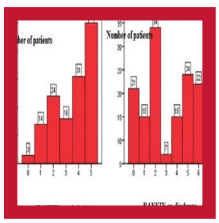
ISSN 2490-3329

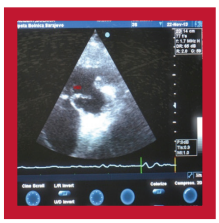
SCRIPTA MEDICA 49

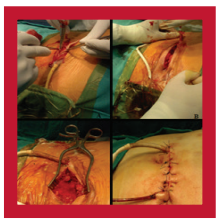
Journal of the Medical Society of the Republic of Srpska
Časopis Društva doktora medicine Republike Srpske

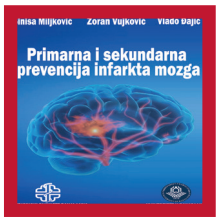
Vol. 49 • No 1 • April 2018.
Medical Society of the
Republic of Srpska

Godina: 49. • Broj 1 • April 2018.
Časopis Društva doktora medicine
Republike Srpske









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Scripta Medica (Banja Luka)

Journal of the Medical Society of the Republic of Srpska

Publishers: *Društvo doktora medicine RS*
Medicinski fakultet, Banja Luka
Printed by: *Grafix s.p., Banja Luka*

ISSN 2490-3329 (Print)
ISSN 2303-7954 (Online)

Printing: 1 000

All articles of the Scripta Medica journal are registered at the National and University Library of the Republic of Srpska, upon which analytic processing of the article was conducted in the international mutual catalogue Cobiss.

This issue of the SM is printed on acid-free paper

Sadržaj

ORIGINAL PAPER

doi: 10.18575/msrs.sm.e.18.01
UDC: 616.831-005.1
COBISS.RS-ID: 7315992

Relationship between Atrial Fibrillation as a Risk Factor and the Outcome of Ischemic Stroke

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ABSTRACT

Introduction: Atrial fibrillation is characterized by uncoordinated atrial activity with consequent deterioration of mechanical function. Patients have 5 times more risk for stroke. These stokes are more severe, more disabling and have a more frequent fatal outcome.

Aim of the Study: The aim was to examine the relationship between atrial fibrillation as risk factor and ischemic stroke.

Patients and Methods: Prospective cohort study was conducted at the Clinic of Neurology, UCC of the Republic of Srpska during the period from January to March 2017. The study included 138 patients who survived ischemic stroke, and atrial fibrillation was identified as a risk factor. Severity of stroke was assessed on admission and discharge with NIHS Scale, and level of disability with Rankin scale. Data was collected and analysed in software programe IBM SPSS Statistics 21.

Results: The sample consisted of 138 patients with ischemic stroke, divided into two groups, with ischemic stroke and atrial fibrillation, and without atrial fibrillation. There were 55.1% male, and 44.9% female patients. Atrial fibrillation was more common in female patients (46.8%) than in male patients (30.3%), and there was a significant relationship between gender and atrial fibrillation ($\chi^2(1, N = 138) = 3.29$, $p = 0.07$). It was most common in the oldest age group. There was no significant relationship between fatal outcome and atrial fibrillation, gender and age.

Conclusion: Recovery of stoke patients with this comorbidity is much more difficult and slower compared to patients without atrial fibrillation. Early detection and use of oral anticoagulant therapy can significantly decrease stroke risks, and also ease the consequences when stroke already happened.

Key words: stroke, atrial fibrillation, fatal outcome

(Scr Med 2018:49:6-12)

Submitted: February 9th, 2018
Accepted: February 27th, 2018

Introduction

Atrial fibrillation is characterized by uncoordinated atrial activity with consequent deterioration of mechanical function.[1] It is one of the most common cardiac arrhythmias, responsible for one-third of hospitalization due to heart rhythm disorders. The estimated prevalence of atrial fibrillation is 0.4-1% in the general adult population, and in the United States 2.2 million people have verified atrial fibrillation.[2] The prevalence increases to about 6% in patients at the age of 65 years and older and up to 10% in patients at the age of 80 years and older.[3] They have a 5 times greater risk of stroke and it is estimated that about 25% of all strokes in elderly is the consequence of atrial fibrillation.[4] These strokes are more severe, resulting in more frequent immobility of patients than in strokes of other etiology , and they more often result in the death of the patient.[5] In accordance with the nature of these events, strokes associated with atrial fibrillation represent a large economic burden of approximately $8 billion annually.[6]

