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RISK FACTORS FOR EARLY POSTOPERATIVE ARRHYTHMIAS IN GENERAL SURGERY PATIENTS AFTER GENERAL ANESTESIA

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FAKTORI RIZIKA ZA NASTANAK POSTOPERATIVNE ARITMIJE KOD PACIJENATA OPERISANIH U OPŠTOJ ANESTEZIJI

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ABSTRACT

Introduction. *Early post-operative arrhythmias after general anaesthesia are serious clinical problems for a significant portion of surgical patients. The aim of our study was to investigate the risk factors for the onset of post-operative arrhythmias in general surgery patients undergoing general anaesthesia.*

Methods. *In this case-control study, the cases were patients with at least one episode of arrhythmias in the first 24 hours after general anaesthesia (n=56), and the controls were sex and age matched surgical patients (n=91) without post-operative arrhythmias.*

Results. *A history of cardiac arrhythmias in the last 5 years was a significant risk factor for early post-operative arrhythmias ($OR_{adjusted}$ 8.43; CI 2.67, 27.13; p = 0.000). Early post-operative arrhythmias occurred more frequently if the patient had a history of cardiac arrhythmias and intra-operative arrhythmias occurred. A history of cardiac arrhythmias and the use of propofol for the induction of anaesthesia were also significant.*

Conclusions. *In patients with a history of arrhythmias in the last 5 years, general anaesthesia should not be induced by propofol.*

Key Words. *Post-operative arrhythmias, risk factors, general anaesthesia, propofol.*

INTRODUCTION

In the immediate postoperative period (the first 24 hours after surgery), arrhythmias requiring the administration of antiarrhythmic therapy occur in 6 to 30% of patients. The majority of these arrhythmias are of supraventricular origins [1,2]. Early postoperative supraventricular arrhythmias are especially frequent and could have profound adverse effects on a patient's outcome [1,2].

Previously, numerous potential risk factors for early post-operative arrhythmias were evaluated, and some of the risk factors were significant. The important risk factors identified include smoking, increased age, atrial enlargement, reduced left ventricular function (especially if ejection fraction is less than 40%), preoperative arrhythmias and angina pectoris [3,4,5,6,7]. There are also other factors that could influence the frequency of early post-operative arrhythmias, such as previous medications, concomitant medications during general anaesthesia, previous diseases, etc. The aim of our study was to analyse new potential risk factors associated with early post-operative arrhythmias in general surgery patients undergoing general anaesthesia.

MATERIALS AND METHODS

Setting

Our study was conducted as part of a wider investigation in early postoperative arrhythmias in a secondary general hospital in Foča, Republic of Srpska, Bosnia and Herzegovina. The inclusion criteria for participants wasere elective non-cardiovascular or non-thoracic surgeries, under general inhalation anaesthesia in the Foča hospital. Patients over the 12 year period had to be an American Society of Anaesthesiologists (ASA) class I or II (n = 520). The data were obtained retrospectively from medical records and patient questionnaires. There was ECG-monitoring during anaesthesia and for two days after recovery using a Lifescope 8 Nihon-Kodhen, Datae Ohmeda monitor. All patients supplied written consent, and the Ethics Committee of the Foča hospital approved the study protocol.

The same type of general anaesthesia was used in all study patients. The anaesthetic protocol included balanced general inhalation anaesthesia with a nitrous oxide/oxygen mixture (3.6l : 1l) and sevoflurane. Controlled mechani-

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cal ventilation was initiated after endotracheal intubation (Sulla 808 V, Fabius Tiro Drager, Datex Ohmeda and Safer 100 AKA). Anaesthesia was induced with either sodium thiopental (3 mg/kg) or propofol (2 mg/kg). Muscle relaxation was achieved with succinylcholine (1-1.5 mg/kg) and maintained with pancuronium bromide (0.05 mg/kg). For intra-operative analgesia, intravenous fentanyl (0.005 mg/kg) was used. The neuro-muscular blockade was reversed by intravenous neostigmine (2.5 mg) after the operation was completed.

Study design: cases and controls

This was a case-control study. Both cases and controls were selected from the list of adult patients (ASA class I and II) operated on using general anaesthesia during the study period at Foča hospital. The patients with ECG records of early post-operative arrhythmias (supraventricular extrasystoles, supraventricular tachycardia, supraventricular flutter or fibrillation, sinus tachycardia (frequency > 110/min), sinus bradycardia (frequency < 50), ventricular extrasystoles, ventricular tachycardia, or all types of heart block) in the first 24 hours after surgery, were considered to be our cases. For each case, at least one sex and age-matched control, without any early post-operative arrhythmias, was randomly selected from the study population.

Potential risk factors

In order to identify potential risk factors, the following data on habits, previous medical history, (co)medications and (co)morbidities were collected from each patient: age, sex, body mass index, profession, type of work (sedentary or active), amount of physical activity, type of surgery, name of surgeon, invasiveness of the surgical technique (as estimated by an anaesthesiologist), duration of general anaesthesia, duration of surgery, type of intravenous anaesthetic, total dose of pancuronium, total dose of fentanyl, intravenous administration of Ringer's solution or hydroxyethyl starch solution during anaesthesia, total volume of each solution given, concomitant diseases like heart failure or arterial hypertension (> 160/95 mmHg for more than 3 months prior to hospitalisation), diabetes mellitus type 1 or 2, or chronic obstructive pulmonary disease (COPD), a history of cardiac arrhythmias in the last 5 years and the type of the arrhythmia, and hypertrophy of the left ventricle. The use of the following drugs, for at least 3 months prior to hospitalizsation, were recorded: beta blockers, angiotensin-converting enzyme inhibitors (ACE inhibitors), diuretics, aminophylline, digoxin, antiaggregatory agents, organic nitrates, oral antidiabetics, antipsychotic or antidepressant, antiarrhythmics, pre-operative antibiotic prophylaxis, and pre-operative thromboprophylaxis. The following habits and diagnostic test results were also recorded: smoking (more than 10 cigarettes per day, for at least the previous 2 years), average number of cigarettes per day, alcohol consumption (more than the equivalent of 25 ml of absolute alcohol daily, for the past 3 years), average consumption of alcohol daily, coffee intake (more than 3 cups everyday for the last 2 years), average number of coffee cups per day, hypoxia (SpO_2 < 96%), hypothermia (core body temperature below 35°C), abnormal levels of serum sodium, potassium, chloride, calcium and magnesium (according to normal reference values for the local biochemical laboratory in Foča hospital), acidosis (pH< 7.4), hypercarbia (pCO_2 > 45 mmHg), anaemia (haemoglobin level below 10 g/l), hyperglycaemia (>6.5 mM/l), hypoglycaemia (<3.5 mM/l), a history of myocardial infarction during the last 5 years, time elapsed from the myocardial infarction, abnormal ECG anytime in the last 5 years and the type of ECG finding, a history of valvular disease and its type, chronic cough (more than 3 months per year for the last 2 years), bronchial asthma, pneumonia, abnormal pulmonary ventilation tests prior to hospitalisation, a history of cerebro-vascular accident, uncontrolled post-operative pain, anti-arrhythmic therapy administered during the surgery, levels of standard biochemical blood tests (cholesterol, glucose, bilirubin, amino-transferases, creatinine, urea, total protein level, albumin level), levels of standard haematology tests (erythrocyte count, leukocyte count, platelet count, haemoglobin level), blood level of C-reactive protein and blood transfusion. The values of laboratory tests refer to the blood samples taken 12 hours prior to surgery.

Data analysis

The frequency of each risk factor was determined for both cases and controls. The differences between cases and controls, according to observed characteristics, were assessed by Student's T-test for continuous variables and the Chi-squared test or Fisher's test for frequencies. The differences were considered significant if the probability of the null hypothesis was less than 0.05. In order to estimate the association between potential risk factors and post-operative arrhythmias, crude and adjusted odds ratios (OR), with a 95% confidence interval (95% CI), were calculated using a logistic regression [8.9].

RESULTS

Among 147 study patients, fifty-six patients (38%) had at least one episode of an early post-operative arrhythmia. The following types of post-operative arrhythmias were recorded: sinus tachycardia (21 cases, 38%), supraventricular extrasystole (25 cases, 45%), paroxysmal supraventricular tachycardia (4 cases, 7%) and ventricular extrasystole (14 cases, 25%). Eight patients (15%) had more than one type of post-operative arrhythmia. There were 91 sex and age-matched control patients.

Baseline characteristics of cases and controls, and differences between them, are shown in Table 1. Significant differences between cases and controls were only found only in the following variables: type of intravenous anaes-

Table 1. Baseline characteristics of cases and controls*.

