included in longitudinal studies on the predictive validity of the instrument (4).

At least 10% of job candidates show the tendency of dissimulation by giving socially desirable answers. Sometimes validity scales by themselves represent a significant score, because they correlate with measures of work success and increase the prediction accuracy (5,6).

Table 1 Montenegrin sample of unemployed by age, education and sex.

Education	Primary School (N=103)		Secondary School (N=84)		University Degree (N=20)	
Sex	M	F	M	F	M	F
16-20 (N=56)	11	11	3	3	0	0
21-30 (N=107)	9	8	18	15	2	2
31-40 (N=102)	8	11	14	11	4	3
41-50 (N=74)	8	12	7	5	3	2
51-60 (N=75)	9	16	6	2	3	1
Total	45	58	48	36	12	8

TOTAL N=207 (males=105, females=102)

The use of clinical instruments can be justified if we know that the contemporary understanding of personality is not typological but dimensional one. Thus it is considered that every factor or personality trait represents dimension in which an individual occupies a certain position. The ultimate values of these dimensions represent psychopathological phenomena, so that those whose particular dimension is low or highly expressed behave in a way that deviates from the statistically defined average behaviour. The dimensions of neuroticism and psychoticism enable us to position every person even if they are not psychiatric patients and do not manifest psychopathological problems. Thus understood model of personality and personality assessment entitle us to apply the clinical inventory on nonclinical population.

MATERIALS AND METHODS

The PAI inventory was applied to 207 unemployed people from eight towns in Montenegro, with no previous psychiatric history, according to the information available to the advisers in the employment agency. All subjects gave written consent to participate in research. Their participation in the survey was voluntary, and the participants were told that the results would not affect their employment opportunities.

The PAI consists of 344 questions that are separated in non-overlapping scales of clinical, treatment focus, personality and validity context. There are 4 validity scales, 11 clinical scales covering major categories of pathologies that correspond to DSM nosology, 5 treatment scales measuring constructs that are relevant to treatment, and 2 interpersonal scales.

The mean scores for each scale were computed and compared with the scores obtained from the standardization - US general population sample (1). The reliability (internal consistency) scale was also checked and compared with the reliability obtained from the US sample. In order to assess internal consistency, we calculated Cronbach`s alpha coefficient (α), mean inter-item correlation (rii), and corrected item-total correlation (rit) for all the PAI scales.

RESULTS

A. Comparison of mean scores between the sample of unemployed Montenegrin and the US normative sample

On 16 out of 22 scales the sample of unemployed Montenegrin people achieved significantly higher scores than the US general population sample. The biggest difference was found on the Infrequency (INF) scale (about one standard deviation) and Paranoia (PAR) scale (more than one standard deviation) .

Table 2 Means (M), standard deviations (SD), test for equality of means (t), effect size: (Cohen`s d), significance level (p) of the Montenegrin and US normative samples.

	US Sample N=1000		Montenegrin Sample N=207		t	Cohen's d	p
	M	SD	M	SD			
ICN – Inconsistency	5.39	3.35	5.46	2.41	-0.35	-0.02	0.73
INF – Infrequency	2.66	2.57	5.08	2.19	-14.03	-0.971	0.002
NIM – Neg Impression	1.69	2.7	3.21	3.45	-5.99	-0.541	0.002
PIM – Pos Impression	15.07	4.36	15.87	4.12	-2.53	-0.19	0.012
SOM – Som Complaints	11.09	10.07	13.53	11.62	-2.81	-0.241	0.012
ANX – Anxiety	16.47	10.56	23.52	11.44	-8.17	-0.661	0.002
ARD – Anxiety- Rel. Dis	19.91	8.3	23.86	8.96	-5.85	-0.471	0.002
DEP – Depression	14.28	9.43	17.24	11.21	-3.55	-0.301	0.002
MAN – Mania	23.01	9.22	29.29	9.03	-9.07	-0.681	0.002
PAR – Paranoia	18.45	8.69	28.88	8.27	-16.36	-1.212	0.002
SCZ - Schizophrenia	13.99	7.79	15.62	8.82	-2.47	-0.201	0.012
BOR – Borderline	18.03	10	23.87	9.51	-7.98	-0.591	0.002
ANT – Antisocial	13.16	9.11	18.44	8.62	-7.95	-0.591	0.002
ALC – Alcohol	4.83	5.62	5.31	5.03	-1.22	-0.09	0.22
DRG – Drug Problems	4.09	4.99	3.85	4.17	0.73	0.05	0.47
AGG – Aggression	14.81	8.42	15.75	7.50	-1.60	-0.11	0.11
SUI – Suicidal Ideation	3.28	4.86	3.33	4.92	-0.14	-0.01	0.89
STR – Stress	5.8	4.45	8.19	4.34	-7.18	-0.541	0.002
NON – Nonsupport	4.9	3.67	5.54	3.42	-2.41	-0.18	0.022
RXR – Treat Rejection	13.76	4.65	14.69	3.97	-2.96	-0.201	0.002
DOM – Dominance	20.6	5.59	21.08	5.31	-1.17	-0.09	0.24
WRM – Warmth	23.48	5.63	24.30	4.50	-2.28	-0.15	0.022

1Effect size (Cohen's d)≥0,20; 2significance level (p) ≤0,05;

B. Reliability of the PAI scales on the sample of unemployed Montenegrin people

On the sample of unemployed Montenegrin people the PAI clinical scales demonstrate satisfactory to good reliability, the reliability of the control scales and additional scales with a smaller number of items is not satisfactory. Furthermore, ICN and INF scales have α coefficient with a negative sign indicating a negative correlation of items within the scale.

Considering that all the PAI scales on the American normative sample are reliable (apart from ICN and INF scales which was expected, because these scales do not measure psychological construct but rather vigilance and thoughtfulness in answering), the mean internal consistency coefficients (α, rii) of all scales on the sample of Montenegrin unemployed people are somewhat lower. On the other hand, the corrected item-total correlation is the same for both samples and at the level of acceptable values (7) suggesting that on the Montenegrin sample, as well as on the US one, most of the items measure the same construct measured by the associated scale.

Table 3 Internal Consistency (Cronbach`s α), Mean Inter-Item Correlation (rii) and Corrected Item-Total Correlation (rit) of the PAI scales for both Montenegrin and US samples.

		Montenegrin Sample N=207			US Sample N=1000		
Scale	Num-ber of Items	á	r_{ii}	r_{it}	á	r_{ii}	r_{it}
ICN – Inconsistency	20	-0.17	-0.01	-0.04	0.45	0.08	0.43
INF – Infrequency	8	-0.12	0.00	-0.02	0.52	0.14	0.09
NIM – Neg.Impression	9	0.69	0.21	0.38	0.72	0.24	0.16
PIM – Pos.Impression	9	0.60	0.14	0.29	0.71	0.17	0.15
SOM – Som.Compl.	24	0.91	0.31	0.53	0.89	0.26	0.49
ANX – Anxiety	24	0.87	0.22	0.44	0.90	0.17	0.51
ARD – Anxiety-RD	24	0.76	0.13	0.31	0.76	0.13	0.32
DEP – Depression	24	0.88	0.25	0.47	0.87	0.24	0.45
MAN – Mania	24	0.75	0.11	0.29	0.82	0.17	0.37
PAR – Paranoia	24	0.73	0.10	0.27	0.85	0.20	0.41
SCZ - Schizophrenia	24	0.81	0.17	0.37	0.81	0.17	0.37
BOR – Borderline	24	0.80	0.15	0.35	0.87	0.22	0.44
ANT – Antisocial	24	0.76	0.14	0.32	0.84	0.20	0.41
ALC – Alcohol	12	0.76	0.23	0.42	0.84	0.36	0.29
DRG – Drug Problems	12	0.62	0.18	0.31	0.74	0.28	0.23
AGG – Aggression	18	0.75	0.15	0.34	0.85	0.19	0.36
SUI – Suicidal Ideation	12	0.84	0.38	0.56	0.85	0.41	0.31
STR – Stress	8	0.66	0.20	0.36	0.76	0.30	0.16
NON – Nonsupport	8	0.59	0.16	0.30	0.72	0.25	0.14
RXR– Treat. Rejection	8	0.58	0.15	0.29	0.76	0.28	0.16

DOM – Dominance	12	0.69	0.15	0.32	0.78	0.22	0.21
WRM – Warmth	12	0.60	0.12	0.27	0.79	0.24	0.23
Median		0.74	0.15	0.32	0.80	0.22	0.32

DISCUSSION

On the sample of 207 subjects of the Montenegrin unemployed general population, we analyzed the mean scores and measurement reliability of the PAI scales. Mean scores for most scales are higher than those obtained for the US normative sample. Internal consistency of the clinical scales is acceptable or good, as well as the one of the US sample, while reliability of validity scales and additional scales with a small number of items is unsatisfactory.

Accuracy (reliability) of the PAI clinical scales obtained on our sample suggests that these scales can be applied in their original form and content to our sample population regardless of socio-cultural differences in relation to the US population. However, this is not the case with the validity scales, especially not with ICN and INF scales. Not because of poor reliability (as we have said before, it is expected and obtained from the US sample, too), but because of the negative intercorrelation of items. This fact shows that they measure not only the heterogeneous properties of our sample, but also the mutually opposing ones, so the correction of items on these scales (by inversion or change content) is necessary. The Montenegrin subjects are less careful in answering than the US ones when it comes to the change of the item direction (positively and negatively reflected items) or if it is related to double negatives in the formulation whose consequence is not only an inter-item negative correlation but also the lower reliability of the scale with a smaller number of items. Such are e.g., the additional PAI scales which are particularly sensitive to response errors. In addition to the correction of items we also should take into consideration an instruction supplement for the subjects in terms of warning on their two-way reflection.

There are several possible explanations why Montenegrin subjects generally achieve higher scores on the PAI scales than the US subjects in the normative sample. The first explanation is that these represent cultural differences. Second, since these people are unemployed it is possible that they represent a less functional part of the population feeling more stressed due to unemployment. The control of subjects' 'normality', i.e. whether these people manifest psychopathological symptoms or not, was only partial and based on the information available to their advisor in the employment agency. On the basis of the above data, we can conclude that it is necessary to have norms for each cultural group we also compare individual scores with the tests for different contexts.

CONCLUSION

On 16 out of 22 scales the sample of unemployed Montenegrin people achieved significantly higher scores than the US general population sample. On the sample of unemployed Montenegrin people the PAI clinical scales demonstrate satisfactory to good reliability, the reliability of the control scales and additional scales with a smaller number of items is not satisfactory. The limitations of this study are related to the need for more reliable control of mental disorders existence in the selected sample (particularly personality disorders and alcoholism). It is better to verbally motivate the subjects to respond to questions honestly because conducting a questionnaire in a state institution (employment agency) suggests that the scores may be important for their future employment. The sample of unemployed subjects can not

be considered representative, so it is necessary to get the reference PAI scores from the general population of Montenegro. The results suggest the need for additional testing on the sources of differences as well as the comparison of the PAI scores of the selected sample to the general population in our country.

Conflict of interest: none declared.

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Morphometric analysis of kidney and renal artery as a possible indicator of the presence of supernumerary renal arteries

Morfometrijska analiza bubrega i bubrežnih arterija kao mogući pokazatelj prisustva prekobrojnih bubrežnih arterija

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ABSTRACT

Due to a possible failure to identify supernumerary renal arteries, there is a need to find the so-called „indirect parameters" which could indicate the occurrence of supernumerary renal arteries. We wanted to make our contribution in detecting secondary indicators useful for identification of supernumerary renal arteries. Our study involved morphometric measurements of the kidney length and width, renal arteries and supernumerary renal arteries. The obtained data was analyzed by means of the correlation test in order to establish their mutual correlation and the extent to which it may contribute to proper identification of supernumerary renal arteries. Morphometric measurements have shown that parameters such as kidney length, and length and width of the renal arteries can serve as an indirect indicator of the presence or absence of supernumerary renal arteries.