The risk of stroke increases from 1.5% for patients aged 50-59 year to 23% for those aged 80-89 years.[7] Several prospective randomized studies have demonstrated a benefit of oral anticoagulant therapies in the prevention of stroke in patients with atrial fibrillation (AFASAK (Petersen, Boysen et al., 1989), BAATAF, SPAF III (SPAF-III-Trial-Investigators 1996), EAFT Atrial-Fibrillation-Trial-Investigators 1993).[8] Risk of stroke can be reduced by about 68% with anticoagulants that are vitamin K antagonists.[9] Oral anticoagulants, either vitamin K antagonists or non-vitamin K antagonists (NOAC), effectively reduce thromboembolism associated with atrial fibrillation and, in the long term, oral anticoagulant therapy is recommended for all patients with atrial fibrillation.[10] Despite the proven benefit and strong desire of patients to prevent stroke, insufficient and improper use of these medications remains a significant problem. Only 20 to 58 % of patients who should receive anticoagulant therapy actually receive one,[11] and 30-50% of them stop taking medications within 12 months.[12]

Inadequate use of medication is partly a consequence of the concern of doctors and patients due to the bleeding caused by these medications. Some patients are not able to take anticoagulant medications due to the inability to perform regular laboratory control of INR, while others can't afford NOAC medications.[13] The occurrence of new anticoagulant medications, such as direct thrombin inhibitor (dabigatran) and direct oral phosphor factor Xa inhibitor (rivaroxaban, apixaban), which act rapidly, have a stable dose-bound anticoagulant effect, with only a few relevant drug interactions between medications and without the constant need to monitor laboratory values, has significantly contributed to the more frequent administration of oral anticoagulant therapy in patients with atrial fibrillation.[14] Serbian Association for Atrial Fibrillation Association (SAFA), in order to gain a better insight into the treatment of atrial fibrillation in the Balkans, has conducted a prospective quarterly study in 7 Balkan countries, Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Montenegro, Romania and Serbia, covering 2712 patients.

The results showed that the quality of oral anticoagulant therapy is still very poor, and that additional efforts are needed to establish a more systematically scientifically proven approach in selecting therapy with the goal of obtaining maximal benefit and minimizing the risks associated with the use of oral anticoagulant therapy and achieving better treatment outcome.[15]

Aim of the Study

The aim was to examine the relationship between atrial fibrillation as risk factor and ischemic stroke.

Patients and Methods

A prospective cohort study was conducted at the Clinic of Neurology of the UCC of the Republic of Srpska in the period from January to March 2017. The study included 138 patients who survived an ischemic stroke, and atrial fibrillation was identified as a risk factor. The inclusion criterion was a CT-certified ischemic stroke. The non-inclusion criterion was the absence of specific changes on CT and verified intracranial hemorrhage. The severity of stroke for each patient on admission and discharge was assessed by the National Institutes of Health Stroke Scale, and the disability degree by the RANKIN scale. NIHSS scale is a neurological instrument for the objective assessment of stroke severity. It consists of 11 questions related to motor and sensory capabilities of patient, each scored from 0 to 4. For each item 0, it indicates a normal or orderly function, while a higher score indicates a degree of disability. The minimum score is 0, while the maximum score is 42. According to the NIHSS scale, the severity of the stroke is determined so that score 0 indicates the withdrawal of stroke symptoms, the score of 1-4 indicates a mild stroke; the score 5-15 is a moderate stroke, from 16-20 moderate to severe, and from 21-40 severe stroke. The degree of disability was assessed with the use of a modified Rankin scale. It consists of 6 degrees of disability, where 0 is the absence of a deficit, while death is 6th degree.