Variable	Cases (n=56)	Controls (n=91)	Test value and significance of null hypothesis	Crude odds ratios with confidence intervals (1.96*SE)
Sex (M/F)	19/37 (34%/66%)	36/55 (40%/60%)	$\chi^2 = 0.470$, p = 0.493	0.78 (0.41, 1.51)
Age (years, mean ± SD)	71.1 ± 10.8	67.8 ± 10.7	T = -1.824, p = 0.071	1.03 (0.99, 1.06)
BMI (mean ± SD)	26.1 ± 3.8	26.2 ± 4.2	T = 0213, p = 0.832	0.99 (0.91, 1.08)
Level of education	High 1 (2%) Middle 5 (9%) Low 50 (89%)	High 4 (5%) Middle 23 (25%) Low 64 (70%)	$\chi^2 = 7.293$, p = 0.065	0.63 (0.42, 0.95)
Name of the surgeon	Not shown due to limited space (16 surgeons)	Not shown due to limited space (15 surgeons)	$\chi^2 = 12.354$, p = 0.578	0.98 (0.92, 1.04)
Rough surgical technique	18 (32%)	25 (27%)	$\chi^2 = 0.465$, p = 0.793	1.25 (0.62, 2.52)
Type of intravenous anaesthetic (propofol vs. thiopental)	27/29 (48%/52%)	22/69 (24%/76%)	$\chi^2 = 9.014$, p = 0.003**	2.92 (1.47, 5.79)
Ringer's solution administered	22 (39%)	31 (34%)	$\chi^2 = 0.410$, p = 0.522	1.25 (0.65, 2.42)
Hydroxyethyl starch solution administered	13 (23%)	8 (9%)	$\chi^2 = 5.889$, p = 0.015**	3.14 (1.22, 8.04)
Smoker	34 (61%)	59 (65%)	$\chi^2 = 0.253$, p = 0.615	0.84 (0.46, 1.54)
Alcohol intake	13 (23%)	25 (28%)	$\chi^2 = 0.328$, p = 0.567	0.80 (0.38, 1.69)
Coffee intake	52 (93%)	85 (93%)	$\chi^2 = 0.017$, p = 0.898	0.92 (0.32, 2.62)
Sedentary job	5 (9%)	10 (11%)	$\chi^2 = 0.161$, p = 0.689	0.79 (0.26, 2.42)
Prior myocardial infarction	3 (5%)	8 (9%)	$\chi^2 = 0.591$, p = 0.442	0.59 (0.15, 2.29)
Stable angina pectoris	7 (13%)	11 (12%)	$\chi^2 = 0.005$, p = 0.941	1.04 (0.38, 2.82)
History of cardiac arrhythmias	37 (66%)	10 (11%)	$\chi^2 = 48.359$, p = 0.000**	15.77 (6.79, 36.64)
History of ECG abnormalities	43 (77%)	28 (31%)	$\chi^2 = 29.397$, p = 0.000**	7.44 (3.56, 15.54)
Hypertrophy of the left ventricle	10 (18%)	12 (13%)	$\chi^2 = 0.594$, p = 0.441	1.43 (0.58, 3.53)
Hypertension	43 (77%)	61 (67%)	$\chi^2 = 1.593$, p = 0.207	1.92 (0.93, 3.96)
Concomitant COPD	20 (36%)	26 (29%)	$\chi^2 = 0.823$, p = 0.364	1.39 (0.70, 2.75)
History of cerebro-vascular accident	9 (16%)	7 (8%)	$\chi^2 = 2.509$, p = 0.113	2.29 (0.81, 6.49)
Concomitant diabetes	12 (21%)	17 (19%)	$\chi^2 = 0.165$, p = 0.684	1.19 (0.53, 2.66)
Hyperglycaemia	17 (30%)	27 (30%)	$\chi^2 = 0.008$, p = 0.930	1.03 (0.51, 2.08)
Hypocalcaemia	31 (55%)	46 (51%)	$\chi^2 = 0.321$, p = 0.571	1.21 (0.65, 2.25)
Chronic use of beta blockers	16 (29%)	19 (21%)	$\chi^2 = 1.131$, p = 0.288	1.52 (0.72, 3.20)
Chronic use of loop diuretics	15 (28%)	6 (7%)	$\chi^2 = 11.543$, p = 0.001**	5.18 (1.90, 14.16)
Chronic use of digoxin	13 (23%)	3 (3%)	$\chi^2 = 14.178$, p = 0.000**	4.06 (1.33, 12.41)
Chronic use of aminophylline	6 (11%)	0 (0%)	Fisher's exact test, p = 0.033**	109.20 (0.20, 56670.27)
Chronic use of antiaggregatory agents	14 (25%)	17 (17%)	$\chi^2 = 0.382$, p = 0.362	1.45 (0.66, 3.17)
Chronic use of organic nitrates	14 (25%)	14 (15%)	$\chi^2 = 2.079$, p = 0.149	1.83 (0.81, 4.13)
Total dose of fentanyl (mg/kg)	0.0086 ± 0.034	0.0094 ± 0.027	T = 1.621, p = 0.107	0.00 (0.00, 8.22)
Duration of surgery (minutes)	95.4 ± 36.7	91.7 ± 38.9	T = -0.558, p = 0.578	1.00 (0.99, 1.01)
Total dose of hydroxyethyl starch solution (ml/kg)	1.62 ± 3.16	0.68 ± 2.27	T = -2.093, p = 0.038**	1.14 (1.00, 1.29)
Serum level of total cholesterol (mM/l)	5.10 ± 1.22	5.60 ± 1.20	T = 2.363, p = 0.019**	0.72 (0.54, 0.95)
Intra-operative arrhythmia	54(96%)	71(78%)	$\chi^2 = 9.229$, p = 0.002**	7.61 (1.81, 32.02)

*For the sake of clarity, variables with a frequency of an event less than 2% and some less important variables with insignificant differences between cases and controls are not shown in the table.
**Significant difference

thetic, total dose of hydroxyethyl starch solution, a history of cardiac arrhythmias in the last 5 years, use of loop diuretics (for at least for 3 months prior to hospitalisation), use of aminophylline (for at least for 3 months prior to hospitalisation), use of digoxin (for at least for 3 months prior to hospitalisation), a history of an abnormal ECG anytime in the last 5 years, intra-operative arrhythmias and serum cholesterol level.

The results of the logistic regression analysis (Cox & Snell R square 0.356, Nagelkerke R square 0.484, Hosmer-Lemeshow Chi square 7.611, df=8, p = 0.472), adjusted for potential confounders, are shown in Table 2. The only significant associations were between early post-operative arrhythmias and a history of cardiac arrhythmias in the last 5 years ($OR_{adjusted}$ 8.43; CI 2.67, 27.13; p = 0.000), and between early post-operative arrhythmias and the type of intravenous anaesthetic ($OR_{adjusted}$ 0.34; CI 0.12, 0.96; p = 0.041). After adjusting, the odds ratios for administration of hydroxyethyl starch solution and its total dose, use of loop diuretics, use of aminophylline, use of digoxin, intra-operative arrhythmias, cholesterol level and a history of an abnormal ECG anytime in the last 5 years lost their significance because the confidence level included the value of one (see Tables 1 and 2).

The interaction between risk factors for early postoperative arrhythmias was also investigated (Table 3). Synergistic effects were proven for patients with a history of cardiac arrhythmias in the last 5 years and intra-operative arrhythmias, as well as for patients with a history of cardiac arrhythmias and the type of intravenous anaesthetic used. Although crude odds ratios increased, and their confidence limits excluded the value of one when the interaction of a history of cardiac arrhythmias with the chronic use of digoxin and the chronic use of loop diuretics were excluded, synergistic effects could not be proven by the adjusted odds ratios because the confidence level became wider and included one.

DISCUSSION

Post-operative arrhythmias are more extensively studied in cardiac surgery patients because there is a higher prevalence of arrhythmias and more serious consequences. The most important risk factors for post-operative arrhythmias in cardiac surgery patients are hypertension, advanced age, hyperlipidaemia, diabetes, a history of smoking and operation time [10,11]. On the other hand, a history of an arrhythmia is a significant risk factor for new peri-operative atrial fibrillation after noncardiac thoracic surgery (two-fold increase in risk)[12], and for other kinds of peri-operative atrial arrhythmias during major elective noncardiac surgery, there is a three-fold increase in risk [13]. In our study, a history of arrhythmias was also associated with early postoperative arrhythmias, but the strength of association between a history of arrhythmias and post-operative arrhythmias was much higher in our study (see Table 2).

A history of arrhythmias and the occurrence of intra-operative arrhythmias were correlated (see Table 3). Although the occurrence of intra-operative arrhythmias was not proved in our study to be an independent risk factor for early postoperative arrhythmias, its interaction with a history of arrhythmia creates a new factor with a strong predictive ability. Recordings of intra-operative arrhythmias and a history of arrhythmias are two factors which, when present together, should be taken seriously by the anaesthesiologists. These patients should be more closely monitored in the early postoperative period so that the appropriate anti-arrhythmic treatments can be administered in a timely manner, if necessary.

In our study, the use of propofol for induction of general anaesthesia increased the risk of early post-operative arrhythmias. Propofol may influence myocardial repolarisation by blocking L-type calcium channels, and by decreasing sympathetic tone and increasing vagal tone [14]. Results of previous studies were not consistent regarding the possibility that propofol prolonged the QT-interval [15]. There are some case

Table 2. Crude and adjusted odds ratios for intra-operative arrhythmia risk factors.

Risk factors	Crude OR (95% CI)	Adjusted* OR (95% CI)
History of cardiac arrhythmias	15.77 (6.79, 36.64)	8.43 (2.67, 27.13)
History of ECG abnormalities	7.44 (3.56, 15.54)	1.54 (0.47, 5.03)
Type of intravenous anaesthetic (propofol vs. thiopental)	2.92 (1.47, 5.79)	0.34 (0.12, 0.96)
Hydroxyethyl starch solution administered	3.14 (1.22, 8.04)	2.44 (0.02, 406.97)
Chronic use of loop diuretics	5.18 (1.90, 14.16)	1.45 (0.30, 7.10)
Chronic use of digoxin	4.06 (1.33, 12.41)	0.79 (0.11, 5.57)
Chronic use of aminophylline	109.20 (0.20, 56670.27)	541.83 (0.00, >10.000)
Total dose of hydroxyethyl starch solution (ml/kg)	1.14 (1.00, 1.29)	0.91 (0.47, 1.78)
Serum level of total cholesterol (mM/l)	0.72 (0.54, 0.95)	0.75 (0.52, 1.11)
Intra-operative arrhythmia	7.61 (1.81, 32.02)	4.34 (0.78, 24.26)

*Adjusted for age†, sex†, type of intravenous anaesthetic, administration of hydroxyethyl starch solution, total dose of hydroxyethyl starch solution, history of cardiac arrhythmias in the last 5 years, use of loop diuretics, use of aminophylline, use of digoxin, history of an abnormal ECG anytime in the last 5 years, serum cholesterol level and intra-operative arrhythmias.
†Crude and Adjusted odds ratios are not shown in the table for the sake of clarity.
OR = odds ratio

Table 2. Interaction between a history of cardiac arrhythmias in the last 5 years and a history of abnormal ECG anytime in the last 5 years, or the chronic use of loop diuretics, or the type of intravenous anaesthetic, or the chronic use of digoxin.