Key words: renal artery, CT angiography, supernumerary renal arteries, morphometry

SAŽETAK

Zbog mogućnosti previda pri identifikaciji prekobrojnih arterija bubrega, nameće se potreba iznalaženja tzv. „indirektnih parametara" koji bi mogli upućivati na pojavu prekobrojnih arterija bubrega. Želja nam je bila da našim istraživanjem damo doprinos u pronalaženju sekundarnih pokazatelja koji se mogu iskoristiti u identifikaciji prekobrojnih arterija. U našem radu pristupili smo morfometrijskom mjerenju dužine i širine bubrega, bubrežnih arterija i prekobrojnih bubrežnih arterija. Svi dobiveni podaci su analizirani uz pomoću testa korelacije kojim smo željeli ustanoviti u kakvom se oni međusobnom odnosu nalaze i kako sve to može pomoći u što preciznijoj identifikaciji prekobrojnih arterija bubrega. Morfometrijska mjerenja su pokazala da parametri kao što su dužina bubrega, te dužina i širina bubrežnih arterija mogu poslužiti kao indirektni pokazatelj o prisustvu ili odsustvu prekobrojnih bubrežnih arterija.

Ključne riječi: renalna arterija, CT angiografija, prekobrojne bubrežne arterije, morfometrija

INTRODUCTION

Variations in the number of kidney arteries that vascularise the kidneys are frequent and occur in the range of 9 to 76% (1). Already in 1552, Eustachi in his work showed interest in supernumerary renal arteries (2), and the interest of other researchers in this subject has not ceased to this day.

The presence of supernumerary renal arteries increases the complexity of transplantation procedures (3,4), affects the course and planning of nephrectomy, especially laparoscopic, with reduced operative field. Therefore, the morphological relation between the kidney arteries and veins is of utmost importance.

A thorough knowledge of the renal artery structure is necessary in order that all procedures could be performed safely and efficiently, which is enabled by modern radiological techniques (5). In recent years, the CT angiography is used in the evaluation of renal arterial anatomy. It has the capacity and precision in reviewing the morphology of kidney blood vessels almost identically, and perhaps even better, than the conventional angiography (6). It is a minimally invasive method and provides detailed information about the position, size and anatomic relations, and it also provides for the identification of anatomical variations and deformations (7). CT angiography is the method of choice and challenges the use of classical, conventional angiography. However, surgeons must be aware of the CT angiography limitations. Although the overall precision in the determination of the renal arterial anatomy is good, from 90% to 100%, in the presence of supernumerary renal arteries it is reduced up to 60.3% (8).

MATERIALS AND METHODS

This anatomical-radiological study included 104 patients (49 male and 58 female), mean age 43.7 ± 10.3 years (in the range from 25 to 69 years) surgically treated at the Urology Clinic of the Clinical Center University of Sarajevo (CCUS) in the period from April 2007 to December 2011. Prior to surgical intervention, during the diagnostic procedure all patients were subjected to the CT scanning at the Institute of Radiology of the CCUS. All scans were performed in the cranio-caudal direction with 4-sectional multi-channel detector CT scanner (MSCT Somatom Plus 4 Volume Zoom Siemens). All images were transferred to the workstation (GE Advantage Windows 4.2, GE Healthcare, USA) and reconstructed with a standard algorithm for CT angiography. The obtained records were analyzed and the following parameters were recorded:

- the number of renal arteries included in renal vascularisation,
- number and size of supernumerary renal arteries,
- morphometric measurement of the kidney dimensions and renal arteries.

In the preparation of this work, the results of the surgical interventions were used as a reference standard. All the disclosed surgical findings, not detected preoperatively, were recorded and data based, and the data were compared my means of statistical methods.

All data was statistically analyzed using the Statistical Package for Social Sciences (SPSS) software version 13 for Windows, and $p < 0.05$ was considered significant. The study used the most contemporary measuring instruments. However, as with any measurement, there was a possibility of error, and hence number of measurements was done and mean values were calculated in order to minimize errors. The Kolmogorov-Smirnov test was used for obtaining data on the level of significance.

RESULTS

The results of morphometric measurements of length and width of the kidney on the CT scans, and results of the statistical data processing are presented in Table 1. It is visible that the average value of the kidney length obtained by CT scan technique was 109.4 ± 13.8 mm, and the average kidney width 54.2 ± 8.5 mm. The average values were obtained by calculating the arithmetic mean, and in order to obtain data on their dispersion in the set, namely data on the average deviation from the standard, the standard deviation was also calculated.

As already pointed out, the Kolmogorov-Smirnov test was used to determine the level of significance of the obtained data related to the length and width of the kidney, renal artery and the supernumerary renal arteries. Based on the test it could be noted that the results on the length of the kidney obtained by CT scan technique substantially deviate from normal distribution, namely they are significant given that for the CT scan technique p=0.012. The width of the kidney measured by CT scan technique did not significantly deviate from the normal distribution, given that based on the Kolmogorov-Smirnov test p=0.201.

The results related to measurement of length and width of the renal arteries obtained from the analysis of the CT images are presented in Table 2.

Table 1 Average length and width of the kidney measured by CT scan technique.

							Percentage		
Diagnostic methods		N	Mean	Std. Deviat	Minimum	Maximum	25th	50th Median	75th
CT	Length of the kidney	214	109.42	13.85	51.0	150.0	102.0	111.0	117.0
	Width of the kidney	214	54.25	8.52	30.0	87.0	48.0	54.0	60.0

Table 2 Statistical analysis of the length and diameter of the renal arteries measured by CT scan technique.

		'ercentage							
Diagnostic methods		N	Mean	Std. Deviatior	Minimum	Maximum	th 25	th 50 Median	th 75
CT	Length of the renal arteries	214	35.30	11.9	15.00	66.00	27.00	42.00	46.0
	Diameter of the renal arteries	214	3.87	0.74	0.734	5.25	3.50	3.90	4.30

The Table shows that the average values of the renal arteries length on the images obtained by CT scan technique were 35.3 ± 11.9 mm, and values of the average width (diameter) of the renal arteries 3.87 ± 0.74 mm. The length of the renal arteries statistically significantly deviate from the normal distribution, namely it is not significant given that based on the Kolmogorov-Smirnov test for CT scan technique p=0.001. The width of the renal arteries statistically significantly deviate from the normal distribution, namely it is significant since based on the Kolmogorov-Smirnov test for CT scan technique p=0.004.

The results of measuring the length and width (diameter) of supernumerary renal arteries obtained by CT scan, and the results of the statistical data processing are presented in Table 3.

Table 3 Statistical analysis of the the length and diameter of supernumerary renal arteries measured by CT scan technique.

		Percentage							
Diagnostic methods		N	Mean	Std. Deviation	Minimum	Maximum	th 25	th 50 Median	th 75
CT	Length supernumerary renal arteries	35	44.40	11.82	15.00	66.00	36.00	48.00	54.0
	Diameter of supernumerary renal arteries	35	2.58	1.09	0.70	5.25	1.75	2.10	3.5

Based on the presented results, we conclude that the supernumerary renal arteries are longer but narrower in relation to the renal arteries.

DISCUSSION

Recent studies related to supernumerary kidney arteries have been focused not only on research of their percentage representation, but also on other morphological and morphometric research including analysis of length, diameter, location, mode of branching and entering the kidney (6). As noted, supernumerary renal arteries correspond to segmental arteries and their bleeding during transplantation causes segmental ischemia, thus increasing the risk of postoperative hypertension due to the loss of renal parenchyma (9).

Using diagnostic CT angiography in our work, we analyzed the presence of supernumerary renal arteries in order to draw attention to the most important parameters which radiologists and surgeons have to take into account during preoperative assessment of renal vascular anatomy. Full studies were carried out in phases in order to obtain data which in clinical practice could serve as markers for identification of supernumerary renal arteries.

The CT scan procedure was used for the analysis of 214 kidneys (107 from right and left side respectively) of which in 35 (16.4%) supernumerary renal arteries were identified. The study of Pollak showed that in 800 kidneys supernumerary renal arteries occurred in 23% of cases, of which in 4% of the cases kidneys were stocked with three, and in 1% with even four renal arteries (9,10, 5,11,12, 13,14,15).

In the past two to three decades, the constant development of modern diagnostic methods has prioritized the application of a less invasive radiological diagnostic method, CT angiography, in the surgical planning of surgery.

That was the reason why we opted for CT scan technique, as a contemporary technique, which has replaced conventional catheter angiography, known as the gold standard, which enabled identification of supernumerary renal arteries with the percentage of security from 91 to 100% (16). Previous studies have shown that CT angiography has some disadvantages, one of which is exposure to ionizing radiation and administration of nephrotoxic iodine contrast media. Therefore, this method is not applicable to young children, pregnant women and patients with renal insufficiency.

In order to find an explanation as to why the identification of some supernumerary renal arteries is not possible, Chai (2008) in his work performed morphometric measurements of renal and supernumerary renal arteries and established that all supernumerary artery with diameter less than 1.7 mm, and mainly those with a value of 1.3 mm, was not possible to identify by the CT scan technique (17). Confirmation of these allegations are also found in the work of Satyapal, et al. (2001) who state that the renal blood vessels can have a diameter ranging from 0.3 to 3 cm and that wider blood vessels are easier to identify than those with a small diameter (18).

Morphometric measurements in our work showed the following results: the average value of the renal artery length on the images obtained by CT scan technique was 35.3 ± 11.9 mm, and the average width of the renal artery was 3.87 ± 0.74 mm. These parameters are the main explanation as to why we could not easily identify all renal arteries in our work.

Morphometric measurements of supernumerary renal arteries established that the average length of arteries measured by the CT

scan technique was 48.0 mm (36.0 mm - 54.0 mm), and the average width 2.10 mm (1.75 mm - 3.5 mm).

Supernumerary renal arteries not identified in the preoparetive preparation of patients had the lowest recorded values of both length and width, and that was the main reason why they were difficult to identify. Our results correspond to the results of Chai and Satyapal (17,18), and with the results of Polish researcher Zahoia (2010), who established that the average length of supernumerary renal arteries was in the range from 4 to 6 cm and the average width approximately 4 mm. Pestemalci, et al. (2009) reported that the average length of supernumerary renal arteries recorded in their work was approximately 5 cm, and the average with from 3 to 4 mm (19). In their work Bordei, et al. (2004) recorded the average length of supernumerary artery from 4 to 6 cm, and the average width from 1 to 2 mm (20).

CONCLUSION

Based on the aforementioned radiologists should pay attention in the identification of supernumerary arteries. Our study showed that each renal artery with a diameter less than 2 mm indicates the possible presence of supernumerary renal artery. Indeed, our research requires confirmation from other researchers who will use the same modalities during the research.

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Our contribution to the reduction of cardiovascular diseases in Bosnia and Herzegovina!
Naš prilog redukciji kardiovaskularnih bolesti u Bosni i Hercegovini!