After the admission to hospital treatment, all patients were examined by the cardiologist, and atrial fibrillation was verified by analyzing the ECG record. Statistical data processing was performed in the software package

IBM SPSS Statistics 21. From descriptive statistics, frequencies and percentages, minimum and maximum values, arithmetic mean and standard deviation were calculated. Additionally, the distribution of average values of numerical variables in the sample is presented graphically. Relations between categorical variables were tested using a chi square test, with Yates' correction for continuity for matrices 2 x 2. The investigation of the significance of differences between RANKIN and NIHSS scores on admission and discharge was done by t-test for paired samples. The differences of the scores in relation to other categorical variables were tested with the t-test for independent samples or ANOVA, depending on the characteristics of the categorical variable. For the margin of statistical significance, a confidence interval 0.05 was taken. Approval of the Ethical Committee of the UCC was obtained, and all patients signed an informed consent before taking part in the study.

Results

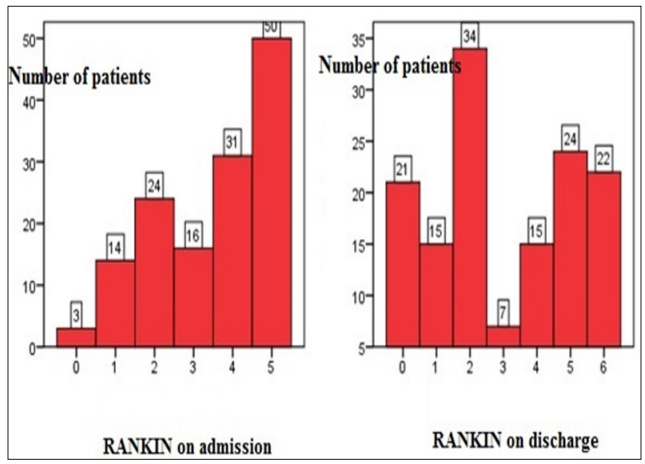
The sample consists of 138 patients classified in two groups. The first group consists of patients with the ischemic stroke without atrial fibrillation and the other with atrial fibrillation. The sample is relatively gender-balanced, with 55.1% male and 44.9% female patients. As for the age structure, the sample is categorized into three groups. The first group, 30-49 years, in which there were 7.2% of patients, the second group, 50-79 years, with the largest proportion of patients at 63.8% and the group with patients over 80 years of age with 29% of patients. There were 52, that is 37.7% patients out of total number of patients with atrial fibrillation..

Atrial fibrillation is slightly more pronounced in females than in female (46.8%) than in male patients (30.3%). Although this difference has not reached statistical significance, it can be said that the reliability value is at its very margin ($\chi 2$ (1, N = 138) = 3.29, p = 0.07). As for the age of patients, this disease is most common in the elderly group of patients (57.5%), significantly higher in the middle group (32.9%) and not registered in the youngest group of patients at all. The registered relationship between the age of patients and the incidence of atrial fibrillation is statistically significant ($\chi 2$ (2, N = 138) = 13.57, p <0.01).

In terms of RANKIN score on admission and discharge, the average value on the admission is 3.51 (SD = 1.49), where the minimum value is 0, and the maximum 5. The average RANKIN score on the discharge is 3.00 (SD = 2.07), that is, the minimum value is also 0 and the maximum value of 6. The results of the t-test for the paired samples suggest that, between the admission and discharge, a statistically significant decrease in the score has appeared (t, 137, N = 138) = 4.00, p <0.01).

Since the average values themselves do not speak much about the individual values in the sample, the distribution of the results is presented graphically in Picture 1. We see that 50 respondents had a value 5, 31 respondents value 4, and a somewhat lower number of subjects had values from 1 to 3. Only 3 respondents had a value 0. On discharge, the situation is largely changed. Even 21 respondents had value 0, suggesting that at least 18 respondents had fully recovered. The growth of the number of respondents with values 1 and 2 as well as the fall in the incidence of higher values (3, 4 and 5) is noticeable. At the same time, 22 patients with grade 6 appeared which refers to a fatal outcome during treatment. If we excluded patients who died from the analysis, we would have a significantly lower average score on discharge, which would allow us to conclude that in surviving patients there has been a significant decrease in the average RANKIN score during the treatment.