	Crude odds ratio (95% CI)	Adjusted* odds ratio (95% CI)
No history of cardiac arrhythmias	1.0 (reference)	1.0 (reference)
History of cardiac arrhythmias only	**15.77 (6.79, 36.64)**	**8.42 (2.67, 27.13)**
Type of intravenous anaesthetic (propofol vs. thiopental)	2.92 (1.47, 5.79)	0.34 (0.12, 0.96)
History of both cardiac arrhythmias and type of intravenous anaesthetic	4.16 (2.45, 7.06)	**2.67 (1.40, 5.05)**
Chronic use of loop diuretics only	5.18 (1.90, 14.16)	1.45 (0.30, 7.10)
Both a history of cardiac arrhythmias and chronic use of loop diuretics	29.99 (3.82, 235.63)	11,94 (0.98, 146.05)
Chronic use of digoxin only	4.06 (1.33, 12.41)	0.79 (0.11, 5.57)
Both a history of cardiac arrhythmias and chronic use of digoxin	13.44 (2.91, 62.21)	3.81 (0.54, 26.87)
Intra-operative arrhythmias only	7.61 (1.81, 32.02)	4.34 (0.78, 24.26)
Both a history of cardiac arrhythmias and intra-operative arrhythmias	17.74 (7.34, 42.90)	**10.58 (3.03, 36.92)**

*Adjusted for age, sex, type of intravenous anaesthetic, administration of hydroxyethyl starch solution, total dose of hydroxyethyl starch solution, history of cardiac arrhythmias in the last 5 years, use of loop diuretics, use of aminophylline, use of digoxin, history of abnormal ECG anytime in the last 5 years, serum cholesterol level and intra-operative arrhythmias.

reports and observational studies in which it was proposed that propofol may cause intra-operative arrhythmias in conjunction with other acquired or hereditary pro-arrhythmic factors [16,17,18]. However, in our study, propofol was used only for the induction of anaesthesia. Taking into account its short elimination half-life (1-3 hours), early post-operative arrhythmias probably were not caused by the direct action of propofol on myocardial cells. The association of propofol and early post-operative arrhythmias might rather explain intra-operative arrhythmias recorded in our patients, which were associated with both propofol and early post-operative arrhythmias. Although we may not know what directly causes early post-operative arrhythmias, in order to avoid them, general anaesthesia induction should be completed with an alternative intravenous anaesthetic, other than propofol.

The chances of early post-operative arrhythmias after noncardiothoracic surgery could be minimizsed by carefully assessing risk factors and avoiding pro-arrhythmogenic drugs during anaesthesia, and consequently providing high-quality patient care.

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COST-EFFECTIVENESS ANALYSIS OF PERCUTANEOUS CORONARY INTERVENTION VERSUS THROMBOLYTIC THERAPY IN PATIENTS WITH AN ST-ELEVATED MYOCARDIAL INFARCTION

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ANALIZA ODNOSA TROŠKOVA/KLINIČKE EFIKASNOSTI PERKUTANE KORONARNE INTERVENCIJE I PRIMENE TROMBOLITIKA KOD PACIJENATA SA AKUTNIM INFARKTOM MIOKARDA SA ST ELEVACIJOM

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ABSTRACT

Background/aim: *An acute myocardial infarction is a life-threating condition that requires urgent hospitalisation and medical treatment. An ST-elevated myocardial infarction indicates a much larger degree of myocardial necrosis and should be treated with reperfusion strategies, such as percutaneous coronary intervention or thrombolytic therapy. The aim of the study was to economically evaluate these treatment methods and determine of their cost effectiveness.*

Methods*: A Markov model was developed using the TreeAge® software and was based on data of effectiveness and local Serbia cost calculations in the literature. The duration of one cycle was one year, and the time horizon was set to 40 cycles, i.e., 40 years. The costs and outcomes were discounted by 3% annually. A Monte Carlo simulation was performed with 1000 virtual patients, as well as a sensitivity analysis, represented by a Tornado diagram, in which the values were varied by ±50%.*

Results: *Percutaneous coronary intervention is not a cost-effective treatment for ST-elevated myocardial infarctions. Treatment with thrombolytic therapy, i.e., streptokinase, had a better cost-effectiveness ratio given that PCI is two times more expensive per one quality adjusted life year gained, 76558 , 11 rsd/QALY for PCI vs. 37263 rsd/QALY for thrombolytic therapy. Even after parameters varying by*

SAŽETAK

Uvod/cilj: *Akutni infarkt miokarda je životno ugrožavajuće stanje koje zahteva urgentnu hospitalizaciju i adekvatnu medikamentnu terapiju. Ukoliko postoji elevacija ST segmenta koja ukazuje na nekrozu čitave debljine zida miokarda, najčešće je potrebna hitna revaskularizacija, bilo u vidu primene trombolitika ili perkutane koronarne intervencije. Cilj ove studije je bio upoređenje ove dve metode lečenja sa farmakoekonomskog aspekta, odnosno upoređenje odnosa troškova/kliničke efikasnosti primene trombolitika i perkutane koronarne intervencije.*

Metod: *Za potrebe ove farmakoekonomske analize urađeno je modeliranje u TreeAge® softveru, bazirano na podacima iz literature o efikasnosti i izračunavajući troškove lečenja u Republici Srbiji. Trajanje jednog ciklusa je godinu dana, dok je vremenski horizont podešen na 40 ciklusa, tj.40 godina. Urađena je Monte Karlo simulacija sa 1000 virtuelnih pacijenata, kao i analiza senzitivnosti, predstavljena tornado dijagramom,u kojoj su vrednosti parametara varirane za ±50%.*

Rezultati: *Primena perkutane koronarne intervencije u lečenju akutnog infarkta miokarda sa ST elevacijom se pokazala kao neisplativa, sa lošijim odnosom troškova/kliničke efikasnosti od primene trombolitika, odnosno streptokinaze. Ova metoda lečenja je oko dva puta skuplja po dobijenoj godini života korigovanoj za kvalitet od trombolitika (76558,11 rsd /QALY za perkutanu koronarnu intervenciju naspram 37263 rsd/QALY za primenu trombolitika). Variranjem vred-*

ABBREVIATIONS:

RSD- Republic of Serbia dinars
QALY- Quality-Adjusted Life Years
PCI- Percutaneous Coronary Intervention
USA- United States of America
SIGN- Scottish Intercollegiate Guidelines Network
ICER- Incremental Cost-Effectiveness Ratio
CABG -Coronary Artery Bypass Graft

SKRAĆENICE:

RSD- dinar Republike Srbije;
QALY- godine života korigovane za kvalitet;
PCI- perkutana koronarna intervencija;
USA- Sjedinjene Američke Države;
SIGN- Škotske nacionalne smernice lečenja;
ICER- Odnos inkrementalnih troškova i inkrementalne efikasnosti;
CABG- Koronarni arterijski bajpas graft.

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±50%, PCI did not become an economically viable treatment with positive net benefits.

Conclusion: *Our results indicated that acute myocardial infarctions with ST elevations should be treated with thrombolytic therapy because of its higher clinical effectiveness and lower costs. The aim of the further analyses should identify the patients with acute myocardial infarctions in Serbia whose condition would economically justify the use of PCI.*

Keywords: *acute myocardial infarction, percutaneous coronary intervention, thrombolytics, cost-effectiveness analysis.*

nosti troškova i kliničke efikasnosti stanja za ±50% , perkutana koronarna intervencija nije dobila na isplativosti.

Zaključak: *Naša studija je pokazala da je u farmakoekonomskom smislu povoljnija primena trombolitika u lečenju infarkta miokarda sa ST elevacijom, usled veće efikasnosti i manjih troškova. Dalja istraživanja su usmerena ka selektiranju pacijenata kod kojih bi primena perkutane koronarne intervecije bila ekonomski isplativa.*

Ključne reči: *Akutni infarkt miokarda, perkutana koronarna intervencija, trombolitici, analiza odnosa troškova/kliničke efikasnosti.*

INTRODUCTION

Currently, one of the main causes of mortality and morbidity in industrial countries is ischemic heart disease. More than 800 thousand people in the world suffer from this problem. For most of them, ischemic heart disease progresses to severe acute unstable coronary syndrome with a large degree of necrosis of myocardial tissue, i.e., an acute myocardial infarction. In the US, over 3 million people annually survive myocardial infarctions.[1] These outcomes are similar in Serbia, where the incidence of ischemic heart disease in 2009 was 643,81 per 100 000 people and 712,27 per 100 000 people in the Sumadija region. [2] According to data available from the Republic Institute of Public Health website, 16 805 people had myocardial infarctions, of which 5016 died in 2007.[3] The latest information indicates that the mortality rate from myocardial infarctions is 5,9% in the 0-75 year age group and 8,2% in the 20-64 year age group. [2]

The World Health Organization has noted that a myocardial infarction is a life-threatening condition that affects a patient's quality of life. This fact is confirmed by high rates of mortality, despite new therapeutic approaches for the treatment of this condition. Studies have shown that 30-50% of patients die within the first two hours after symptoms of a myocardial infarction appeared. The administration of adequate therapy, i.e., thrombolytic therapy or coronary intervention with adjuvant drugs (glycoprotein IIb/IIIa inhibitors), can reduce the mortality of myocardial infarctions. In fact, after creating coronary care units, performing coronary interventions and administrating appropriate therapy (thrombolytics), the early mortality rate has decreased to 6-7%.[1]

An acute myocardial infarction is an urgent condition that requires hospitalisation in an intensive care unit. Thus, costs can be divided in four main categories: the cost of hospitalisation, the cost of appropriate pharmacotherapy, the cost of the revascularisation method and the cost of possible compli-