ABSTRACT

The aim of this study was to investigate the role of fibrinogen elevated values in serum as a good indicator of the acute phase of inflammation in patients with different types of glaucoma which can be linked to pathogenesis and glaucoma progression. The study included 180 eyes of both gender patients, ages 40 to 70 years, diagnosed with glaucoma based on diagnostic tests. Based on the type of glaucoma patients were divided into three groups: 60 eyes with glaucoma simplex (GS), 60 eyes with normotensive glaucoma (NG) and 60 eyes with angular glaucoma (GA). The fourth, control group, consisted of 60 eyes with senile cataract without glaucoma. All respondents were subjected to a detailed ophthalmological examination which included: visual acuity measurement, applanation tonometry, gonioscopy, ophthalmoscopy, field of vision and optical coherence tomography (OCT). The plasma fibrinogen concentration was determined by the method in which the citrated plasma coagulates with increasing thrombin (BCT apparatus, Behring Coagulation Timer) at the Institute of Clinical Chemistry and Biochemistry of the Clinical Center University of Sarajevo (CCUS). Multifibren U (Dade Behring) was used as a reagent for this method. Values of 1.8 to 3.8 g/L were considered as referent values of fibrinogen in plasma in this method. The plasma concentration of fibrinogen in the control group was 3.55 ± 0.13, while in the group of patients with NG it was 3.57 ± 0.15. In the group of patients with GS, the plasma fibrinogen concentration was 3.20 ± 0.10, and in the group of patients with GA it was 2.10 4.02 ± 0.18. Statistically significant difference in plasma fibrinogen level was observed in patients with GS compared to the control group ($p=0.039$), between patients with GS and patients with NG ($p=0.045$), and between patients with GS and GA ($p<0.05$). Statistically significant difference in plasma fibrinogen level was also observed in patients with GA compared to the control group ($p=0.041$). There was no statistically significant correlation between the concentration of fibrinogen in plasma and OCT parameters in either glaucoma patients or the control group. There was a statistically significant positive correlation between plasma fibrinogen concentrations and right eye optic nerve papilla (PNO) in patients with GS ($rho=0.375$, $p<0.05$) (Figure 11) and statistically

SAŽETAK

Cilj ovog rada je bio ispitati ulogu povišenih vrijednosti fibrinogena kao dobrog pokazatelja akutne faze inflamacije u serumu pacijenata sa različitim tipovima glaucoma, a koji se mogu dovesti u vezu sa samom patogenezom kao i progresijom glaukoma. U istraživanje je uključeno 180 očiju pacijenata oba spola, starosne dobi od 40 do 70 godina kod kojih je dijagnostičkim pretragama ustanovljeno da boluju od glaukoma. Pacijenti su na osnovu tipa glaukoma podijeljeni u tri grupe: 60 očiju sa glaukomom simpleks (GS), 60 očiju sa normotenzivnim glaukomom (NG) i 60 očiju sa glaukomom angulare (GA). Četvrtu grupu, kao kontrolnu grupu činilo je 60 očiju sa senilnom kataraktom bez glaukoma. Svim ispitanicima urađen je detaljan oftalmološki pregled koji je uključivao: mjerenje vidne oštrine, aplanacionu tonometriju, goniskopiju, oftalmoskopiju, vidno polje i koherentnu tomografiju retine (OCT). Koncentracija fibrinogena u plazmi ispitanika određivana je metodom kojom se citrirana plazma koaguliše s povećanjem trombina (aparat BCT, Behring Coaugulation Timer) na Institutu za kliničku hemiju i biohemiju KCUS. Kao reagens za ovu metodu korišten je Multifibren U (Dade Behring). Kao referentne vrijednosti fibrinogena u plazmi korištenjem ove metode, uzimaju se vrijednosti od 1,8 do 3,8 g/L. Koncentracija fibrinogena u plazmi kontrolne skupine iznosila je 3,55±0,13, dok je u skupini pacijenata sa NG iznosila je 3,57±0,15. U skupini pacijenata sa GS, koncentracija fibrinogena u plazmi bila je 3,20±0,10, a u skupini pacijenata sa GA ista je bila 2,10 4,02±0,18. Statistički značajna razlika u nivou fibrinogena u plazmi uočena je kod pacijenata sa GS u odnosu na kontrolnu grupu ($p=0,039$), između pacijenata sa GS i pacijenata sa NG ($p=0,045$), te između između pacijenata sa GS i pacijenata sa GA ($p<0,05$). Također statistički značajna razlika u nivou fibrinogena u plazmi uočena je između pacijenata sa GA u odnosu na kontrolnu grupu ($p=0,041$). Nije uočena statistički značajna korelacija između koncentracije fibrinogena u plazmi i parametara OCT-a ni kod pacijenata sa glaukomom, kao ni u kontrolnoj skupini ispitanika. Uočena je statistički značajna pozitivna korelacija između koncentracije fibrinogena u plazmi i vrijednosti PNO (papile nervi optici) desnog oka kod pacijenata sa GS ($rho=0,375$, $p<0,05$) (Grafikon 11), te statistički značajna negativna korelacija između koncentracije

significant negative correlation between fibrinogen concentration in plasma and MDD values in patients with GA (rho=-0.372, p<0.05).

Key words: fibrinogen, inflammation, glaucoma, optical coherent tomography

fibrinogena u plazmi i vrijednosti MDD kod pacijenata sa GA (rho=-0,372, p<0,05).

Ključne riječi: fibrinogen, inflamacija, glaukom, optička koherentna tomografija

Medical Journal (2017) **Vol. 23, No 1**, 24 - 28 **Original article**

The role of fibrinogen elevated values as the indicator of the acute phase of inflammation with different types of glaucoma

Uloga povišenih vrijednosti fibrinogena kao pokazatelja akutne faze inflamacije kod različitih tipova glaukoma

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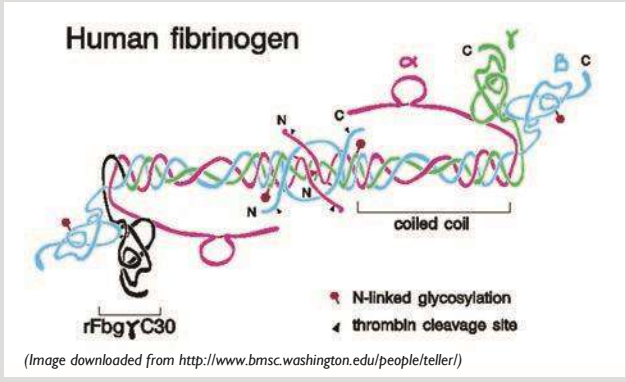
INTRODUCTION

Glaucoma is a syndrome characterized by a triad of symptoms: intermittent or permanent elevation of intraocular pressure, changes in the optical nerve and visual field damage. It is a progressive optic neuropathy with irreversible loss of retinal ganglia cells leading to blindness (1.2). Previous research has shown that glaucoma is associated with numerous risk factors such as age, sex, race, genetics, increased eye pressure, refractive anomalies etc. (3). Newer studies have shown that oxidative stress and inflammation contribute to the development of this disease (4.5).

Fibrinogen is a glycoprotein consisting of two alpha, two beta and two gamma chains interconnected by disulfide bonds (Figure 1). The molecular mass of fibrinogen is 340 kD.



(Image downloaded from http://www.bmsc.washington.edu/people/teller/)

Figure 1 Fibrinogen structure.

Fibrinogen is encoded by three genes, each for each chain, located on the short arm of chromosome 4. Numerous polymorphisms of the mentioned genes have been described, as well as numerous mutations that may affect the value of fibrinogen in the blood and its function (6).

The highest percentage of fibrinogen is synthesized in the liver, and a small part in megakaryocytes. About 5-10% of fibrinogen in plasma is found in platelets. Fibrinogen is a highly complex glycoprotein with numerous genetic and acquired variations in the structure of which depend on its functional properties, especially the speed of the thrombus formation, as well as its strength (6). It has been shown that the newly formed fibrinogen has a higher content of phosphorus and oligosaccharide sequences, as well as higher molecular weight, and also creates more rigid thrombuses. This is just one of the reasons why states like inflammation show procoagulant character. The fibrinogen is in the plasma physiological conditions at a concentration of 2 to 3.5 g/L. Plasma fibrinogen concentrations are influenced by numerous factors, such as gene mutations encoding his synthesis, cardiovascular diseases such as infarcts, inflammatory diseases, diabetes mellitus and many other illnesses.

It has been observed that one of the risk factors for glaucoma in elderly persons is higher plasma levels of fibrinogen as compared to younger respondents. The possible explanation mechanism lies in the fact that older adults have higher IL-6 production, which is directly associated with increased fibrinogen production (6,7).

Fibrinogen is an acute phase protein and forms part of the protein coagulation cascade. The amount of fibrinogen in plasma can be measured as a non-specific indicator of the presence of inflammation in the body. Recent studies have shown that oxidative stress and inflammation contribute to endothelial vascular dysfunction in the trabecular meshwork and elevated fibrinogen values, which contributes to the development of this disease. Necrosis of endothelial cells induced by oxidative stress, inflammatory conditions, prolonged use of corticosteroids and atherosclerosis, leads to edema, intimal hyperplasia, small blood vessel occlusion and attracting leukocytes and necrosis detritus which leads to thickening of the trabecular net at the chamber angle, thus preventing normal eye discharge to the episcleral capillary network resulting in an increase in intraocular pressure. Increased intraocular pressure leads directly to the optic nerve ischemia, narrowing of the visual field or glaucoma (1,6,8).

Significant role of fibrinogen or autologous fibrinogen concentrate (AFC) has been demonstrated through Yieh FS study (100): "The use of autologous fibrinogen concentrate in treating ocular hypotonia after glaucoma filtration surgery." Very often, following the filtration of the glaucoma, persistent hypotension occurred, with the effect of AFC application in the filtering pad alone, yielding significant results of normalized intraocular pressure raised for 4.2 mmHg. The author also states the normalization of the depth of the ocular chamber as well as the diminished macular edema. The aim of this study was to examine serum concentrations of fibrinogen in patients with different types of glaucoma.

MATERIALS AND METHODS

The study was designed as a clinical, cross-sectional study. It included 90 patients of both sexes, ages 40 to 70, diagnosed with glaucoma, and 30 patients with senile cataract-free glaucoma as a control group. Both eyes were considered. Patients were selected at the Clinic of Eye Diseases, Clinical Center University of Sarajevo (CCUS), in the Cabinet for Glaucoma and Intraocular Hypertension.

Based on the type of glaucoma patients were divided into three groups:

- 60 eyes with glaucoma simplex
- 60 eyes with normotensive glaucoma
- 60 eyes with glaucoma angulare

Group I - patients diagnosed with glaucoma simplex included 60 ophthalmologic examinations with glaucoma simplex diagnosis.

Group II - patients diagnosed with normotensive glaucoma included 60 ophthalmologic examinations with a diagnosis of normotensive glaucoma.

Group III - patients with glaucoma angulare diagnosis included 60 ophthalmologic examinations with glaucoma angulare diagnosis.

The control group consisted of patients diagnosed with senile cataracts who based on the ophthalmologic examination were excluded from glaucoma diagnosis.

Inclusion criteria:

The study included patients diagnosed with glaucoma simplex, normotensive and glaucoma angulare in the last 3, 5 or more years.

Exclusion criteria:

The study did not include patients with subjective and objective data pointing to signs such as:

- acute or chronic inflammatory conditions
- asthma
- liver cirrhosis
- Chron disease and ulcerative colitis
- malignant neoplasms
- diabetes mellitus
- nonglaucoma eye diseases
- myocardial infarction and cardiovascular disease,due to potential impact on acute phase protein values in serum.

All patients were informed in detail about the research plan and procedure, after which a written consent was requested for participation in the study.

The procedure for glaucoma diagnosis

Visual acuity

The best corrected visual acuity was determined at a distance of 6 m without correction or with correction by Snellen optotypes.

Aplanning tonometry

Goldmann Applanation Tonometry is a method of choice for measuring intraocular pressure of respondentss. Intraocular pressure was measured with calibrated Goldmann Applanation Tonometer (HaagStreit, Mod. 900.4.2.130621.) and expressed in mmHg.

Gonioscopy

Gonioscopy was performed using the Haag-Streit prism for gonioscopy with a single mirror, which, after the local anesthetic is laid on the cornea, then looks at the chamber angle at 360 degrees starting from the lower pole upward.