Picture 1. Distribution of Average Vaules of Rankin Score on Admission and Discharge



In the case of NIHSS score, the average value on admission was 9.80 (SD = 7.51), with a minimum value 0 and a maximum 40, while on discharge, the average was 11.75 (SD = 14.25), with a minimum value 0 and maximum 42. The difference in the value on admission and discharge is at the margin of statistical significance (t (137, N = 138) = -1.95, p = 0.05). The fact that the average NIHSS score was higher on discharge may lead to the wrong conclusion that during the treatment, there was no recovery of patients, so for this reason we will present the distribution of results in the sample below, and graphically depict it in Picture 2. On admission, there were 4 registered respondents with NIHSS score 0 indicating the absence of stroke symptoms, while the majority of respondents was located in the range of 1 to 15

(milder and moderate stroke), a slightly smaller number in the range of 16 to 20 (moderate-severe stroke), and the smallest number (total of 11) in the range from 21 to 42 which refers to a severe stroke. On discharge, we see a significant change of scores in the sample. The number of patients without symptoms increased to 15, suggesting that at least 11 patients were recovered according to the NIHSS scoring criteria. In addition, there was a growing number of patients with low scores indicating weaker symptoms of stroke, and the number of scores on the scale that indicate moderate to severe symptoms was reduced. Here, as in the case of distribution of RANKIN scores on discharge, we see that 22 respondents with a maximum score of 42 appeared, which refers to a death outcome during treatment. It is clear that this growth in the number of respondents with extreme values on the scale significantly influenced the average value, and that by excluding the deceased patients, there would be the reduction of the average NIHSS score during treatment in patients who survived.

Picture 2. **Distribution of Average Values of NIHSS Scores on Admission and Discharge and Based on Stroke Severity**

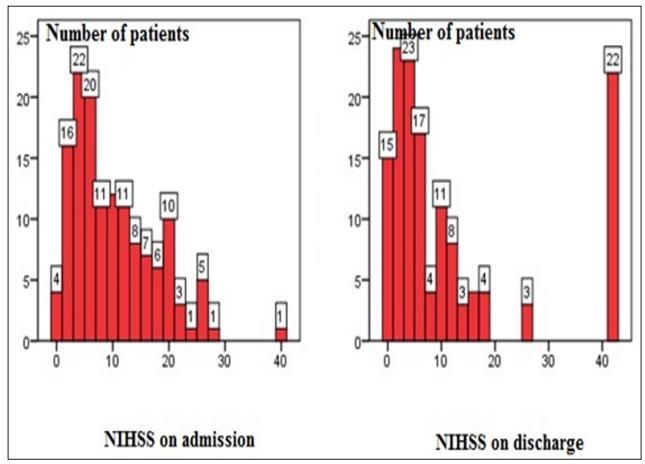


Table 1. **Values of NIHSS and Rankin Scores in Patients with Atrial Fibrillation**

Score	Atrial fibrillation	N	M	SD	t	df	p
RANKIN on admission	Yes	52	3.90	1.33	2.48	136	.014*
	No	86	3.27	1.53			
RANKIN on discharge	Yes	44	2.80	1.62	1.67	114	.098
	No	72	2.24	1.83			
NIHSS on admission	Yes	52	11.19	7.25	1.71	136	.090
	No	86	8.95	7.58			
NIHSS on discharge	Yes	44	6.89	6.00	1.27	114	.208
	No	72	5.49	5.64			

** significant at p<0.05*

Since we have previously found that patients who died during the treatment received the maximum RANKIN and NIHSS rates for release, it is clear that the very average value of these scans is directly related to patient mortality. In this regard, when examining the relationship of these values with socio-demographic variables and the presence of atrial fibrillation, the mortality of the patient would have the role of a confounding variable and could lead us to the wrong conclusions. For this reason, when examining the connection with the mentioned variables on discharge, only patients who did not died during treatment were taken into analysis.

From Table 1. we see that in patients with atrial fibrillation, there were consistently higher values of RANKIN and NIHSS scores, both on admission and discharge. This difference, however, reached a statistical significance only in the case of RANKIN score on the admission ($t(136, N = 138) = 2.48$, $p < 0.05$).

In female patients, there were consistently higher values of RANKIN and NIHSS scores, both on admission and discharge. These differences were statistically significant in the case of the RANKIN score on the admission ($t(136, N = 138) = 2.65$, $p < 0.01$) and discharge ($t(114, N = 138) = 3.09$, $p < 0.01$), as well as in the NIHSS rate on discharge ($t(114, N = 138) = 2.49$, $p < 0.05$), while the difference in NIHSS was at the margin of statistical significance.