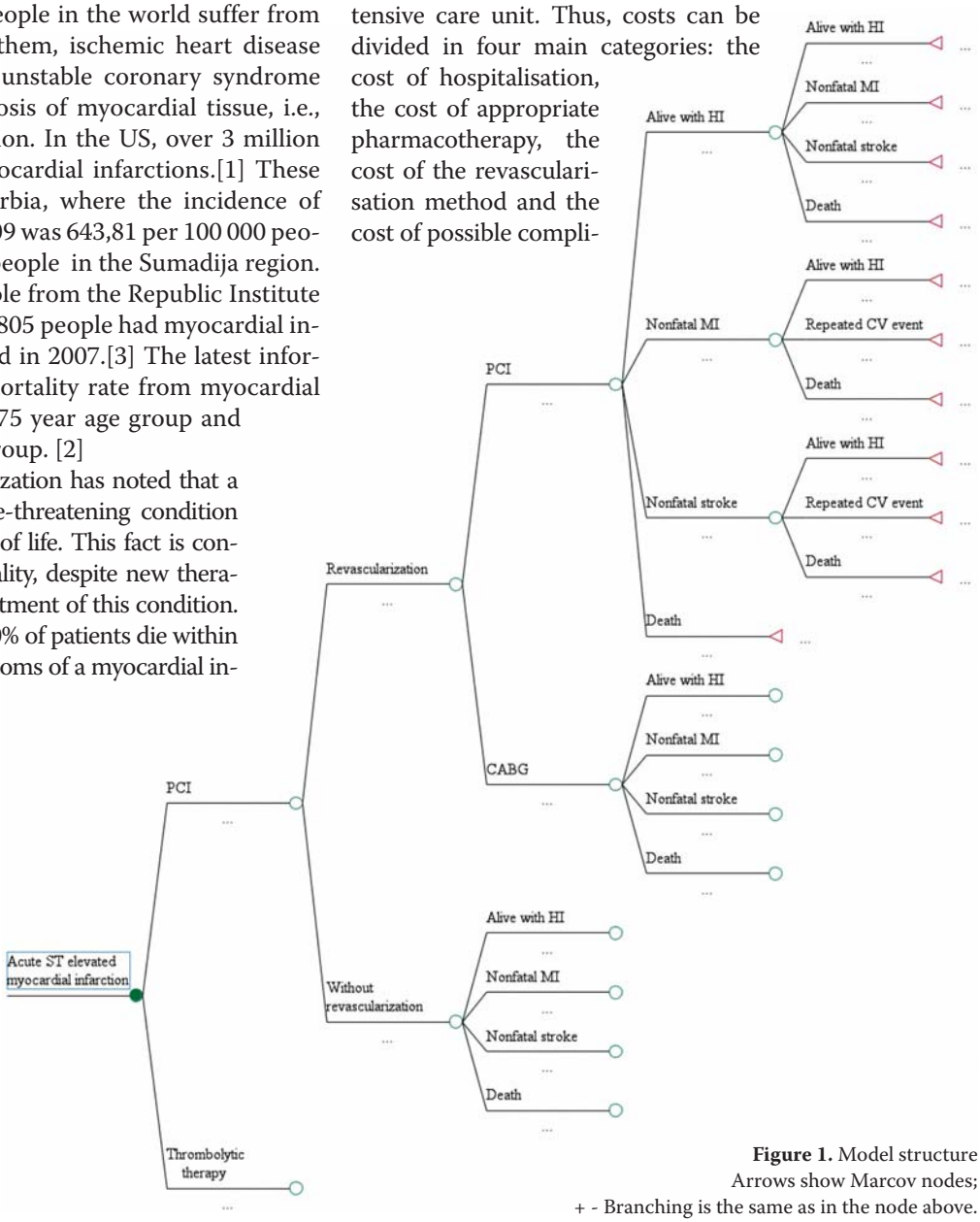

Figure 1. Model structure
Arrows show Marcov nodes;
+ - Branching is the same as in the node above.

cations.[4] The aim of this research was to determine the cost-effectiveness ratios of two revascularisation methods used in the treatment of acute myocardial infarctions: percutaneous coronary intervention and thrombolytic therapy.

MATERIAL AND METHODS

For the purpose of our study, we developed a Markov model using the TreeAge Pro® software [5] to compare the cost-effectiveness ratios of two therapeutic strategies used in acute ST-elevated myocardial infarctions. These strategies include percutaneous coronary intervention and intravenous administration of a thrombolytic drug or, for this study, streptokinase. The model was designed according to the model used in the study by Vegrel, Palmer, Asseburg et al. [6] In our analysis, we divided the patients with myocardial infarctions into four health states: alive with heart insufficiency, nonfatal myocardial infarction, nonfatal stroke and death. All health states could transition to other states or to death. The necessary data for the probabilities and the clinical effectiveness were taken from Vergel, Palmer, Asseburg et al. [6] and other valid clinical trials.[7,8] Data are shown in Table 1, and the model structure is presented in Figure 1.

The duration of one cycle in the model was set to one year. The time horizon was 40 cycles or 40 years. The study involved analyszinged the direct costs, such as hospitalisation expenses, and the health-state treatment costs determined using the SIGN (Scottish Intercollegiate Guidelines Network) guidelines for the treatment of myocardial infarction [9], stroke [10] and heart insufficiency [11]. The prices of health services and drugs were taken from the Republic Institute for Health Insurance Tariff Book.[12] Costs were expressed in 2011 Serbian dinars (RSD). The health states' clinical effectiveness were determined from the model and expressed in quality-adjusted life years (QALY). The incremental costs and incremental effectiveness were discounted by 3% annually. The final result of the study was obtained by comparing the cost-effectiveness ratios of percutaneous coronary intervention with thrombolytic therapy, expressed in RSD per QALY. Monte Carlo simulations with 1000 virtual patients were performed where cohorts of patient passed through all hypothetical scenarios. A two-way sensitivity analysis was performed (±50% of baseline values of a variable) to validate the model results; its outcomes are shown in a Tornado diagram in Figure 4. The annual willingness to pay was set to 1 500 000 RSD.

Table 1. Values of probabilities and clinical effectiveness of the health states used in the model

Parameter	Value	Reference
Probability of health states after PCI		
Alive with HI	0,13	[5]
Nonfatal myocardial infarction	0,25	[5]
Nonfatal stroke	0,21	[5]
Death	0,41	[5]
Revascularisation	0,89	[6]
Probability of health states after thrombolytic therapy		
Alive with HI	0,85	[5]
Nonfatal myocardial infarction	0,06	[5]
Nonfatal stroke	0,02	[5]
Death	0,07	[5]
Revascularisation	0,32	[7]
Annual transient probability		
Alive with HI to Alive with HI in the first year	0,844; 0,653; 0,702	[5]
Alive with HI to Alive with HI in the second+ year	0,914; 0,865; 0,914	[5]
Alive with HI to Nonfatal CV event in the first year	0,059	[5]
Alive with HI to Nonfatal CV event in the second+ year	0,027	[5]
Alive with HI to Death in the first year	0,038	[5]
Alive with HI to Death in the second+ year	0,032	[5]
Nonfatal CV event to Death in the first year	0,26	[5]
Nonfatal CV event to Death in the second+ year	0,048	[5]
Nonfatal MI to Nonfatal CV event	0,087	[5]
Nonfatal stroke to Nonfatal CV event	0,038	[5]
Probability of revascularisation		
Repeated PCI after primary PCI	0,5	[5]
CABG after primary PCI	0,5	[5]
PCI after thrombolytic therapy	0,8	[5]
CABG after thrombolytic therapy	0,2	[5]
Clinical effectiveness of health states		
Alive with HI in the first year	0,701	[5]
Alive with HI in the second+ year	0,683	[5]
Nonfatal myocardial infarction in the first year	0,683	[5]
Nonfatal myocardial infarction in the second+ year	0,718	[5]
Nonfatal stroke in the first+ year	0,612	[5]

PCI- percutaneous coronary intervention;
HI- heart insufficiency;
CV- cardiovascular;
MI- myocardial infarction;
CABG- coronary artery bypass graft.

RESULTS

The results of the cost-effectiveness analysis showed that thrombolytic therapy in the treatment of acute ST-elevated myocardial infarction had a better cost-effectiveness ratio, 276491,52± 139130,86 rsd for 7,42 ±6,12 QALYs (37263 rsd per QALY), compared towith percutaneous coronary intervention, 418007,29±158819,19 rsd for 5,46±7,43 QALYs (76558,11 rsd per QALY). Therefore, percutaneous coronary intervention was considered not to be cost effective assince it was two times more expensive per one QALY than thrombolytic therapy. The Monte Carlo simulation output is shown in Table 2.

Table 2. Results of the Monte Carlo simulation

	Percutaneous coronary intervention				Thrombolytic therapy			
	Mean ±SD	Minimum	Median	Maximum	Mean ±SD	Minimum	Median	Maximum
Cost (rsd)	407685,01± 158819,19	206706,39	360111,58	832951,99	272085± 139130,86	59132,85	253858,16	626066,25
Clinical effectiveness (QALY)	5,17±7,43	0	0	25,12	7,14±6,12	0	6,34	15,73
ICER	-72201,92*				/ **			

SD- standard deviation;rsd- Republic of Serbia dinars; QALY- quality-adjusted life years; *- PCI is considered as the alternative therapeutic method; **- thrombolytic therapy is used as the standard therapeutic method.

The difference in costs between these two therapeutic methods is high, mostly because of the high initial cost. More than 30% of the percutaneous coronary intervention costs are related to the intervention itself and adjuvant therapy (glycoprotein IIb/IIIa inhibitors). However, the high initial costs in thrombolytic therapy were related to the price of the thrombolytic drug or, in our case, streptokinase. The difference in clinical effectiveness was not as high as expected, according to the data from other pharmaco-economic studies. In our study, the difference was 1,96 QALYs (7,42 QALYs for thrombolytic therapy versus 5,46 QALYs for PCI). The distribution of incremental cost-effectiveness ratios (ICER) for these two treatment approaches for ST-elevated myocardial infarctions is shown in Figures 2 and 3.