Ophthalmoscopy

Direct ophthalmoscopy was performed using a hand-held ophthalmoscope (Heine Ophtalmoscop, Germany) on enlarged pupils, and the subjective appearance of the head of the visual nerve was determined, its excavation (dent), which is marked E/D from 0.1 to 0.9, and the edge when the diameter of the healthy edge of the optical nerve is completely lost in which case we are talking about the atrophy of the visual nerve.

Field of view

The visual fields were measured by a computerized static perimeter (Octopus perimeter 101, Interzeag AG, Schlieren, Switzerland). The computerized static perimetry is done with G2 program, seven in one test, with Goldman III stimulus size, 100 millisecond exposure time, 4-apostilb backlight, maximum 1000 apostilb stimulus intensity, and the so-called 4-2-1 dB method that determines the retina sensitivity with accuracy of 1 dB.

The following was monitored: MD (mean defect) - medium defect which should not be greater than 2 microns and which, if greater than 2, does not refer to glaucoma given that it can be caused by cataract, refractive anomaly, opacity in corpus vitreum etc, and the value of LV (loss variance) - the loss of mean variation - the depth of sensitiv-

ity loss, which should not be greater than 6. The LV value suggests the existence of glaucoma failure in the field of view whether it is increased alone or together with elevated MD values when it can safely be claimed to be a nerve ganglia cell damage.

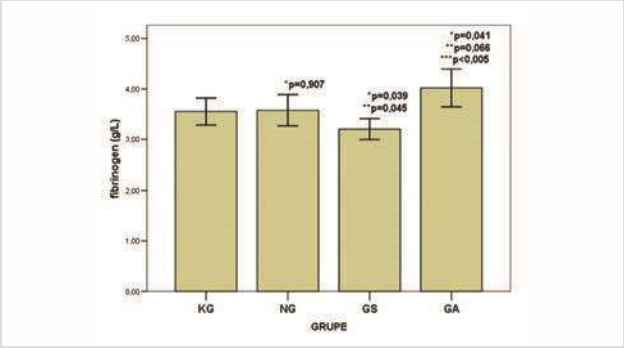
Coherent retinal tomography (OCT)

Coherent retinal tomography (OCT) was performed in all subjects (Stratus OCT Model 3000, Carl Zeiss MEDITEC, Jena, Germany). Numerical values of the excavation of the optical nerve as well as the relation between horizontal and vertical cavities will be taken. When performing an OCT recording, the subject is positioned so that the chin and the forehead are placed in the foreseen support, the subject is instructed to fix the examined eye at the target point in the instrument. If the examinee cannot fix the examined eye for damage to central fovea, then he or she may fix the external target with another eye. The maximum midriasis makes it easy to test, although it is possible to shoot with a tight pupil of at least 3mm. The resulting footage is displayed on the monitor through the software program, and technically satisfactory can be memorized or entered into the other data carrier.

Statistical data processing

The results were processed using standard statistical methods on SPSS-Statistical Package for Social Sciences version 13.0. The results were shown as median and interquartile interval (25-75 percentiles). The Shapiro-Wilk test was used to test the significance of the difference in deviation from the normal distribution. The results were analyzed by appropriate nonparametric tests (Mann-Whitney U test, Kruskal-Wallis test). The degree of correlation was determined by the Sperman method. The values of $p<0.05$ were taken as statistically significant.

RESULTS



The results are displayed as mean ± standard mean error (x ± SEM)
p - probability
KG - control group (n=30)
NG - patients with normotensive glaucoma (n=30)
GS - patients with simplex glaucoma (n=30)
GA - patients with angular glaucoma (n=30)
** relative to the control group*
*** relative to the group of patients with normotensive glaucoma*
**** relative to the group of patients with simplex glaucoma*

Figure 1 Concentration of fibrinogen in plasma of the control group and glaucoma patients.

The plasma concentration of fibrinogen in the control group was 3.55 ± 0.13, while in the group of patients with NG it was 3.57 ± 0.15. In the group of patients with GS, the plasma fibrinogen concentration was 3.20 ± 0.10, and in the group of patients with GA it was 2.10 4.02 ± 0.18.

A statistically significant difference in plasma fibrinogen level was observed between patients with GS and the control group (p=0.039), between patients with GS and patients with NG (p = 0.045), and between patients with GS and patients with GA (p<0.05). Also statistically significant difference in plasma fibrinogen level was observed in patients with GA compared to the control group (p=0.041) (Figure 1).

Table 1 Correlation of fibrinogen in plasma and OCT parameters.

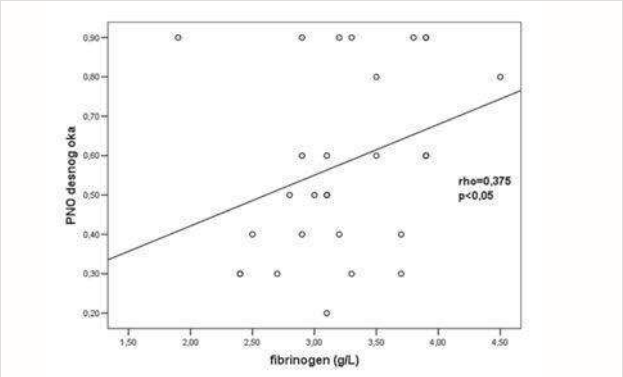
Variable	Fibrinogen KG (n=30)	Fibrinogen NG (n=30)	Fibrinogen GS (n=30)	Fibrinogen GA (n=30)
OCT1 OD	r= 0.089	r= -0.002	r= 0.232	r= -0.313
OCT2 OD	r= 0.235	r= 0.091	r= 0.232	r= -0.166
OCT3 OD	r= 0.140	r= 0.185	r= 0.347	r= -0.353
OCT1 OS	r= 0.215	r= -0.002	r= 0.060	r= -0.229
OCT2 OS	r= 0.129	r= -0.025	r= 0.039	r= -0.022
OCT3 OS	r= 0.146	r= 0.127	r= 0.196	r= -0.051

r - coefficient of correlation
KG - control group
NG - patients with normotensive glaucoma
GS - patients with glaucoma simplex
GA - patients with angular glaucoma

There was no statistically significant correlation between plasma fibrinogen concentrations and OCT parameters in either glaucoma patients or control group (Table 1).

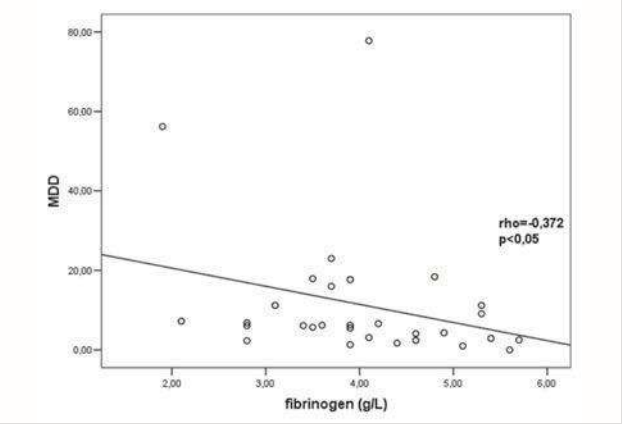
There was a statistically significant positive correlation between the concentration of fibrinogen in the plasma and the value of the right eye PNO (optic nerve papille) excavation in patients with GS (rho = 0.375, p <0.05) (Figure 1.1) and statistically significant negative correlation between fibrinogen concentrations in plasma and MDD values in patients with GA (rho = -0.372, p <0.05) (Figure 1.2).

In other groups of patients and in the control group, no statistically significant correlation was found between plasma fibrinogen concentrations and field of view parameters, nor statistically significant correlation between fibrinogen plasma and visual acuity on both eyes, or statistically significant correlation between plasma fibrinogen and intraocular pressure at both eyes (the results were not shown).



rho - coefficient of correlation
p - probability
PNO - optic nerve papille

Figure 1.1 Ratio of plasma fibrinogen concentrations to optic nerve papille of the right eye in patients with GS.



rho - coefficient of correlation
p – probability
MDD - right eye MD

Figure 1.2 Ratio between fibrinogen concentration in plasma and right eye MD values in patients with GA.

DISCUSSION

Previous researches have shown that inflammation can play an important role in the pathogenesis of this disease. Inflammatory eye diseases that most often precede the onset of glaucoma are the front and back uveitis. The glaucoma ethiopathogenesis lies in the explanation that front uveitis causes eye capillary endothelial cell tight junction decomposition, thus creating the ability to pass leukocytes through the blood-eye barrier, for which it is impermeable in physiological condition. This pathology of vascular permeability leads to an increase in tissue protein concentration, most likely entering the front chamber at the base of the iris and within the ciliary body. Paradoxically, acute frontal uveitis can also cause ocular eye pressure hypothony as well as glaucoma, depending on the stage of the disease and the relative influence on the formation of the eye water and its flux (1-3).

The glaucoma will appear when, due to inflammatory mechanisms, the system in charge of eye water flux of the eye is weakening to the extent that it is unable to take out the water produced. The acute inflammatory open angle glaucoma of the anterior chamber usually arises from the direct obstruction of the aquatic ducts in charge of drainage, by platelets, white blood cells and macrophages, the aggregation of which increases the concentration of proteins in the eye water and in the trabecular meshwork (9,10).

Previous research has shown that inflammatory processes can be associated with optical neuropathy and glaucoma. There was a connection between certain cytokines and glaucoma. Interleukin-6 (IL-6) was shown to be involved in apoptotic processes in the retina (11,12) with correlation with inflammatory processes in optical neuropathy.

Studies have shown that inflammatory processes in the eye can cause a characteristic glaucoma optical disc with field of view damage and increased intraocular pressure (13,14). Also, it has been shown that inflammation causes ischemia and infiltration on the visual nerve (13).

A wide range of acute phase proteins are fibrinogen, CRP and α2M, which are considered to be good indicators of the degree of inflammation in the human body (9).

Fibrinogen as a coagulation protein along with erythrocyte sedimentation, is the most commonly used non-specific marker of tissue damage and inflammation. The concentration increases especially in cases of inflammatory processes of bacterial etiology, although a slight increase in its concentration as a subinflammatory response may be associated with numerous cardiovascular, metabolic diseases, and ophthalmic diseases including glaucoma.

Our results showed a statistically significant difference in the plasma fibrinogen level in patients with GS compared to the control group ($p=0.039$), between patients with GS and patients with NG ($p=0.045$), and between patients with GS and patients with GA ($p<0.05$). Also statistically significant difference in plasma fibrinogen level was observed in patients with GA compared to the control group ($p=0.041$).

The results of our study did not show a statistically significant correlation between plasma fibrinogen concentrations and OCT parameters either in glaucoma patients or in the control group of respondents. Examining the correlation between plasma fibrinogen levels and ophthalmological parameters showed a statistically significant positive correlation between plasma fibrinogen concentrations and right eye PNO values in patients with GS ($rho=0.375$, $p<0.05$) and statistically significant negative correlation between concentrations plasma fibrinogen and MD OD values in patients with GA ($rho=0.372$, $p<0.05$). Statistically significantly higher levels of fibrinogen were found in patients with glaucoma with open ocular angle compared to the control group of respondents.

Matsumoto et al. (8) have shown that patients with primary glaucoma as well as NG patients are associated with increased thrombocyte aggregation. The authors have shown that patients with glaucoma have significantly higher levels of factors that determine the increase in platelet aggregation, including fibrinogen compared to the control group of the subjects. Although increased platelet aggregation was recorded in both primary and NTG, the results of their study showed that the tendency of this disorder was more pronounced in patients with NG.

Bojić et al. (14) did not find a statistically significant correlation between the platelet aggregation index and the progression of visual acuity loss in glaucoma patients.

Several years later, Rogošić and al. (15) showed that the inclination to platelet aggregation was significantly higher in patients with PGOU than patients with pseudoglucoma.

Fibrinogen is a protein that is involved in coagulation and in some ways is its concentration of tendency for hypercoagulability as well as the circulating platelet aggregation index. Increase in fibrinogen concentration increases hypercoagulability.