Table 2. Values of Rankin and NIHSS Scores in Relation to Age of Patients

Score	Age	N	M	SD	F	df	p
RANKIN on admission	30-49 years	10	2.50	1.43	7.74	2	.001**
	50-79 years	88	3.32	1.54			
	80-over 80 years	40	4.18	1.08			
RANKIN on discharge	30-49 years	9	0.89	1.69	7.32	2	.001**
	50-79 years	78	2.33	1.73			
	80-over 80 years	29	3.24	1.53			
NIHSS on admission	30-49 years	10	3.70	3.27	12.13	2	.000**
	50-79 years	88	8.61	6.65			
	80-over 80 years	40	13.93	8.18			
NIHSS on discharge	30-49 years	9	4.22	8.12	5.37	2	.006**
	50-79 years	78	5.14	4.54			
	80-over 80 years	29	8.93	7.11			

*** significant at p < 0.01*

We see that the RANKIN and NIHSS scores on the admission and discharge were consistently highest in the oldest group of respondents, and that those values decreased over the years, and all registered values were statistically significant at p <0.01, as shown in Table 2.

During the treatment, 22 patients or 15.9% of the total sample died. The results of the chi square test suggest that there was not a statistically significant relationship between the mortality of patients and their gender or age. In terms of gender, mortality was slightly more common in male (19.7%) than in female respondents (11.3%). Registered differences in mortality in relation to the age of patients were somewhat more pronounced, so in patients older than 80 years, death was recorded in 27.5% of patients, while in the younger group, deaths occurred in 10% and 11.4% of respondents. The difference in mortality in relation to age was at the very margin of statistical significance ($\chi 2$ (2, N = 138) = 5.63, p = 0.06), and no mortality associated with the presence of atrial fibrillation in patients was registered.

Since it is known that the mortality of the patient affects the very score of these scales on discharge, in the analysis of the potential correlation of the frequency of fatal outcome with the scales, only the values on admission were used. Also, in order to fulfil the prerequisite for applying the chi square test, the values on these scales were ranked in three categories.

The results of the chi square test suggest that there was a statistically significant relationship between the mortality of patients and NIHSS score on admission ($\chi 2$ (2, N = 138) = 11.41, p <0.01). The mortality rate was registered in 34.5% of patients who scored a score above 15 and ranked in the group of patients with moderate-severe or severe stroke, while in patients with moderate stroke (NIHSS 5 - 15) mortality was present in 14.9%, and only 4.8% patients with mild stroke. As for the RANKIN score, the same tendency of the mortality rate was registered, where mortality was more frequent in higher scores registered on admission, and the tested link was at the margin of statistical significance ($\chi 2$ (2, N = 138) = 11.41, p <0.01).

Discussion

Our study has shown the importance of atrial fibrillation as a risk factor for the emergence of ischemic stroke. The results indicate a slightly higher incidence in female population and in the population of patients over the age of 80. Furthermore, the results show higher scores on NIHSS and Rankin on admission, which indicates that patients with atrial fibrillation have a severe stroke. These results are in correlation with the results of the studies that have been carried out so far and do not deviate from them to a greater extent. Although our study did not show a significant relationship between atrial fibrillation and higher fatal outcome in patients, found in other studies, the results again show that mortality was slightly higher in male population and was correlated with the height of NIHSS and Rankin score on admission.

The asymptomatic nature of atrial fibrillation, as well as the severity of complications of its inadequate treatment, suggests that greater effort is needed for its early detection and the introduction to therapy. Considering that a large number of patients still remain undiagnosed, and those who have been diagnosed often do not receive adequate therapy, as indicated by our results as well, it is evident that new models of approaches in public health need to be developed to overcome these problems. The emergence of new anticoagulant medications has significantly reduced the resistance to the introduction to this therapy, which was formerly present due to the high risk of bleeding, inability of adequate laboratory monitoring of INR values, and the maintenance of the same in reference values. For now, only one medication from the NOAC group has been registered in our area and its price is still quite high, which is a significant limiting factor for prescribing this therapy, and therefore a better control of atrial fibrillation as a risk factor, especially in older population, which is also visible in our results. In our everyday practice, there are missed opportunities to prevent stroke and our previous failures in improving and implementing prevention strategies should serve as a motive for further work in order to minimize the number of strokes and its consequences.