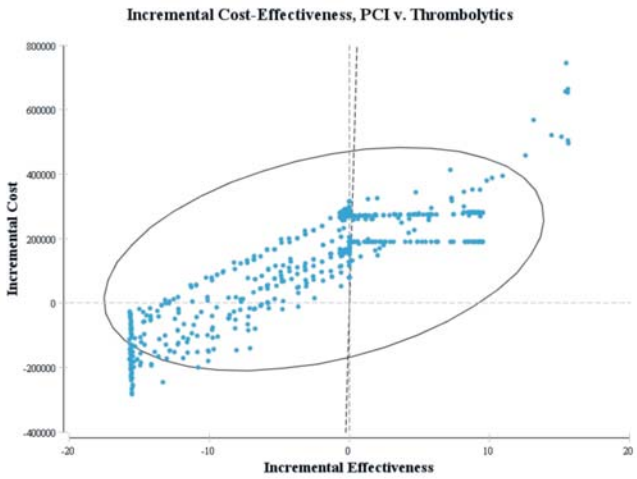

Figure 2. ICE Scatterplot of PCI vs. Thrombolytics

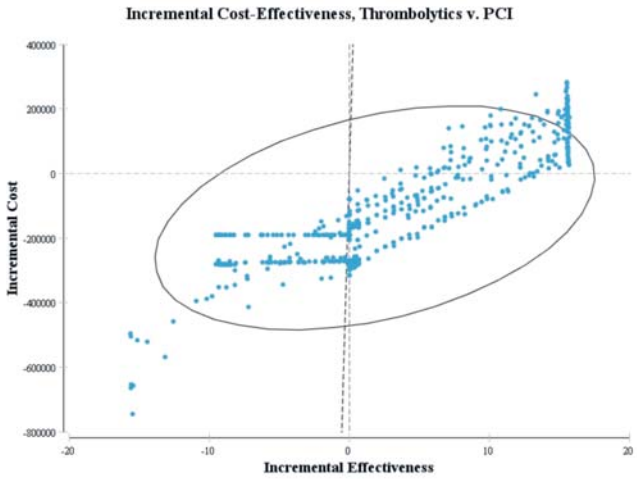

Figure 3. ICE Scatterplot of Thrombolytics vs. PCI

For therapeutic options, the PCI-calculated ICERs for the majority of virtual patients are found in quadrant II, as shown at the scatterplots (Figure 2). This finding explains why coronary intervention is not cost effective. Coronary intervention has a low effectiveness and high cost, which is categorised as the worst treatment scenario economically. Because this therapy is above the willingness-to-pay threshold, it should be rejected as a therapeutic method. However, the thrombolytic therapy ICERs are mostly found in quadrant IV, where the effectiveness is high and costs are low. Because they are below the willingness-to-pay threshold, thrombolytics should be accepted as the therapeutic choice for myocardial infarctions.

A sensitivity analysis has shown that the initial costs of the primary PCI and repeated revascularisations are the most influential parameters. This finding confirms that the largest share of PCI costs are directed toward the intervention and the potential need for revascularisation. The negative net benefit suggests that the costs of PCI exceed the intervention's effectiveness. Even after varying parameters by ±50%, percutaneous coronary intervention did not become economically viable with positive net benefits.

DISCUSSION

The results of this study indicate that percutaneous coronary intervention is not as cost effective as thrombolytic therapy, i.e., streptokinase, for the treatment of ST-elevated acute myocardial infarctions. Some authors have reported that coronary intervention has a better cost-effectiveness ratio than thrombolytic therapy . [6] However, in our research, coronary intervention is more expensive but more effective, 7,12 QALY's as compared with 6,83 QALY's for thrombolytic therapy. The difference in gained quality adjusted life years in our study, 1,96 QALYs, favours thrombolytic therapy . Regarding cost, percutaneous coronary intervention is two times more expensive than

thrombolytic therapy per one QALY gained. Our results were compared with other valid studies that analysed the cost effectiveness of these two treatment methods. In one study, the cost effectiveness of coronary interventions related to thethe time delay of the procedure was investigated.[6] If the time delay was 30 minutes or less, coronary intervention was cost effective and had a lower mortality and incidence of re-infarction. But with an increased delay (30-90 minutes), coronary intervention had a seven times higher cost-effectiveness ratio, which did not justify the intervention.[6] Time delay was no't investigated in our study, which is a study limitation. A valid systematic review article also has demonstrated the economic viability and clinical effectiveness of percutaneous coronary intervention. [13] With small statistically significant differences in the costs and the important differences in clinical effectiveness, coronary intervention had an incremental cost-effectiveness ratio between 268£ and 29093£ per QALY, depending on the length of hospitalisation, thrombolytic price and the location requiring "life-saving PCI" after primary thrombolytic therapy.[13] In our model, we also included the percentage of patients who required repeat revascularisations (CABG or repeat PCI), thus increasing costs. Most studies had a short time horizon, mostly up to six months, without examining the possible economic effects of rehospitaliszation, health consequences and their treatments. Long-term benefits of PCI and thrombolytic therapy were investigated in one study for a period of 5±2 years.[14] During this period, didboth the costs of PCI andincrease, its clinical effectiveness increased, which confirms the economic superiority of PCI.[14] Repeated revascularisation is a very important factor, with a significant influence on the results of the analysis.

Several studies have demonstrated that frequent revascularisations among patients treated with primary PCI or thrombolytic therapy. In one study, 16,9% of patients older than 65 years required one or more revascularisation during the one-year follow-up period. Each revascularisation costs more than $19000, which, increases ethe cost by five times.[15] Our study partially included the possible complications of PCI, including the followingany major cardiovascular and cerebrovascular event (death, myocardial infarction, urgent revascularisation, stroke) and haemorrhages. The treatment of complications comprised 25,7% of all direct costs of coronary interventions. Bleeding complications were not included in our research, although they appear in 7,9% of patients and can increase costs.[16]

Numerous studies have investigated the clinical effectiveness of PCI as compared with thrombolytic therapy. [17,18,19,20,21] These studies expressed the clinical effectiveness as a reduction of mortality rate and re-infarction or stroke frequency. The results of most studies demonstrated that PCI had an increased clinical effectiveness, but the result of some studies who do not agree with this finding .[22,23] The limitation of these studies is the short follow-up period of 30 days, in contrast to our time horizon of 40 years. This longer time period may explain our

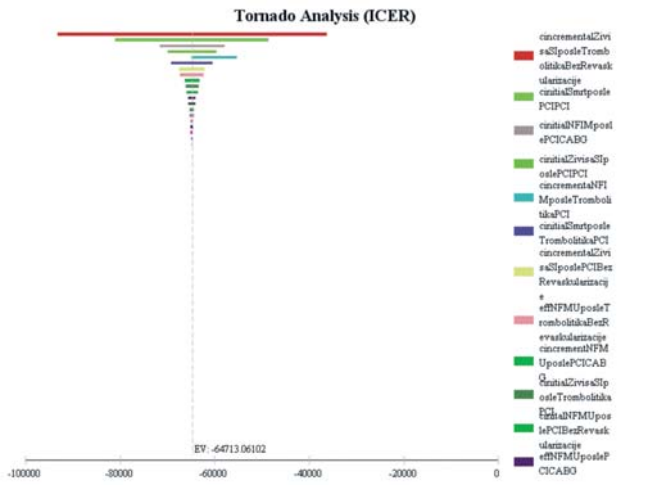

Figure 4. The multiple univariate analysis presented as a Tornado diagram

different results of a lower clinical effectiveness of PCI compared with thrombolytic therapy.

The results of our study can be explained by the health system in Republic of Serbia and the low drug prices compared with the high price of coronary interventions. The study limitations mentioned above also justify our cost-effectiveness results. Similar results have been found in studies conducted in countries with well-organiszed health systems, such as England and Sweden. [23,24]

CONCLUSION

Our study suggests that percutaneous coronary intervention is not a cost-effective option for the treatment of myocardial infarction with ST elevations. Thrombolytic therapy with streptokinase has a higher clinic effectiveness and lower costs. Further research should be conducted to define the group of patients with acute myocardial infarction in Serbia whose condition economically justifies the use of percutaneous coronary intervention.

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ATTITUDES TOWARDS ANTIPSYCHOTIC DRUGS AND THEIR SIDE EFFECTS: A COMPARISON BETWEEN STUDENTS OF MEDICINE IN SPAIN AND SERBIA

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POREĐENJE STAVOVA STUDENATA MEDICINE ŠPANIJE I SRBIJE PREMA ANTIPSIHOTICIMA I NJIHOVIM NEŽELJENIM EFEKTIMA

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ABSTRACT

Background. *The appropriate use of antipsychotics by general practitioners is correlated with a positive attitude towards this group of drugs during their undergraduate studies.*

Objective. *The aim of our study was to investigate and compare the attitudes of medical students in Spain and Serbia wards about the effectiveness and adverse effects of antipsychotic medications.*

Methods. *In a cross-sectional study, 60 final-year medical students from Spain and Serbia were exposed to a case of a patient treated with antipsychotics who was experiencing side effects. A Likert-type questionnaire was then given to the students, capturing their attitudes towards antipsychotics.*

Results. *Compared to the Spanish peers, the students from Serbia were more eager to use antipsychotics as a means of protecting the patients' families than forto help the patients themselves. The majority of the Serbian students thought that psychotic patients were supposed to tolerate the side effects of their medications, while the Spanish students were ready to change their treatment. The Serbian students were older than their Spanish peers, mostly males and Orthodox .*

Conclusions. *Additional educational efforts are needed to improve the attitudes of older and more religious students, but these efforts will pay off in the future with more appropriate drug treatment of schizophrenic patients and improved patient adherence to the treatment.*

Key Words: *Antipsychotics; medical students; attitude; education.*

SAŽETAK

Uvod. *Adekvatno propisivanje antipsihotika od strane lekara opšte prakse u korelaciji je sa njihovim pozitivnim stavom o ovoj grupi lekova stečenim u toku osnovnih akademskih studija medicine.*

Cilj. Ispitati *i uporediti stavove studenata medicine iz Španije i Srbije o terapijskoj efikasnosti i neželjenim efektima antipsihotika.*

Metode. *U ovoj studiji preseka, 60 studenata završne godine medicine iz Španije i Srbije primarno je upoznato sa slučajem pacijenta kome je indikovana terapija karakterističnim antipsihotikom uz razvoj određenih pratećih nuspojava. Učesnici u istraživanju su potom, u cilju procene njihovog stava prema antipsihoticima, popunjavali upitnik Lickert tipa.*

Rezultati. *U poređenju sa španskim "vršnjacima", studenti iz Srbije bili su više naklonjeni antipsihoticima kao sredstvu zaštite porodice pacijenta nego kao vidu medikamentozne pomoći samim pacijentima. Većina studenata iz Srbije je smatrala da bi psihotični pacijenti trebalo da tolerišu eventualna manifestna neželjena dejstva lekova iz pomenute grupe, dok španski studenti, u takvim slučajevima bi preferirali promenu terapijskog tretmana. Srpski studenti završne godine bili su stariji od španskih kolega, uglavnom muškog pola i Pravoslavne veroispovesti.*

Zaključak. *Potrebni su dodatni obrazovni napori kako bi se unapredili stavovi starijih i religioznijih studenata i koji bi se u budućnosti isplatili adakvatnim terapijskim izborom kod psihotičnih pacijenata i njihovom povećanom adherencom na indikovani medikamentozni tretman.*

Ključne reči: *Antipsihotici; studenati medicine, stav, obrazovanje.*

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INTRODUCTION

Attitudes towards antipsychotic medications are very important for achieving success in the treatment of patients with schizophrenia (1). Positive attitudes of prescribing physicians and good doctor-patient communication and relationships can improve patient compliance with prescribed medications and tolerance of their side effects (2,3). Because the attitudes of general practitioners towards diseases and treatments are mostly formed during their undergraduate studies (4), creating positive attitudes among medical students is an important challenge for medical educators. Potentially successful programs should consider the numerous factors that may influence attitude, including religion and national and local culture (5).