Rogošić et al. (15) have shown that there is marked hypercoagulability in patients with NTG, patients with PGOU, and that platelet aggregation plays a role in pathogenesis of the optic nerve head neuropathy, although further studies are needed to clarify the association between platelet aggregation and the glaucoma stage of the affected eye.

Previous studies have shown that H. pylori infection can affect glaucoma pathophysiology in a way that promotes platelet and leukocyte

aggregation, releasing pro-inflammatory and vasoactive substances such as cytokines, eicosanoids, and acute phase proteins such as fibrinogen and CRP (13).

Conflict of interest: none declared.

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Medical Journal (2017) **Vol. 23, No 1**, 29 - 33

Original article

Hypothetical models of inheritance in the first line relatives of people with schizophrenia regarding morbidity and frequency of the disease

Hipotetski modeli nasljeđivanja kod prvostepenih srodnika oboljelih od shizofrenije u odnosu na morbiditet i učestalost pojave bolesti

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ABSTRACT

Introduction: the aim of the study was to determine the hypothetical models of inheritance with heritability in the first line relatives of people with schizophrenia, regarding morbidity and frequency of the disease. Materials and methods: the study included 453 subjects classified into two groups: patients with schizophrenia and patients` first line relatives. It was conducted at the Department of Psychiatry of the Clinical Center University of Sarajevo over the period of five years. Results: there was statistically significant difference between subjects regarding gender (p=0.013) with no difference regarding age (p=0.182). The incidence of morbidity in relation to the first line relatives and gender in various subtypes of schizophrenia showed statistically significant difference. The real proportion indexes in this study corresponded to the expected polygenic model of inheritance regarding the group of paranoid schizophrenia with the same results in all other types (disorganized, undifferentiated and residual). Heritability calculation based on the incidence of schizophrenia among first line relatives was higher if it was considered in diagnostic category of paranoid schizophrenia in relation to disorganized. Conclusion: schizophrenia certainly has a significant genetic component and the basic model for determining the type of heredity characteristics of individual behavior in humans is based on the formation of family trees. Genetic predisposition could be a demonstrator of the disease course and outcome, which should enable better understanding of underlying illness mechanisms and better approaches in the treatment of this complex disorder.

Key words: clinical syndrome, genetic epidemiology, models of inheritance

SAŽETAK

Uvod: cilj istraživanja je bio utvrditi hipotetske modele nasljeđivanja kod prvostepenih srodnika oboljelih od shizofrenije u odnosu na morbiditet i učestalost oboljenja.

Materijali i metode: istraživanje je obuhvatilo 453 ispitanika podijeljena u dvije grupe: pacijenti oboljeli od shizofrenije i prvostepeni srodnici oboljelih. Istraživanje je sprovedeno na Klinici za psihijatriju Kliničkog centra Univerziteta u Sarajevu u periodu od pet godina. Rezultati: statistički značajna razlika je evidentirana u odnosu na polnu zastupljenost (p=0,013), bez razlika u dobnim razredima (p=0,182) u grupama ispitanika. Također je postojala značajna razlika u odnosu na incidencu oboljevanja kod prvostepenih srodnika različitih subtipova shizofrenije u odnosu na pol. Stvarne proporcije su korespondirale sa očekivanim poligenim modelom nasljeđivanja u grupi oboljelih od paranoidne shizofrenije sa istim rezultatima kod svih ostalih tipova (dezorganizovana, nediferencirana i rezidualna). Proračun heritabilnosti se zasnivao na incidenci bolesti među prvostepenim srodnicima i koja bila je viša u kategoriji paranoidne shizofrenije u odnosu na dezorganizovanu. Zaključak: shizofrenija evidentno ima značajnu genetsku komponentu i osnovni model za određivanje tipa nasljednosti se zasniva na formiranju porodičnih stabala. Genetska predispozicija bi trebala biti pokazatelj toka bolesti i njenog ishoda, što omogućava bolje razumijevanje samog mehanizama njenog nastanka uz kvalitetniji terapijski pristup.

Ključne riječi: klinički sindrom, genetska epidemiologija, model nasljeđivanja

INTRODUCTION

Schizophrenia is a collection of mental and behavioral phenomena, a clinical syndrome, which most commonly has its onset in the first half of adult life. Genetic epidemiology refers to a variety of study designs that can be used to establish the extent to which genetic and environmental factors influence traits or disease and how that genetic risk is transmitted across generations

- the mode of inheritance (1,2). Heritability (the degree of genetic contribution), generally referring to the proportion of liability to a disorder in a population that is attributable to genetic factors (3,4). The evidence from family studies suggests that schizophrenia is a complex disorder which does not conform to simple, Mendelian inheritance. It appears to be multifactorial, likely involving many genes and environmental influences (5).

The aim of the study was to determine the hypothetical models of inheritance with heritability in the first line relatives of people with schizophrenia, regarding morbidity and frequency of the disease.

MATERIALS AND METHODS

Patients and study design

This prospective, comparative study included 453 subjects of both sexes, 24-67 years old, classified into two groups: S group included 121 patients with schizophrenia (63 males and 58 females) and S-FLR group (control) consisted of 332 patients` first line relatives (157 males and 175 females). The study was conducted at the Clinic of Psychiatry of the Clinical Center University of Sarajevo over the period of five years (2005-2009).

The Ethics Committee of the University Clinical Center Sarajevo had given an ethical consent before the enrollment.

The study (S group) included patients from 23 to 44 years of age, diagnosed with schizophrenia according to ICD-10 criteria, hospitalized and treated with antipsychotic drugs at the Department of Psychiatry. Patients were included into the research on the basis of consecutive admissions, taking into account that all of them had a long psychiatric history (at least 5 years of hospital treatment) and on the basis of obtained signed information consent. The exclusion criteria related to the appearance of psychotic phenomenology within neurological disease, organic psychosyndrome, somatic disease, neurological disorder (head trauma, brain insult, epilepsy), information on drug or alcohol abuse, or the absence of signed informed consent for voluntary participation.

For the group of patients with schizophrenia, the average age was 32.4 (SD± 6.4; range 22-45) years.

The control group (S-FLR group) included subjects, patients` first line relatives, aged between 27 and 67, tested with the test scales of assessment and with the signed informed consent for voluntary participation. This group included subjects who had never suffered psychotic or severe neurological disorders (head injuries, epilepsy) or diseases, and with anamnesis not containing information on drug or alcohol abuse. The average age of this group was 39.0 (SD± 5.8; range 23-54) years.

Statistical analysis

The task of the study was to define the differences between patients with schizophrenia and first line relatives according to demographic data (gender, age) regarding morbidity and frequency of the disease. For the purposes of associative multivariate analysis of variance, Pearsons correlation coefficient and Point-biserial correlation was applied using $\chi 2$ test, T-test of independent samples, T-test of paired samples, Mann-Whitney test, Kruskal-Wallis test, Tukey Test, ANOVA. Statistically significant differences were considered at $p<0.05$.

RESULTS

Demographic data

The study was conducted on a group of 453 subjects divided into two groups: patients with schizophrenia (121) and control group (332).

Out of the total of 121 patients with schizophrenia 63 (52.1%) were males and 58 (47.9%) females; the control group consisted of 157 (46.4%) males and 175 (43.4.0%) females, (p=0,013). The average age of patients with schizophrenia was 32.4± 6.4 years, and 39.0± 5.8 years in the controls. The youngest subject in schizophrenia group was 23, and the oldest was 55; in the control group the youngest patient was 26, and the oldest 60 years of age (p=0,182) (Table 1).

Table 1 Patients with schizophrenia and first line relatives.

			First line relatives					
			Male			Female		
			Fathers	Brothers	Total	Mothers	Sisters	Total
Patients with schizophrenia N (	M	63	38	46	84	38	61	99
	F	58	34	39	73	34	42	76
Average age years (	M	26	60	28		58	35	
	F	32	55	33		60	38	

The incidence of morbidity in relation to the first line relatives (parents, brothers, sisters) and regarding gender in various subtypes of schizophrenia (paranoid, disorganized, undifferentiated) showed statistically significant difference. With regard to gender, the number of affected mothers in the group of male patients (n=12.5) was higher than number of affected fathers in the group of male patients (n=10.4). Statistically significant difference was recorded in disorganized type of schizophrenia with higher number of affected brothers in the group of male patients (n=19.6) than the number of affected brothers in the group of female patients (n=7.7).

With regard to undifferentiated form of the disease there was almost equal number of affected fathers in the male group of patients (n=5.3) and affected sisters in the group of female patients (n=4.8) (Table 2).

Table 2 First line relatives-disease frequency.

Diagnostic categories	First line relatives according to gender							
	Fathers		Mothers		Brothers		Sisters	
	M=38	F=34	M=38	F=34	M=46	F=39	M=61	F=42
Paranoid schizophrenia	10.4	8.8	12.5	6.5	19.6	7.7	6.6	4.4
Disorganized schizophrenia								
Undifferentiated schizophrenia	5.3	2.9	-	-	4.3	2.6	1.6	4.8
Residual schizophrenia	5.3	-	-	-	-	-	-	2.4
Schizophrenia simplex	-	-	-	-	-	-	1.6	-

The real proportion indexes in this study corresponded to the expected polygenic model of inheritance regarding the group of paranoid schizophrenia with the same results in all other types of schizophrenia (disorganized, undifferentiated and residual) (Table 3).

Table 3 Hypothetical models of inheritance according to proportions.

		PROPORTION OF PATIENTS BETWEEN FIRST LINE RELATIVES		PROPORTION INDEXES EXPECTED			
Diagnostic categories	Gender	Patients (r)	First line relatives (e)	Proportion r/e	Dominant	Recessive	Polygenic
Paranoid schizophrenia							
	F	0.074	0.004	18.5	125	63	16
	Total	0.075	0.002	37.5	250	125	22.2
Diagnostic categories	Gender	Patients (r)	First line relatives (e)	Proportion r/e	Dominant	Recessive	Polygenic
Disorganized schizophrenia	M	0.089	0.015	6	33.3	17	8.2
	F	0.086	0.012	7.2	42	21	9.2
	Total	0.087	0.007	12.4	71.4	36	12
Diagnostic categories	Gender	Patients (r)	First line relatives (e)	Proportion r/e	Dominant	Recessive	Polygenic
Undifferentiated schizophrenia	M	0.019	0.005	3.8	100	50	14.1
	F	0.017	0.004	4.3	125	63	16
	Total	0.018	0.002	9	250	125	22.2
Diagnostic categories	Gender	Patients (r)	First line relatives (e)	Proportion r/e	Dominant	Recessive	Polygenic
Residual schizophrenia	M	0.013	0.01	1.3	50	25	10
	F	0.006	0.008	1	63	31.2	11.2
	Total	0.009	0.004	2.3	125	63	16
Diagnostic categories	Gender	Patients (r)	First line relatives (e)	Proportion r/e	Dominant	Recessive	Polygenic
Schizophrenia simplex	M	-	-	-	-	-	-
	F	0.006	-	-	-	-	-
	Total	0.003	-	-	-	-	-

r=real, e=expected

Table 4 **Patients with schizophrenia-morbidity risk.**

	Paranoid schizophrenia		Disorganized schizophrenia		Undifferentiated schizophrenia		Residual schizophrenia		Schizophrenia simplex	
	MR	SE	MR	SE	MR	SE	MR	SE	MR	SE
Brothers/ sisters	14.1	3.755	21.4	4.626	4.0	2.000	1.6	1.265	0.48	0.693
Parents	4.1	2.025	9.3	3.049	2.5	1.581	0.7	0.837	-	-
Total	9.1	1.202	15.4	1.385	3.3	0.946	1.2	0.725	0.24	0.416

MR=morbidity risk, SE=standard error

Overall morbidity risk in the first line relatives (brothers, sisters, parents) for paranoid schizophrenia was 9.1±1.2%, disorganized schizophrenia 15.4±1.4%, undifferentiated schizophrenia 3.3±1.0%, residual schizophrenia 1.2±1.0%, and schizophrenia simplex 0.24±0.4%. When siblings were considered separately statistically significant differences were in relation to the parents group in both diagnostic groups together. In the category of paranoid schizophrenia the morbidity risk of siblings was 14.1±3.7% in relation to parents with 4.1±2.0%. The maximum value was obtained for the disorganized type in a group of siblings with 21.4±4.6%, in relation to parents with 9.3±3.0% (Table 4).