Conclusion

From our study, it is evident that higher rates of NIHSS and Rankin score on admission, and particularly on discharge, indicate that patients with atrial fibrillation have a severe stroke, followed by a greater degree of disability. The recovery of stroke patients with this comorbidity is significantly more difficult and slower in relation to patients without atrial fibrillation. New and larger studies are needed to demonstrate a more significant role of atrial fibrillation in the fatal outcome of patients with ischemic stroke. Timely detection and introduction to an adequate therapy can significantly reduce the risk of stroke as well as the consequences of already formed stroke.

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Povezanost atrijalne fibrilacije kao faktora rizika sa ishodom ishemijskog moždanog udara

SAŽETAK

Uvod: Atrijalna fibrilacija se karakteriše nekoordinisanom atrijalnom aktivnošću sa posljedičnom deterioracijom mehaničke funkcije. Pacijenti imaju 5 puta veći rizik za nastanak moždanog udara. Ovi moždani udari su teži, rezultiraju češćom nepokretnošću pacijenata i češćim smrtnim ishodom.

Cilj rada: Ispitati povezanost atrijalne fibrilacije kao faktora rizika sa ishodom moždanog udara.

Ispitanici i metode: Prospektivna kohortna studija je provedena na Klinici za neurologiju UKC Republike Srpske u periodu od januara do marta 2017. god., a obuhvatila je 138 pacijenata sa ishemijskim moždanim udarom. Kao faktor rizika identifikovana je atrijalna fibrilacija koja je verifikovana EKG zapisom. Težina moždanog udara procjenjivana je NIHSS skalom, a stepen onesposobljenosti procjenjivan je RANKIN skalom. Atrijalna fibrilacija verifikovana je analizom EKG zapisa.

Rezultati: Pacijenti su svrstani u dve grupe, sa ishemijskim moždanim udarom i atrijalnom fibrilacijom i bez atrijalne fibrilacije. Od toga je 55,1% muških i 44,9% ženskih pacijenata. Češća je kod ženskih (46,8%) nego kod muških pacijenata (30,3%). Statistički je značajna veza između pola i atrijalne fibrilacije $\chi^2(1, N = 138) = 3,29, p = 0,07)$. Veza između starosti i učestalosti atrijalne fibrilacije je statistički značajna ($\chi^2(2, N = 138) = 13,57, p < 0,01$). Nije utvrđena statistički značajna veza smrtnosti sa prisustvom atrijalne fibrilacije, polom i starošću pacijenta.

Zaključak: NIHSS i Rankin skor na prijemu, a naročito na otpustu ukazuje da pacijenti sa atrijalnom fibrilacijom imaju teži moždani udar, praćen većim stepenom onesposobljenosti. Oporavak je znatno teži i sporiji u odnosu na pacijente bez atrijalne fibrilacije.

Ključne riječi: moždani udar, atrijalna fibrilacija, smrtnost

ORIGINAL PAPER

doi: 10.18575/msrs.sm.e.18.02
UDC: 616.831-005.1
COBISS.RS-ID: 7316504

Effects of Transcranial Galvanic Stimulation on Post Stroke Depression

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ABSTRACT

Introduction: Transcranial galvanic stimulation (TGS), a non-invasive method in modulation of cortical excitability, shows potentially positive effects on post stroke depression (PSD).

Aim of the Study: The aim of this study was to estimate the effects of transcranial galvanic stimulation on post-stroke depression in patients after acute stroke.

Patients and Methods: The study group (N=11) received TGS and conventional physical and occupational therapy. All patients were stimulated with transcranial galvanic stimulation for 20 minutes with 1mA current intensity, once a day for two weeks (five days a week).The Beck Depression Inventory was applied to score the depression levels in patients before and after the intervention.

Results: Application of TGS therapy, along with a conventional rehabilitation treatment entailed a statistically significant decrease in the level of depression in our group of patients. There was no statistically significant difference regarding depression in relation to gender, localization and type of stroke.

Conclusion: The study has confirmed that the application of transcranial galvanic stimulation during stroke rehabilitation improves the depression symptoms in patients.