There are several studies in different countries that have reported mostly negative attitudes of medical students towards schizophrenia (6,7,8). One recent cross-cultural study demonstrated a significant influence of religion on the attitudes of medical students towards schizophrenia (9). However, we are not aware of any published studies dealing with the attitudes of medical students towards the effectiveness and adverse effects of antipsychotic medications, although this is an important aspect of a schizophrenic patient's life. The attitudes towards antipsychotic medications may influence thethe students' overall attitudes towards these patients. The aim of our study was to investigate and compare the attitudes of medical students in Spain and Serbia wards about the effectiveness and adverse effects of antipsychotic medications.

MATERIALS AND METHODS

Study population

The study population consisted of final-year students of medicine from the Medical Faculties in Madrid (Spain) and Kragujevac (Serbia) who were studying during the winter semester of the 2010-2011 school year. The students in both Medical Faculties had completed their lessons on psychiatry. Out of 300 students from Barcelona and 195 students from Kragujevac, two samples of 30 students each were chosen according to the convenience of the investigators.

Study protocol

After being approached by the investigators and presented with the purpose of the study, the students were given the following case of a patient receiving antipsychotics to read: "Male patient B.N. of Caucasian origin, 35 years old, has been suffering from schizophrenia for more than 5 years. For the last three years, the signs and symptoms of his disease have been well controlled by one antipsychotic drug, fluphenazine 5 mg daily, orally. However, the patient has several side effects from this medication. He is constantly tired, sweats heavily, and he has to consume large amounts of water with meals due to a dry mouth. His body mass index is now 27, and it anis continuing to increase. He has become impotent and has lost any interest for the leisure and sport activities that were his main preoccupation before he started taking the medication. His hands shake during both rest and activity, and he frequently puckers and purses his lips involuntarily. He also has a feeling of unrest. In spite of all these side effects, the patient is consistently taking his medication every day". As soon as the students read the case, the same investigators gave them a questionnaire, already used by Helbling and associates[1], which was composed of two parts. In the first part, there were 7 Likert-type questions that measured the attitudes of the students towards antipsychotic drugs. The second part listed the 10 adverse reactions experienced by the patient described in the case, giving the students an opportunity to express their opinions about how long the described patient should tolerate such reactions. The religious beliefs of the students were determined from their statements. The students' participation in the study was finished after completion of the questionnaire.

Study design

The study was set up as observational cross-sectional study, conducted on one occasion at two remote sites. Based on an expected difference of 36% in the attitudes of the students from Barcelona and Kragujevac, a probability of type I (alpha) error of 0.05 when using the Chi-squared test, and a power of 80%, the minimal sample size was calculated by G*Power3 software (10,11) to be 29 patients per group.

Statistics

For the continuous variables in each group, the mean and standard deviation were calculated. The differences between the means were tested by Student's T-test for small independent samples. The differences in frequencies of the dichotomous variables among the groups were tested for significance by the Chi-squared test (12). The probability of the null hypothesis was set to a value of 0.05. All calculations were made by the statistical software SPSS version 18.

CHARACTERISTIC	MADRID	KRAGUJEVAC	DIFFERENCE
Number of students	30	30	N/A
Age (± standard deviation)	23.3 ± 1.1	25.7 ± 1.1	T-test = 9.224, df =56, p=0.000
Sex (M/F)	7/23	18/12	χ^2=8.400, df=1, p=0.004
Religion (Catholic/Orthodox/atheist)	16/0/14	0/29/1	χ^2=52.231, df=2, p=0.000

Table 1. Characteristics of the study groups.

RESULTS

The baseline characteristics of the study groups are shown in Table 1. The study groups did not differ significantly in their attitudes towards the risk of dependency on antipsychotics (χ^2=3.527, df=2, p=0.171), benefit/risk ratio (χ^2=3.419, df=2, p=0.181), effectiveness (χ^2=1.967, df=2, p=0.374), safety (χ^2=5.426, df=2, p=0.066) or beneficial effect of antipsychotics on social functioning (χ^2=0.481, df=2, p=0.786). However, while 25 (83%) of the students from Spain agreed that antipsychotics are the most effective way to treat mental illness, only 13 (43%) of the students from Serbia shared the same attitude (χ^2=14.076, df=2, p=0.001). On the other hand, 21 (70%) of the students from Serbia thought that mentally ill people are only tolerable to their families due to antipsychotics, while only 2 (7%) of the students from Spain had the same opinion (χ^2=49.915, df=2, p=0.000).

The study groups did not differ significantly in their readiness to accept the following adverse reactions in patients taking antipsychotics: unpleasant dry mouth (χ^2=1.144, df=2, p=0.564), heavy sweating (χ^2=0.678, df=2, p=0.996), constant tiredness (χ^2=1.036, df=2, p=0.596), continuous feeling of unrest (χ^2=0.530, df=2, p=0.767), significant weight gain (χ^2=3.764, df=2, p=0.152) and visible movement disorder (χ^2=3.546, df=2, p=0.170). However, the students in Spain were significantly less ready to tolerate frequent sexual dysfunction (χ^2=9.866, df=2, p=0.007), continuous anhedonia (χ^2=14.901, df=2, p=0.001), risk of drug dependency (χ^2=7.533, df=2, p=0.023) and marked tremor (χ^2=14.346, df=2, p=0.001) (Figure 1).

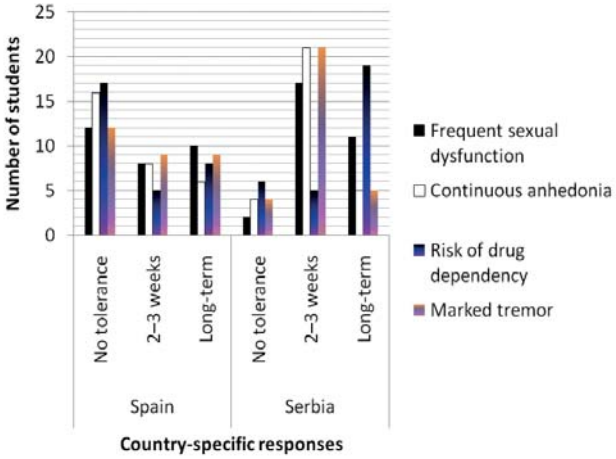

Figure 1. Differences between countries in attitudes towards the tolerability of antipsychotic medication adverse reactions.

DISCUSSION

This comparison of the attitudes of medical students from Spain and Serbia towards antipsychotics has shown important differences. The students from Serbia mostly saw antipsychotics as a means of protecting the patients' families rather than a means of helping the patients themselves. AlsoAdditionally, the majority of the Serbian students thought that psychotic patients were supposed to tolerate the side effects of their medications without complaint, while the Spanish students were ready to help to the virtual patient by changing something in his drug regimen. Behind these differences, there could be a hidden negative attitude towards psychotic patients among the majority of the Serbian students, making them believe that these patients should not be treated in the same way as patients suffering from physical illnesses.

The observed differences in attitudes could be associated with differences in age, sex orand religion. The Serbian students were mostly older, male and Orthodox. It has already been shown that cultural beliefs and religion have a stronger influence than experience in learning psychiatry on the attitudes of medical students and physicians towards psychotic patients (13,14). Older age of health workers is also a significant predictor of discriminating attitudes towards psychotic patients (15), but male sex is not associated with a negative view of the disease itself or antipsychotic drugs (16).

To make attitudes towards psychotic patients and their medications more rational among medical students, educators should pay special attention to the cultural beliefs of the students. Additional educational efforts are needed to improve the attitudes of older and more religious students, but these efforts will pay off in the future with more appropriate drug treatment of schizophrenic patients and increased patient adherence to the treatment.

Our study was limited by an unrepresentative sample and failure to account for other factors that may affect students' attitudes related to the usage of antipsychotics. Additionally, the degree of religiosity was not investigated. For these reasons, the results of this research should be considered only preliminary; new studies, with much larger sample sizes and a significantly larger number of studied parameters, are needed to provide a definitive conclusion.

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PAEDIATRIC ANTIPHOSPHOLIPID SYNDROME

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ABSTRACT

Antiphospholipid syndrome (APS) is a thrombotic disorder characterised by the association of arterial and venous thrombosis with antibodies directed against phospholipids. The onset of APS must occur before the patient's 18th birthday. Clinical manifestations were temporally correlated to the presence of antiphospholipid (aPL) antibodies if they occurred within 6 months. In contrast with adults, however, transient non-thrombocytogenic aPL antibodies are seen more commonly, usually after childhood infections. The presence of aPL antibodies, specifically aCL antibodies, was significantly associated with thrombotic events. Patients with childhood-onset APS presented with significantly more episodes of chorea and jugular vein thrombosis than adults. The aPL antibodies are tested by coagulation or immunologic assays. The presence of a prolonged prothrombin time in the setting of lupus anticoagulant (LA) may be a marker of paediatric systemic lupus erythematosus (SLE). This review highlights recent clinical advances in the field of APS in children.