The morbidity risk of siblings compared to the control group was more than seven times higher for paranoid schizophrenia and five times higher for disorganized type of schizophrenia (Table 5).

Table 5 **First line relatives-morbidity risk.**

	Paranoid schizophrenia		Disorganized schizophrenia		Undifferentiated schizophrenia		Residual schizophrenia		Schizophrenia simplex	
	MR	SE	MR	SE	MR	SE	MR	SE	MR	SE
Brothers/ sisters	2.2	1.483	4.4	2.098	-	-	2.2	1.483	-	-
Total	1.1	1.049	2.2	1.483	-	-	1.1	1.049	-	-

MR=morbidity risk, SE=standard error

Heritability calculation based on the incidence of schizophrenia among the first line relatives was higher if considered in diagnostic category of paranoid schizophrenia in relation to disorganized. In general, heritability had a lower value for disorganized schizophrenia, and it was higher when the analysis was extended to the cases of paranoid schizophrenia (Table 6).

Table 6 **Heritability by groups of relatives.**

Relation with patients	Heritability coefficient				
	Paranoid schizophrenia	Disorganized schizophrenia	Undifferentiated schizophrenia	Residual schizophrenia	Schizophrenia simplex
Brothers	0.567±0.170	0.611±0.194	0.285±0.107	-	-
Sisters	0.521±0.165	0.564±0.189	0.250±0.098	0.152±0.048	0.125±0.243
Total	0.588±0.168	0.544±0.192	0.268±0.103	0.076±0.024	0.063±0.122

Although the absolute differences in the values of heritability coefficient calculated on different grounds may seem quite large (diagnostic category of paranoid schizophrenia), none of them was statistically significant.

DISCUSSION

Schizophrenia is devastating neuropsychiatric disorder without clearly identified etiology. It has a similar incidence (0.6% -1.1%) around the world, but it progresses at varying degrees of severity. It is quite likely that a crucial role in the disease development is played by molecular mechanisms mediating the interaction between genes and environment. Those who have a third degree relative of a proband are twice as likely to develop it as those in the general population and with a second degree relative have a several-fold higher incidence of schizophrenia than the general population, and first degree relatives have an incidence of disease of magnitude higher than the general population (6,7). Overall, risk in the first degree relatives of a proband is about 9%, an approximately 10-fold increase over that in the general population, with a rapid decline as the degree of genetic relatedness to the proband becomes more distant (8). The evidence from family studies suggests that schizophrenia is a complex disorder which does not conform to simple, Mendelian inheritance. The causes of schizophrenia appear to be multifactorial, likely involving many genes and both shared and nonshared environmental influences (9).

Multifactorial etiology is an issue and schizophrenia is evolving through a complex interaction of inherited predispositions and a number of unfavorable factors, of biological, psychological and social nature. Despite numerous studies based on organic, psychodynamic and sociodynamic position, as well as a large number of hypotheses

derived from these studies, the etiology and pathogenesis of disorder is not yet sufficiently illuminated (10).

However, it is of much interest, that the correlation of schizophrenia between identical twins, who have identical genomes, is less than one-half. This indicates that disorder is not entirely a genetic disease. In recent studies higher incidence of schizophenia was observed in male gender, but it is also believed that majority of these studies are not strictly directed to studying gender distribution as a part of this disease.

Our results completely match the results of the studies analyzing morbidity risk regarding gender in various subtypes of schizophrenia in the first line relatives (11-15). In a group of male patients it more affected mothers than fathers, with statistically significant difference in disorganized schizophrenia with a higher number of affected brothers in a group of male patients than in the group of female patients. With regard to undifferentiated form of the disease almost equal number was recorded in a group of male and female patients, but statistically significant difference was not observed (16,17,18).

Calculation of the real and expected values of relative indicator regarding the various subtypes of schizophrenia corresponds to the expected polygenic model of inheritance. Overall morbidity risk for paranoid schizophrenia in the first line relatives was the highest compared to other subtypes of the disease with least in schizophrenia simplex. The morbidity risk in a group of siblings in relation to parents was higher in the category of paranoid schizophrenia with the maximum value in the disorganized type. Calculation of heritability based on the incidence of schizophrenia among the first line relatives was higher if considered in diagnostic category of paranoid schizophrenia in relation to disorganized schizophrenia. Although the absolute differences in the values of heritability coefficient calculated on different grounds may seem quite large (diagnostic category of paranoid schizophrenia), none of these differences were statistically significant (19,20).

This must betray a lot about the underlying mechanisms of brain and mind, and the connectivity required to generate its features. It is a complex multifactorial and polygenic disease (21,22).

Although family, twin and adoption studies have consistently

suggested that genetic factors play an important aetiological role in schizophrenia, until now, very little is known about the nature and

number of these genetic factors. It does run in families and by no means everyone with schizophrenia has an affected relative (23,24).

CONCLUSION

Schizophrenia certainly has a significant genetic component and genealogy detection is very important for studying the genetic mechanism of inheritance. The basic model for determining the type of heredity characteristics of individual behavior in humans is based on the formation of family trees showing how a trait is manifested in the descendants and ancestors. In schizophrenia, genetic predisposition could be a demonstrator of the disease course and outcome, which should enable better understanding of underlying illness mechanisms and better approaches in the treatment of this complex disorder.

Conflict of interest: none declared.

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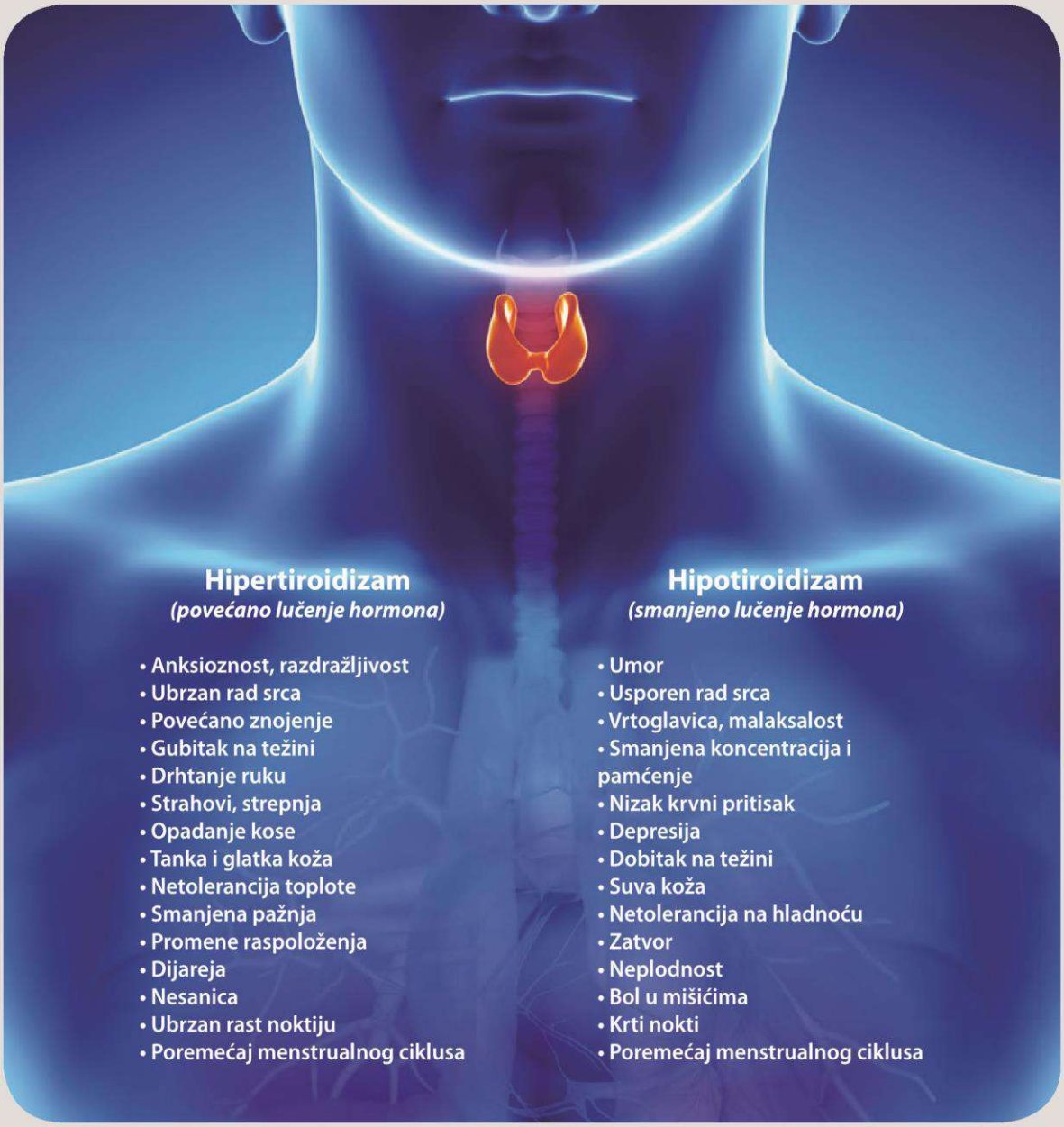

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Outcomes of fibrinolytic vs. invasive treatment of patients with acute myocardial infarction

Ishodi fibrinolitičke terapije u poređenju sa invazivnom terapijom kod pacijenata sa akutnim infarktom miokarda

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ABSTRACT

Introduction: acute myocardial infarction (AMI) is treated with fibrinolytic or percutaneous coronary intervention (PCI) procedure. Taking into account the time elapsed from the pain occurrence to the moment of admission to hospital, the cardiologist evaluates whether the patient is a candidate for fibrinolytic therapy or whether the patient should be referred to the invasive cardiologist. The aim of the study was to determine: sample analysis of patients based on age and gender, speed of recovery (dynamics of troponin), and the outcomes of patients with acute myocardial treated with two different methods (PCI and fibrinolytic therapy). Materials and methods: the study was clinical-manipulative, descriptive-analytical, controlled, retrospectiveprospective study. Data was collected from anamnesis and medical history, clinical examination and laboratory findings (troponin) of patients. The sample included 100 patients with AMI divided into two groups: a study group (n=50) patients treated with PCI and control group (n=50), patients treated with fibrinolytic therapy. Results showed that myocardial infarction patients treated with PCI method had fewer complications (23.33%), shorter period of hospitalization (5.3 days), lower total cost of the treatment, faster recovery and return to normal life activities. Conclusion: health care of patients with acute myocardial infarction treated with PCI method is better and more efficient compared to the health care of patients treated with fibrinolytic therapy: faster recovery, fewer complications and shorter hospitalization. Also, PCI treatment method is less expensive due to shorter hospitalization.