Key words: Transcranial Galvanic Stimulation, Post Stroke Depression

(Scr Med 2018:49:13-17)

Submitted: March 3rd, 2018
Accepted: March 27th, 2018

Introduction

Transcranial galvanic stimulation (TGS), a non-invasive method in modulation of cortical excitability, shows potentially positive effects on post stroke depression (PSD). PSD occurs in about 40% of patients with stroke and is associated with cognitive failure, slowing down of recovery of motor and daily activities, prolonged hospitalization period and increased mortality rate. It is defined as a depressive disorder that occurs after acute focal cerebrovascular events and in the presence of clinical signs of apparent stroke. This mental disorder is one of the key factors in the rehabilitation process and the main negative prognostic factor for the quality of life after a stroke.

Typical symptoms are reduced mood, loss of interest and satisfaction, reduced energy, increased fatigue and reduced participation in activities.Pharmacological treatment is often limited by side effects, pharmacological interactions and severe outcome in elderly patients. As an alternative, TGS may be a very useful treatment for such conditions. Although studies show modest significance of those effects, neurorehabilitation leads to reduction of functional disability measured by index of daily life activities.[1]

Neurorehabilitation studies have many limitations such as heterogeneity of impairments and disabilities, poorly defined rehabilitation treatments, lack of randomization process and absence of sensitive monitoring parameters.[2]

Generally speaking, recovery, especially during the first weeks after stroke, is a reflection of changes in neurotransmission that occurs due to the recovery of hemodynamics and metabolic factors in the zone of neurologic lesion. After stroke, hypo-activation in cortical and subcortical area occurs thus correlating with the onset of neuropsychological symptoms such as depression, aphasia and neglect. The possibility that transcranial non-invasive stimulation methods induce selective modulation of neural circles and systems has brought about their use in therapy.

TGS is a non-invasive method used for modulation of cortical excitability by direct application on brain structures.[3] The method is cheap and simple, and unlike epidural stimulation, it is completely non-invasive.[4]

Methods of non-invasive transcranial neuromodulation have a long history, but only in the past decades, there has been some significant progress in terms of technical methodology and understanding of physiological mechanisms. Compared to surgical methods, non-invasiveness is an apparent advantage, and compared to pharmacotherapeutic methods, the advantage is functional selectivity of stimulation.[5]

The primary result of TGS is that there is a change of potential in brain neurons of corticospinal system so that in the anode stimulation there is an increase of cortical excitability, and in the cathode stimulation, there is a decrease of cortical excitability.[6]

Stimulation lasting more than 5 minutes can induce significant “after”effects that can last for a few hours. The facilitating effects of TGS may be also used to improve the mood in healthy people,[7,8] thus making it possible to treat people who suffered from stroke.

Beck’s Depression Inventory (BDI) is one of the most commonly used instruments for testing the intensity of signs of depression in the clinical and general population. BDI was developed in 1974 (Beck et al., 1974), and since then, in an unchanged form, it has showed continuously good psychometric characteristics. It has its applicability and usefulness, not only in research but also in practical - clinical domain.

Aim of the Study

The aim of this study was to estimate the effects of transcranial galvanic stimulation on post-stroke depression in patients after acute stroke.

Patients and Methods

The study included eleven patients with post stroke depression. Each patient was previously given a detailed description, and shown the protocol and device. Each of them had to submit the written consent in accordance with the Helsinki Declaration. The study was conducted in Rehabilitation Clinic “Dr Miroslav Zotović” Banja Luka in January and February, 2018.

The stroke diagnosis was confirmed by neuroradiologic diagnostics NMR or CT Scan. All examinees were examined by specialists in neurology who had 10 years of experience in neurological rehabilitation. Inclusion criteria were:depression after stroke which occurred in the past 3 months, capability to understand simple instructions; minimal active mobility. Non-inclusion criteria were:severe sensory deficits; severe accompanying illnesses,presence of metal in endocranium and epilepsy. Besides monitoring parameters, demographic data (gender, age) and information regarding the stroke (localization and type of lesion) were recorded.

The study group was consisted of patients with moderate to severe depression who were measured with Beck’s depression level above 20. The TGS protocol was achieved

by the clinical standard device- The Soterix Medical tDCS 1x1 CT system, USA. Respecting the International 10-20 system, the anode was placed on the left dorsolateral prefrontal cortex (DLPFC) while the cathode was positioned on the right supraorbital area.