Key words: *antiphospholipid syndrome, antiphospholipid antibodies, paediatrics*

In recent years, antiphospholipid (aPL) antibodies and their associated clinical features have been increasingly recognised in various autoimmune and non-autoimmune diseases. Antiphospholipid syndrome (APS) can occur in children, as in adults, with the same diverse spectrum of thrombotic sites. APS is the most common acquired state of hypercoagulation in both adults and children. A close association between aPL antibodies and recurrent arterial and/or venous thrombosis has been supported by several retrospective and prospective studies, and it appears that aPL antibodies have a direct role in the pathogenesis of the thrombophilic state of APS (1-3). Recurrent thrombotic events seem less frequent than in adults (4,5). The most common presentation in the paediatric population is stroke. Stroke in children is significantly less common than stroke in adults. Childhood stroke is uncommon but is an important cause of mortality and morbidity in children. The most common cause of ischaemic stroke in children is thrombotic vessel occlusion. Whereas APS in adults has been well characterised, only a few studies of children with APS have been reported (6). Paediatric patients with APS constitute a sufficient sample to investigate the relationship between aPL antibodies and the associated clinical manifestations, such as thrombocytopenia, haemolytic anaemia, chorea, livedo reticularis, and the specificities of aPL antibodies that are linked to thrombosis. The recently revised criteria for the diagnosis of APS in adults are currently used for paediatric patients, but there is no confirmation of these criteria for children (7).

Several tests for aPL antibodies are available. However, the prolonged activated partial thromboplastin time test has a low sensitivity; kaolin clotting time is too complicated to assay; andbut dRVVT (Russell viper venom time) is very sensitive and is currently the preferred test for lupus anticoagulant (LA) detection. Other tests for measuring aPL antibodies are immunological, namely the enzyme-linked immunosorbent assay, which detects different isotypes of antibodies to many other phospholipids (phosphatidylserine, phosphatidylinositol, phosphatidylcholine). Their specificity increases with the titer and the aCL IgG antibody is more specific than aCL IgM. Another group of antibodies is directed against protein co-factors

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that bind the phospholipids, such as beta-2 glycoprotein-I (β2GPI) and annexin. It is important to use more than one test to detect them . The detection of persistently elevated levels of aPL antibodies is a requisite laboratory feature for the diagnosis (8,9).

The laboratory criteria include : a positive LA test, the presence of medium or high titre aCL antibodies, or anti-β2GPI IgG and IgM antibodies, on two occasions at least 12 weeks apart, or the presence of at least one type of autoantibody, known as an aPL antibody, in the plasma. Low titer aCL antibodies and anti-β2GPI antibodies have been reported in 11% and 7% of healthy children, respectively (10).

Serum levels of aCL IgA antibodies are lower in children than in adults, whereas the highest levels of anti-β2GPI IgG antibodies were found in preschool children (11,12).

Persistent aPL antibodies are associated with an increased risk of arterial thrombosis (mainly cerebrovascular events) (13).

The prevalence and levels of aPL antibodies in children with SLE are higher than in healthy controls, with aCL antibodies ranging from 27-57% and LA ranging from 16-29% (14,15). The presence of an aPL antibody was significantly associated with anti-double-stranded DNA antibodies but was not significantly associated with neuropsychiatric manifestations or thrombocytopaenia. The presence of an aCL antibody was significantly associated with haemolytic anaemia. A prolonged prothrombin time, in the setting of LA (all with a prolonged activated partial thromboplastin time), was associated with life-threatening disease. The presence of an aPL antibody, specifically an aCL antibody, was significantly associated with thrombotic events. The presence of a prolonged prothrombin time in the setting of LA may be a marker of a more serious disease in paediatric SLE. In paediatric SLE, aCL antibodies are frequently found, high levels of aCL IgG antibodies are often associated with central nervous system involvement, and aCL antibodies have a low predictive value in the development of vascular thrombosis (16).

With the exception of stroke, anti-β2GPI antibody detection does not improve identification of paediatric APS over that of traditional aPL assays. Anti-β2GPI antibodies are rare in paediatric primary APS, but may predict the evolution of chronic thrombocytopenia to SLE (17).

Deep vein thrombosis of the lower limbs is the most common thrombosis in paediatric APS patients. Arterial thrombosis is much more common in children than in adults (7).

A wide variety of central nervous system symptoms in APS has been described, including chorea, dementia, migraine, intracranial hypertension, neurocognitive deficits, psychosis, depression, epilepsy, Guillain-Barré syndrome, transverse myelopathy, and optical neuritis (18,19).

Cardiac disease is rare in children with APS. In a cohort of paediatric APS patients, thrombocytopenia and haemolytic anaemia were found in 10% of the patients. Livedo reticularis, the reticular cyanosis caused by vascular stasis of deep dermal vessels, is the most common skin manifestation of the syndrome, although it rarely appears in children. Renal and pulmonary involvement isare also rare in paediatric patients. In a cohort of 28 paediatric APS patients, the most common initial APS manifestations were venous thrombosis, stroke and thrombocytopaenia. Lupus anticoagulant was detected in almost all of the patients. Recurrent thrombotic events were less common in patients who received anticoagulant therapy. A high rate (45% of patients) of inherited thrombophilias was found in our series, implying that aPL antibodies may serve as a “second vascular hit” in children. Positive aPL antibody tests were observed in most infants and the clinical presentation consisted of arterial and venous thrombi in multiple localisations, which is similar to adult APS patients. In a cohort of children with APS, five patients presented with perinatal stroke (6).

In a review of 115 patients with catastrophic APS, only 3 were children. Rare cases of perinatal thrombosis in infants born to mothers with APS or aPL antibodies have been reported (20).

Antiphospholipid syndrome is an important cause of acquired thrombophilia. The presence of a prolonged prothrombin time in the setting of LA may be a marker of more serious disease in paediatric SLE. This syndrome is the most common cause of acquired thrombophilia and is and is associated with either venous or arterial thrombosis, or both. The prevalence of thrombophilia markers is increased in children with stroke compared with control subjects. Furthermore, factor V Leiden and aPL antibodies contribute significantly to stroke occurrence (13).

In APS, skin involvement is often the first sign (livedo reticularis, ulcerations, digital gangrene, subungueal splinter haemorrhages, superficial venous thrombosis, thrombocytopaenic purpura, pseudovasculitic manifestations, extensive cutaneous necrosis, and primary anetoderma) (21).

Neonatal APS is a rare clinical entity. It is characterised by neonatal thrombotic disease that is due to the transplacental passage of maternal aPL antibodies (22).

Data from paediatric APS studies have confirmed that APL antibody-related thrombi in children are frequently associated with multiple APL antibody positivity and the concomitant presence of inherited prothrombotic disorders. Comparisons between paediatric patients with primary APS and APS that is associated with an underlying autoimmune disease revealed several differences. Children with primary APS were significantly younger and had a higher frequency of arterial thrombotic events, particularly cerebrovascular ischaemic events. In contrast, children with APS that was associated with an underlying autoimmune disease were significantly older and had a significantly higher frequency of venous thrombotic events that were associated with haematologic and skin manifestations (23).

However, because of the high frequency of infectious processes in early life, children may have a greater prevalence of non-pathogenic and transient aPL antibodies. Due to the rarity of aPL antibody-related thrombosis in children, its natural history and optimal management can be determined only through large, multicentre, controlled studies (2).

We recommend that all children with idiopathic ischaemic stroke should be completely investigated and evaluated for aPL antibodies. Due to the rarity of APS in children, multicentre prospective studies are warranted.

CONCLUSION

Antiphospholipid syndrome is considered to be the most commonly acquired hypercoagulation state of autoimmune disorders in children. The clinical and laboratory characterisation of patients with paediatric APS imply several important differences between APS in paediatric and adult populations. Children with APS have frequently demonstrated associated nonthrombotic manifestations, particularly haematological, skin and neurological manifestations. APS in children occurs predominantly with deep vein thrombosis and stroke. SLE may develop in a significant percentage of girls presenting with APS . Antiphospholipid antibodies reflect the lower prothrombotic haemostatic state of childhood.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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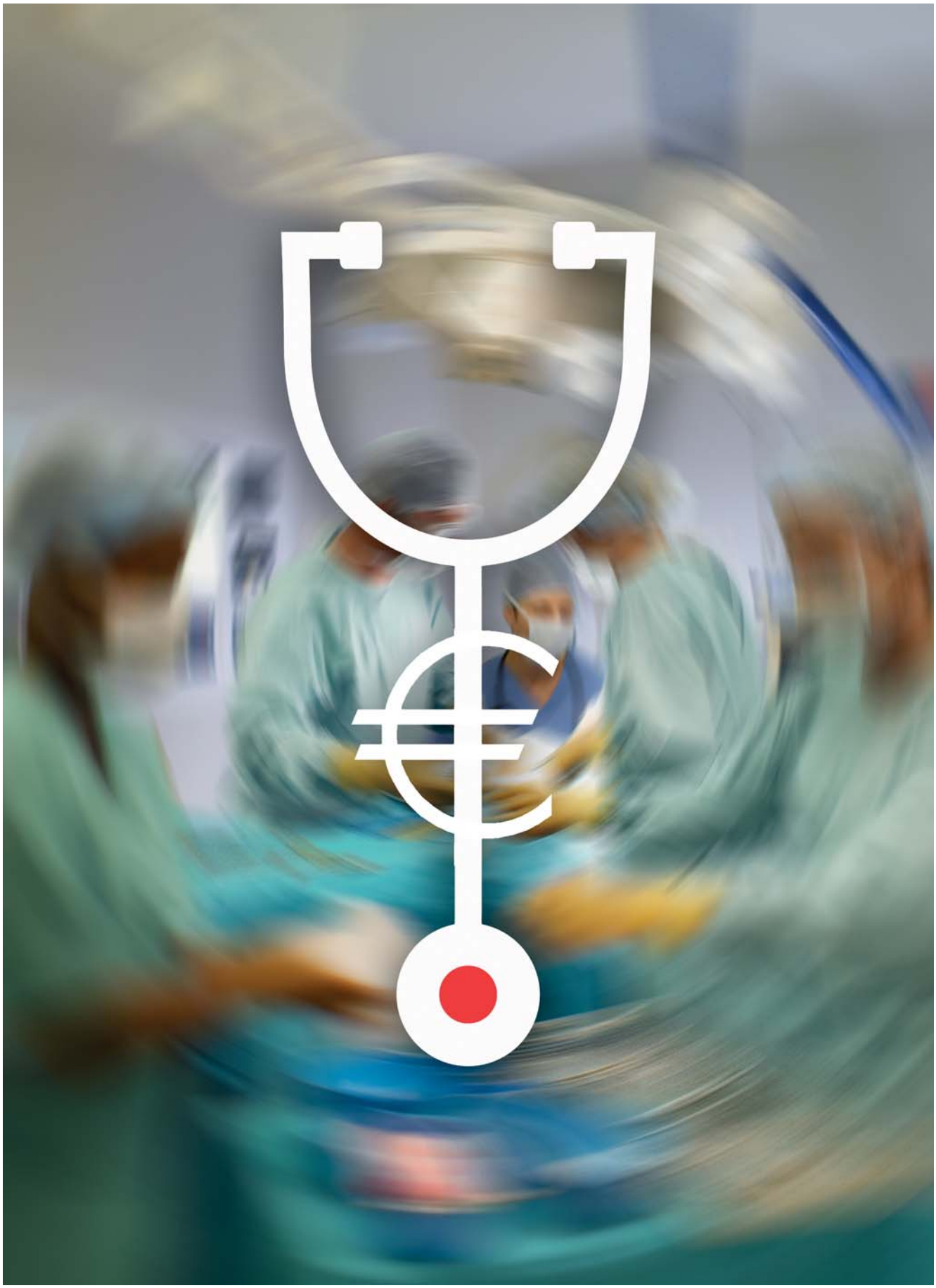