Key words: acute myocardial infarction, fibrinolytic therapy, PCI procedure

SAŽETAK

Uvod: liječenje akutnog infarkta miokarda (AIM) provodi se reperfuzionom terapijiom, fibrinolitičkom terapijom ili perkutanom koronarnom intervencijom (PCI). Obzirom na vrijeme od pojave bola do momenta dolaska u bolnicu, kardiolog procjenjuje da li je pacijent kandidat za ordiniranje fibrinolitičke terapije ili je indicirana perkutana koronarna intervencija. Cilj istraživanja je utvrditi: brzinu oporavka (dinamika kretanja troponina), pojavu komplikacija (poremećaj ritma, kardiopulmonalna reanimacija i na kraju preživljanje) i dužinu hospitalizacije te cijenu koštanja hospitalnog tretmana kod dvije grupe pacijenata s dijagnozom akutnog infarkta miokarda tretiranih s dvije različite metode (PCI i fibrinolitička terapija). Materijali i metode: istraživanje je kliničko-manipulativna, deskriptivno-analitička, kontrolna, retrospektivno-prospektivna studija. Podaci su prikupljani iz: anamneze i istorije bolesti, kliničkog pregleda bolesnika i laboratorijskih nalaza (troponin). Uzorak je obuhvatio 100 pacijenata s AIM, podjeljenih u dvije grupe: ispitivanu grupu (n=50) koju su činili pacijenti liječeni PCI i kontrolnu grupu (n=50), pacijenati liječeni fibrinolitičkom terapijom. Rezultati su pokazali da pacijenti s infarktom miokarda tretirani PCI metodom imaju manji broj komplikacija (23,33 %), manju dužinu hospitalizacije (5,3 dana), manju cijenu ukupnog tretmana i brži oporavak i vraćanje životnim aktivnostima. Zaključak: tretman pacijenata s akutnim infarktom miokarda tretiranih PCI metodom je bolji i kvalitetniji u odnosu na pacijente tretirane fibrinolitičkom terapijom: pacijenti se brže oporavljaju, imaju manji broj komplikacija te je dužina hospitalizacije kraća. Također, tretman PCI metodom je jeftiniji radi manjeg broja dana hospitalizacije.

Ključne riječi: akutni infarkt miokarda, fibrinolitička terapija, PCI metoda

INTRODUCTION

Acute myocardial infarction (AMI) occurs due to a sudden obstruction of blood flow through coronary arteries supplying the heart muscle with oxygen and nutrients, causing derogation in the limited part of the heart muscle, i.e. loss of cells (1). Due to the reduced activity of cardiac mass, the heart can no longer pump the blood normally, which could result in immediate cardiac arrest.

Insufficient blood flow or obstruction of the flow through the coronary artery is usually caused by a blockage of arteries or by a blood clot, which is gradually formed in the underlying blood vessel damaged by atherosclerosis. Atherosclerotic plaques narrow the blood vessels diameter, creating a foundation for blood clot which further narrows the blood vessels. Conceptually, the myocardial infarction presents myocardial necrosis caused by ischemia (2).

Epidemiology of coronary artery disease

Cardiovascular diseases (CVD) are the leading cause of death in the developed countries of the world and the majority of developing countries. They are also an important cause of absenteeism, disability and high costs of hospitalization (3). Acute myocardial infarction is the leading cause of sudden cardiac death in adult patients. Most deaths caused by AMI occur in pre-hospital environment (52%), followed by death in hospital within 24 hours (19%), death within 48 hours (8%), while 21% of patients die within thirty days. Given that 52% of patients die in pre-hospital conditions, it is obvious that a well-organized pre-hospital service can significantly reduce the number of deaths caused by AMI (4).

The etiology of myocardial infarction

Factors influencing the occurrence of myocardial infarction are divided into:

- Non-modifiable: gender, age, genetics;
- Modifiable: hypertension, obesity, hyperlipidemia, diabetes, smoking, alcohol, physical inactivity, stress, oral contraceptives etc. (5).

Myocardial infarction diagnosis

The diagnosis of AMI is set based on the characteristic history of the disease, necrosis markers and changes observed on the ECG. Pain is a dominant symptom in the history of the disease. The pain is localized primarily in retrosternal space, with tendency of spreading to the left shoulder, partly on the ulnar side of the left hand, and continues to the small and ring finger. The pain may radiate towards the left half of the lower jaw, sometimes towards the stomach and interscapular region. The pain can be described as stinging, burning, squeezing, pulling, lasting more than 20 minutes, without stopping upon administration of nitro preparations. It can be accompanied by nausea, vomiting, sweating, paleness, dyspnea, dizziness and general weakness (6). Values of necrosis markers are other indicators of myocardial infarction.

Laboratory tests used in the diagnosis of acute myocardial infarction are:

- Troponins are protein molecules that are part of cardiac and skeletal muscle not normally present in the serum, and are released into circulation when myocardial necrosis occurs.
- Levels of creatinine kinase (CK) and CK MB fraction are increased in the serum 3 to 12 hours after the pain onset, reaching its peak value within 24 hours, gradually decreasing during the next 48 to 72 hours.
- Myoglobin is a protein released from the heart muscle faster than troponin. The levels of myoglobin in urine increases 1-4 hours after the pain onset.
- In addition to the above-mentioned analysis it is necessary to do a complete blood count, basic biochemical analysis, lipids levels, C-reactive protein (CRP) and other markers of inflammation (7).

Treatment of acute myocardial infarction

Acute myocardial infarction is treated with fibrinolytic or percutaneous coronary intervention (PCI) procedure, a non-surgical procedure used to treat narrowing (stenosis) of the coronary arteries (8).

This procedure requires coronary angiography in order to register atherosclerotic lesion within the coronary artery. The lesion can be reduced or eliminated by balloon dilatation and further by placing a stent in the coronary artery which compresses atherosclerotic lesion resulting in an increase of its diameter and blood flow. Taking into account the time elapsed from the pain occurrence to the moment of admission to hospital, the cardiologist evaluates whether the patient is a candidate for fibrinolytic therapy or whether the patient should be treated by percutaneous coronary intervention (9).

The aim of the study was to:

- analyse sample based on age and gender;
- determin the speed of the recovery (dynamics of troponin), and
- treatment outcome in two groups of patients diagnosed with acute myocardial infarction and treated with two different methods (PCI procedure and fibrinolytic therapy).

MATERIALS AND METHODS

This was a clinical, descriptive-analytical, control and retrospective study which used data from the records of patients treated at the Clinic of Heart Diseases, Blood Vessels and Rheumatism of the CCUS.

The study included 100 patients with acute myocardial infarction and divided into two groups:

- Study group (n=50) - patients treated with PCI procedure in the Cath Lab within two hours, and
- Control group (n=50) - patients treated with fibrinolytic therapy within 12 hours.

Statistical analysis

The statistical analysis included descriptive statistics of the groups, analysis and statistical data processing, applying appropriate statistical methods on the obtained parameters. Parametric data were tested by Student's t-test, while non-parametric data was processed by chisquare ($\chi 2$) test and proportions. The obtained results are shown in textual, numerical and tabular form.

RESULTS

Table 1 Gender structure of the observed groups.

Gender	PCI group	Control group	Total
Male	34 (68%)	44 (88%)	78
Female	16 (32%)	6 (12%)	22
Total	50 (100%)	50 (100%)	100

p=0.016 ($\chi 2$=5.82, N=100, df=1, p<0.05).

Given that the independent variable (gender) was of nominal type we used $\chi 2$ test. Based on cross-tabulation the prevalence of male patients was observed in both groups. However, based on gender structure of patient treated with fibrinolytic therapy there was a significantly larger number of male patients (88%) in respect to those treated with PCI procedure (68%). This difference is statistically significant with a significance level, p=0.016 ($\chi 2$=5.82, N=100, df=1, p<0.05).

Table 2 Age structure of the respondents.

Age	PCI group	Control group	Total
35 - 44	9 (18%)	6 (12%)	15
45 - 54	15 (30%)	20 (40%)	35
55 - 64	14 (28%)	15 (30%)	29
>65	12 (24%)	9 (18%)	21
Total	50 (100%)	50 (100%)	100

(t=0.61, N=100, df=98, p=0.95).

Given that the independent variable (age) was of numeric type we used independent Student's t-test. The average age of patients in both groups was equal with minor differences in decimals. The formal t-test showed insignificant difference (t=0.61, N=100, df=98, p=0.95).

Table 3 Troponin's dynamic.

	PCI group	Control group
The average value of troponin - on admission	58.03	20.94
Range	0.3 - 143.7	0.3 - 115.4
The average value of troponin - at discharge	4.03	1.48
Range	0.04 - 9.95	0.03 - 8.21

In the study group, the average value of troponin in patients on admission was 58.03 ng/ml. The range was from 0.3 ng/ml to 115.4 ng/ ml (the lowest value of troponin was 0.3 ng/ml, and the highest value was 115.4 ng/ml). In the control group, the average value of troponin in patients on admission was 20.94 ng/ml. The range was from 0.3 ng/ ml to 143.7 ng/ml (the lowest value of troponin was 0.3 ng/ml, and the highest value was 143.7 ng/ml).

Table 4 Length of hospitalization (days) in both groups.

	PCI group	Control group
The average length of hospitalization	5.3	13.04
Range	2 – 8	9 - 19
Shortest hospitalization	2	9
Longest hospitalization	8	19

(t =6.89, N=100, df=98, p<0.001).

The average length of hospitalization for PCI group was 5.3 days and in control group 13.4 days. This was in line with our expectations that patients in PCI group had significantly shorter hospitalization, significance of t=6.89, N=100, df=98, p<0.001.

DISCUSSION

Acute myocardial infarction is the leading cause of a sudden cardiac death in adult patients. For the outcome of the disease, the pre-hospital period (the time from the infarction to admission at the hospital) is extremely important. Experts suggest that in 30% of cases, death can be prevented by proper organization of health services in emergency departments (10).

Reperfusion therapy in AMI can be performed by fibrinolytic treatment or by percutaneous coronary intervention. This was the reason for the selection of the study topics which compare the quality of care of patients with acute myocardial infarction treated with two types of therapy (9-10).

Statistical analysis established that the groups were homologous in terms of gender representation. In fact, with regard to both groups it can be concluded that there was significantly larger number of male patients in the study group (68%) and in the control group (88%) respectively. The statistical analysis related to the risk assessment of patients with acute myocardial infarction was based on intrahospital mortality data. Out of the total of 396 patients included in the study (62.9% men and 37.1% women) lethal outcome was registered in 80 cases, or in 20.2% (12.9% men and 32.0% women). Worse outcome in women with AIM came as a result of later onset of the disease (69.7±10.0 years to 61.6±11.8 for men) (11).

The largest number of patients was in the age group between 45 and 54 years or 30% : 40%, whereas slightly smaller number of patients was in the age group of 55-64 years (28%: 30%). The research conducted by the Department of Cardiovascular and Interventional Cardiology of the General Hospital Dubrovnik (Nurses Gazette, 2016, 21.2: 153-157), shows that patients over 50 years of age are more susceptible to myocardial infarction and angina pectoris than those under 50 (11).

In the study group, the average value of troponin in patients on admission was 58.03 ng/ml. The range was from 0.3 ng/ml to 115.4 ng/ml (the lowest value of the troponin was 0.3 ng/ml, and the highest value was 115.4 ng/ml). In the control group, the average value of troponin in patients on admission was 20.94 ng/ml. The

range was from 0.3 ng/ ml to 143.7 ng/ml (the lowest value of the troponin was 0.3 ng/ml, and the highest value was 143.7 ng/ml). The reason for the significant difference in the value of troponin at the beginning of the treatment was in the fact that the first troponin measurement was performed at the Department of Cardiology, while at the Department of Invasive Cardiology it was measured following the procedure, specifically after PCI. Furthermore, patients lost time going from the Emergency Department to the Clinic of Cardiology and subsequently to the Department of Invasive Cardiology. The research conducted at the Department of Cardiology of the Clinical Center of Serbia shows that if the first value of troponin was normal, the analysis should be repeated in 6-9 hours. In NSTEMI, small increase in troponin can be registered within 48-72 h. The introduction of highly sensitive troponin (hsTn) enabled an early diagnosis and identification of persons at increased risk, applying the protocol on fast exclusion of AKS (3 hours) (12).

Among the complications observed in global studies, primary investigation was focused to lethal outcome. In the study of Le May RM et al., intrahospital mortality proved to be significantly lower in patients treated with PTCA (1.9%), compared to those treated with streptokinase (8.9%) (13). For comparison, the WHO stated that the hospital standardized mortality rates for acute myocardial infarction in the group of countries covered by their report in 2012 ranged from 3.0% in Denmark to 27.2% in Mexico. From the countries involved in the analysis the standardized mortality rate over 10% was recorded only in Mexico (22.1%), Hungary (13.9%), Japan (12.2%), Chile (10.8%) and Turkey (10.7%). From the neighboring European countries Austria had a rate of 7.7%, Slovakia 7.6%, Slovenia 7.0%, France 6.8% and Italy 5.8% (12-13).

Analysis of the treatment costs of patients in the control study group showed that there was no statistically significant difference. However, patients treated with fibrinolytic therapy with all accompanying costs, did not have their problems solved out. Those patients had to repeat the PCI treatment which at least doubled the cost of treatment or eventually surgical intervention on coronary blood vessels, which was even more expensive.

CONCLUSION

Structure of patient treated with fibrinolytic therapy was significantly larger in respect of male patients (88%) compared to those treated with PCI procedure (68%). This difference is statistically significant, $p<0.05$). The average age of patients in both groups was equal with minor differences in decimals. The formal t-test showed insignificant difference, $p=0.95$. The average value of troponin in patients of the study groups at admission was 58.03 ng/ml, and 4.03 ng/mg at discharge, whereas in the control group, the average value of troponin at admission was 20.94 ng/ml, and 1.48ng/mg at discharge. The average duration of hospitalization in the study group was 5.3 days, while in the control group it was 13.04 days. The difference was statistically significant, $p<0.001$. Overall health care of patients with acute myocardial infarction treated with PCI procedure was better and of higher quality compared to health care of patients treated with fibrinolytic therapy.

Conflict of interest: none declared.

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ODOBRENE INDIKACIJE: TENVAL®: Liječenje esencijalne hipertenzije u odraslih, kao i hipertenzije u djece i adolescenata uzrasta od 6 do 18 godina. Liječenje simptomatskog zatajenja srca u odraslih pacijenata, u slučajevima kada se inhibitori angiotenzin konvertirajućeg enzima (ACE inhibitori) ne mogu primijeniti, ili kao dodatno liječenje uz ACE inhibitore kada se beta blokatori ne mogu primijeniti. **TENVAL duo®:** Liječenje esencijalne hipertenzije u odraslih, u kojih krvni pritisak nije adekvatno kontroliran monoterapijom s valsartanom ili hidroklortiazidom.
KONTRAINDIKACIJE: TENVAL®: Preosjetljivost na aktivnu supstancu i/ili na bilo koju od pomoćnih supstanci u sastavu lijeka; teško oštećenje funkcije jetre, bilijarna ciroza i holestaza, drugi i treći trimestar trudnoće; istovremena primjena antagonista angiotenzinskih receptora, ili inhibitora angiotenzin konvertirajućeg enzima, s aliskirenom u pacijenata s dijabetesom ili oštećenom funkcijom bubrega (GFR <60 mL/min/1,73 m2). **TENVAL duo®:** Preosjetljivost na valsartan, hidroklortiazid, druge sulfonamidne lijekove i/ili na bilo koju od pomoćnih supstanci u sastavu lijeka, drugi i treći trimestar trudnoće, teško jetreno oštećenje, bilijarna ciroza i holestaza, teško bubrežno oštećenje (klirens kreatinina <30 ml/min), anurija, refraktorna hipokalijemija, hiponatrijemija, hiperkalcijemija i simptomatska hiperurikemija, istovremena primjena antagonista angiotenzinskih receptora ili inhibitora angiotenzin konvertirajućeg enzima s aliskirenom u pacijenata s dijabetesom ili oštećenom funkcijom bubrega (GFR <60 mL/min/1,73 m2).
NAJČEŠĆE NUSPOJAVE: TENVAL®: Vrtoglavica, umor, hipotenzija, mučnina, proljev, kašalj, omaglica, glavobolja, osip, svrbež, hiperkalijemija, hiponatrijemija, reakcije preosjetljivosti. **TENVAL duo®:** omaglica, sinkopa, zamagljen vid, hipotenzija, umor, tinitus, dijareja, mijalgija.
MJERE OPREZA: TENVAL® i TENVAL duo®: Ne preporučuje se istovremena primjena sa suplementima kalija, kalij štedećim diureticima, zamjenskim solima koje sadrže kalij ili s drugim agensima koji mogu povisiti nivo kalija (heparin, itd). U pacijenata s blagim do umjerenim oštećenjem jetre, bez holestaze, valsartan treba primjenjivati oprezno. Deplecija natrija i/ili volumena treba korigovati prije početka liječenja s valsartanom, npr. smanjenjem doze diuretika. Pacijente s primarnim hiperaldosteronizmom ne bi trebalo liječiti s valsartanom, jer njihov renin-angiotenzin sistem nije aktiviran. Kao i u slučaju ostalih vazodilatatora, neophodan je poseban oprez u pacijenata sa stenozom aortnog ili mitralnog zaliska ili s opstruktivnom hipertrofičnom kardiomiopatijom.
DOZIRANJE I NAČIN UPOTREBE: TENVAL®: Preporučena početna doza u liječenju hipertenzije iznosi 80 mg jedanput na dan. Antihipertenzivni efekt se pouzdano ispoljava unutar 2 sedmice, a maksimalni efekti lijeka se ostvaruju unutar 4 sedmice. U nekih pacijenata, u kojih krvni pritisak nije adekvatno kontrolisan, doza se može povećati do 160 mg, odnosno, do najviše 320 mg. Također, valsartan se može primjenjivati u kombinaciji s drugim antihipertenzivima. Dodatak diuretika, kao što je hidroklortiazid, dodatno će sniziti krvni pritisak u ovih pacijenata. U liječenju zatajenja srca, preporučena početna doza valsartana je 40 mg dva puta na dan. Titriranje doze do 80 mg, odnosno, 160 mg dva puta na dan, treba provesti tako da se doza do one najveće povećava tokom najmanje dvije sedmice, ovisno o pacijentovoj podnošljivosti liječenja. Potrebno je razmotriti smanjenje doze diuretika koji se primjenjuju istovremeno. Najveća dnevna doza primijenjena u kliničkim ispitivanjima iznosila je 320 mg u podijeljenim dozama. Valsartan se može primjenjivati s drugim lijekovima indiciranim kod zatajenja srca. Međutim, ne preporučuje se trostruka kombinacija ACE inhibitora, beta blokatora i valsartana. Može se primijenjivati u liječenju hipertenzije kod djece starosne dobi iznad 6 godina i to početna doza je 40 mg jedanput na dan za djecu težine ispod 35 kg, a 80 mg jedanput na dan za djecu težine 35 kg i više. Dozu treba prilagoditi vrijednostima krvnog pritiska. **TENVAL duo®:** Jedna tableta jedanput dnevno. Potrebno je procijeniti klinički odgovor na **TENVAL duo®** nakon uvođenja terapije, te ukoliko krvni pritisak i dalje nije pod kontrolom, doza se može povećati povećavanjem bilo koje komponente lijeka do maksimalne doze od 320 mg valsartana i 25 mg hidroklortiazida.

PROMASS®

alendronat

TEŠKA PITANJA TRAŽE PAMETNE ODGOVORE

"Zlatni" standard u tretmanu osteoporoze

BH.PRO.2016.01.

Pakovanje:
Tablete 70 mg x 4 (br. rješenja: 04-07.3-1-3225/15)

Lijek se izdaje na ljekarski recept.
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ODOBRENE INDIKACIJE: Indiciran za liječenje osteoporoze kod žena u postmenopauzi. Smanjuje rizik od nastanka prijeloma kičmenih prsljenova i kuka. **KONTRAINDIKACIJE:** Preosjetljivost na aktivnu supstancu ili neku od pomoćnih supstanci lijeka, abnormalnosti jednjaka i drugi faktori koji usporavaju njegovo pražnjenje kao što su strikture ili ahalazija, nemogućnost stajanja ili uspravnog sjedenja u trajanju od najmanje 30 minuta i hipokalcijemija. **NAJČEŠĆI NEŽELJENI EFEKTI:** Glavobolja, omaglica, poremećaj okusa, upala oka, vrtoglavica, bol u trbuhu, dispepsija, opstipacija, dijareja, nadutost, ulkus jednjaka, otežano gutanje, abdominalna distenzija, regurgitacija želučane kiseline, alopecija, pruritus, osip, crvenilo, bol u mišićno-koštanom sistemu koja je ponekad jaka, oticanje zglobova, astenija, periferni edem. **MJERE OPREZA:** Alendronska kiselina se mora s oprezom primjenjivati u pacijentica s aktivnim oboljenjima u gornjem dijelu gastrointestinalnog sistema kao što su disfagija, bolesti jednjaka, gastritis, duodenitis, ulkusi ili nedavna anamneza (u posljednjih godinu dana) ozbiljnih gastrointestinalnih bolesti kao što su peptički ulkus ili aktivno gastrointestinalno krvarenje ili hirurški zahvat u gornjem dijelu gastrointestinalnog sistema, osim piloroplastike. U pacijentica s osteoporozom, koje su primjenjivale peroralne bisfosfonate zabilježena je osteonekroza vilice, te je prije početka liječenja u pacijentica sa lošim dentalnim statusom potrebno sprovesti stomatološki pregled uz primjenu odgovarajućih preventivnih stomatoloških mjera, a tokom liječenja ove pacijentice moraju izbjegavati invazivne stomatološke zahvate ako je to moguće. U pacijentica koje uzimaju bisfosfonate zabilježeni su i simptomi kao što su bolovi u kostima, zglobovima i/ili mišićima, koji su se povukli nakon prekida liječenja. U pacijentica koje su liječene bisfosfonatima, posebno kod onih koje su primale dugotrajnu terapiju zabilježene su i atipične frakture subtrohantera i dijafizealni prijelomi bedrene kosti, te treba sugerisati pacijenticama da prijave bilo kakvu bol u području bedra, kuka ili prepona. Prije početka liječenja potrebno je korigovati hipokalcemiju i druge poremećaje koji utiču na metabolizam minerala (nedostatak vitamina D i hipoparatireoidizam). Alendronat se ne preporučuje pacijentima s oštećenjem funkcije bubrega u kojih je klirens kreatinina manji od 35 ml/min. Ne primjenjuje se kod trudnica i dojilja. Bolesnici sa rijetkim nasljednim poremećajem nepodnošenja galaktoze, nedostatkom „Lapp laktaze" ili glukoza-galaktoza malapsorpcijom ne bi trebali uzimati ovaj lijek. **DOZIRANJE I NAČIN UPOTREBE, UPOZORENJA:** Preporučena doza je jedna tableta od 70 mg jednom sedmično. Lijek se mora uzimati ujutro, nakon ustajanja, najmanje 30 minuta prije uzimanja prvog dnevnog obroka, napitka ili drugih lijekova s punom čašom obične vode (najmanje 200 ml). Tableta se mora progutati cijela. Ne smije se drobiti ni žvakati, niti dopustiti da se tableta rastopi u ustima zbog mogućnosti razvoja orofaringealnih ulkusa. Nakon uzimanja lijeka pacijentice ne smiju leći najmanje 30 minuta. Ako je unos hranom nedovoljan, pacijentice uz lijek moraju uzimati suplemente kalcija i vitamina D (pričekati najmanje 30 minuta nakon uzimanja alendronata). Nije potrebno prilagođavati dozu u starijih osoba. Ne preporučuje se primjena alendronata u djece mlađe od 18 godina.

Molimo Vas da prije propisivanja lijeka proučite odobreni sažetak glavnih karakteristika lijeka i uputstvo o lijeku.