CURRENT EFFORTS AND PROPOSALS TO REDUCE HEALTHCARE COSTS IN SERBIA

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SADAŠNJI NAPORI I PREDLOZI ZA OGRANIČENJE TROŠKOVA ZDRAVSTVENE ZASTITE U REPUBLICI SRBIJI

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Ključne reči: *zdravstvena ekonomija, pozitivno zakonodavstvo, zdravstveni budžet, troškovi zdravstvene nege, Srbija*

FUNDING AND REIMBURSEMENT OF HEALTH CARE SERVICES IN SERBIA

During the past few decades, health care decision makers have become aware of rapidly increasing health care expenditures in most northern hemisphere economies. National drug agencies worldwide, headed by the developed pharmaceuticals market, have accepted economic health assessments, acquired through clinical trials, as necessary evidence for marketing new drug approvals.

The health system in Serbia is financed by one core fund, which consists primarily of compulsory medical insurance taxes on the employed population. Most inpatient care, which accounts for more than half of the expenditures, is provided by a contract between the Republic Health Insurance Institute and clinical facilities (1). According to purely economic criteria, most of the institutions responsible for providing public sector services in southeastern European middle-income economies show more than modest performance. The limited availability of reimbursement for various treatment options requires pharmacoeconomic evidence for decision making. The national Health Insurance Fund has created two boards for this purpose. The first board is the Central Experts Committee on Medicines, and the second board is the Pharmacoeconomics Committee. These boards decide on the inclusion of specific drugs in the positive reimbursement list based on evidence from foreign pharmacoeconomic assessments, mostly Cochrane reviews and NICE reports. The conclusions of these systematic reviews and meta-analyses of the comparative cost effectiveness of medicines are developed within the complex hierarchy of the United Kingdom's NHS. Unfortunately, these conclusions are usually not directly transferable to the clinical setting of the western Balkans. ICER's must be recalculated, and many equations must be adjusted. The main argument in favour of these adjustments is the substantially cheaper labour force, which is sufficient to move the assessment significantly in one direction. Another argument is the "willingness to pay" threshold. Its current value is assessed at €14,500 in Serbia and at €39,00 0 in Britain per life year gained.

The statements of the aforementioned committees can significantly impact the local drug pricing process. Recently, some tertiary care hospitals, particularly the hospital in the city of Kragujevac, have imposed a mandatory internal procedure when introducing new drugs. This formulary on drug acquisition criteria requires drug candidates to provide pharmacoeconomic justification and a budget impact analysis as an appropriate step forward.

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SEARCHING FOR LOCAL EVIDENCE - DOMESTIC RESEARCH EFFORTS IN PHARMACOECONOMICS

The main domestic sources of research and reliable local evidence are state-owned universities. A Thomson Reuters ISI report in July 2011 called Serbia as the dominant country among countries considered "rising stars" in terms of their number of published and indexed ISI research papers. These developments began in 2002 with the introduction of one of the earliest evidence-based medicine programmes as part of an undergraduate curriculum of medicine in a university in the Western Balkans. Approved financing was available for two consecutive four-year cycles of projects on pharmacoeconomics in 2006-2010 and 2011-2014. Both of these projects provided financial resources for further research. The home institution assisted these local efforts by forming the only Internal Research Fund in Serbia, providing up to 25,000,000 CSD through smaller-scale "junior" research projects.

These contributions by the Ministry of Science and Technological Development and the Medical Faculty in Kragujevac have allowed for the successful publication of several pharmacoeconomic trials. Some of these cost evaluations in clinical settings have examined patients suffering from diabetes mellitus type 2, chronic obstructive pulmonary disease, alcohol addiction, rheumatoid arthritis, haemodialysis, preterm labour management and other medical conditions that have the most significant budgetary impact in the domestic health care setting (2-5). Some of these analyses were designed as classical cost of illness analyses, others were designed as comparative economic evaluations (cost/utility and cost/effectiveness trials) and the remaining analyses used an in-depth modelling approach with TreeAge commercial software. One of the positive domestic developments in the field is the recent publication of the first pharmacoeconomic guidelines in the Serbian language on behalf of the Serbian Pharmaceutical Chamber. In this context, it is necessary to mention two consecutive cycles of the World Bank's substantial investment in projects on capacity building, from 2005-2007 , and the systemic implementation of the Health Technology Assessment (HTA) in Serbia, in 2007-2008. Larger-scale changes have also been initiated by the Serbian Government and the Ministry of Health within the framework of the "Serbia Health Project", for which two steps were planned. The first step was the "Feasibility Study on HTA Agency in Serbia", and the second step was the "Basic Benefit Package on the Way towards Evidence-Based Health Care in Serbia".

These and other ongoing efforts throughout the country contribute to a healthy core and to achieving a critical mass of awareness on the necessity of pharmacoeconomic evaluation in local conditions. We must mention that the process is still underway and that our country has no formally established HTA agency, unlike many middle-income new EU members (such as Hungary, Poland, and Latvia). Only a significant investment of money, time, and human resources as well as wise management can provide the long-term basis for the reasonable allocation of resources and evidence-based health care in a small, upper-middle-income market in the EU economic zone.

RECOMMENDED LEGAL FRAMEWORK CHANGES TO FACILITATE FURTHER DEVELOPMENTS

Serbia's national health care expenditure, expressed as a percentage of the nominal Gross Domestic Product, falls well below the Organization for Economic Co-operation and Development (OECD) average. Although Serbia has a comparatively modest mature pharmaceutical market, it has recently experienced rapid growth. The value of drug turnover in the market has increased up to three times in terms of unit consumption. This increase is explained by the decline of domestic currency in favour of the euro and decreasing prices in the nearby "reference markets".

Due to insufficiently established administrative procedures for examining cost effectiveness, there is still room for improvement. We should base the strategic changes in our national health policy on the experiences of the huge health care markets worldwide, which have gained substantial historical experience with the weaknesses of a market-oriented economy. According to contemporary health economists, Serbia's current legislative framework for approval of new drugs and medical technologies should be adapted in several ways:

- We should expend every effort to provide contracting between small and medium private health care facilities and the governmental Health Insurance Fund in charge of financing public medical care delivery;
- We should downregulate the administrative procedures and taxes necessary for academic unsponsored clinical trial approval;
- Under the current circumstances, the legislative framework for drug-related clinical trial approval imposes significant expenses and long delays on academia, effectively serving to limit biomedical research activity in Serbia without improving patient protection;
- Because we currently have two professional associations in the field, the Pharmacoeconomic section of the Serbian Pharmaceutical Society and the International Society for Pharmacoeconomics and Outcomes Research – Chapter Serbia, whose members mostly belong to one of these associations, we believe that much more horizontal and vertical networking is required;
- There is a need for the acquisition and dissemination of economic evidence, particularly by including the basics of pharmacoeconomics in undergraduate curricula of pharmacy and medicine studies; and, above all,
- Introducing "the fourth hurdle", evidence on cost effectiveness as a requirement during submission for new drug and/or medical technology approval for marketing.

It is clear that a society with scarce resources cannot afford to prioritise the reimbursement of health goods and services based on any criteria other than a straightforward analytical framework. Policy makers will come under increasing pressure to comply with these matters during the EU accession policy. It can be assumed that the harmonisa-

tion of health care legislative requirements will follow a similar trend. Espicom Business Intelligence released its latest report on Serbia's pharmaceutical market in October 2011. It assumes that overall economic recovery and increased health care spending, which is currently the highest in the region (expressed as a percentage of the Gross Domestic Product), will boost further development after the recessional slowdown of 2009. We must further develop our own research efforts aimed at economic assessments of medical technologies. We must also identify a unique formula to achieve complementary roles between academia, policy makers and the pharmaceutical industry. Although these groups work on different sides, they have the common goal of the greatest possible quantity and quality of health for the nation with the available resources.

We believe that we must search for our own middle way while observing older health care systems that learned difficult lessons from market economy weaknesses that we may be able to avoid.

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