All patients were stimulated by TGS for 20 minutes with 1mA current intensity, once a day for two weeks (five days a week). They carried out conventional physical and occupational therapy, each in duration of forty-five minutes per day. The monitoring parameters were taken at the beginning and at the end of the treatment. The significance indifference between scores measured before and after treatment was determined with the use of paired t-test. The statistical significance level (p) was set at 0.05.

Results

The treatment group consisted of 6 men and 5 women, 7 patients had left sided hemiparesis, while 4 patients had right-sided hemiparesis. The cause of stroke was cerebral infarction in 8 patients and cerebral hemorrhage in 3 patients.The average age of the patients was 59.2 ±10.4 (Table 1).

Table 1. The general characteristics of the subjects (N=11)

Gender	Male	6	54.5%
	Femalei	5	45.5%
Age (years)	59.2 ±10.4		
Paretic side	Left	7	63.6%
	Right	4	36.4%
Cause of disease	Cerebral infarction	8	72.7%
	Cerebral hemorrhage	3	37.3 %

The depression level in patients according to BDI before TGS therapy was 32.2±3.6 (the level of severe depression 30-40) and it significantly decreased to 21.8±4.2(moderate depression) after TGS treatment intervention (Table 2).There was no statistically significant decrease in depression in relation to gender, localization and type of stroke.

Table 2. The changes in depression after TGS

	Before TGS	After TGS
Depression	32.2±3.6	21.8±4.2

**p<0.05*

Discussion

Our results in a small sample of patients show that the therapeutic intervention of TGS significantly reduces the level of depression in patient with PSD.Previous studies regarding the effectiveness of TGS in clinical rehabilitation practice have pointed to heterogeneity of examined population, small samples of examinees and non-standardized methodology of monitoring.

The results of studies on the TGS use presented in meta-analyses show that generalization on effectiveness cannot be done because the parameters of monitoring are not the same, and the TGS method can be very different depending on duration and place of stimulation.

The sample does not include a large number of patients as these patients are hardly recruited due to a dominant interest in motor deficit while depression symptoms are often neglected. Furthermore, these patients can hardly be included in the treatment because they seem not to be interested.[9]

The biological way of looking at PSD was most prominent in the research of Robinson and his associates (Johns Hopkins University, USA) who first described the significant association of PSD with lesions in the left frontal lobes and left-sided in the basal ganglia.[10]

The results of this study correspond to the study of Valiengo and associates who observed the effects of TGS in forty eight patients with PSD and without antidepressants in therapy. After 6 weeks of TGS administration in the regimen, one procedure per week produced a statistically significant reduction in depression scores in the experimental group.This study has several significant limitations such as a small sample size that does not allow generalization, absence of a control group and existence of uncontrolled external effects on depression in the observed patients.[11]

Due to all these reasons, further studies are needed on a larger number of patients and randomized control groups for the definitive confirmation of the efficacy of TGS in the treatment of depression after stroke. TGS is a promising therapeutic tool in the treatment of stroke due to the ease of application, accessibility and minimal side effects of the method.

Conclusion

The application of transcranial galvanic stimulation in patients during stroke rehabilitation may decrease the depression symptoms.

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Efekti transkranijalne galvanske stimulacije na depresiju nastalunakon moždanog udara

SAŽETAK

Uvod: Transkranijalna galvanska stimulacija je neinvazivni metod u modulaciji kortikalne ekscitabilnosti i pokazuje potencijalno pozitivne efekte na depresiju nakon moždanog udara.

Cilj rada: Cilj ove studije je procjena efekata dejstava transkranijalne galvanske stimulacije (TGS) na pacijente sa znacima depresije nastale nakon preživljenog akutnog moždanog udara.

Ispitanici i metode: Pacijenti u studijskoj grupi (N=11) su sproveli terapiju transkranijalne galvanske stimulacije uz konvencionalnu fizikalnu i radnu terapiju. Svi su stimulisani transkranijalnom galvanskom stimulacijom u trajanju od 20 min, intenzitetom struje od 1mA, jednom dnevno, dvije sedmice, (pet dana sedmično). Bekova skala depresivnosti je primjenjena u određivanju stepena depresivnosti kod pacijenata prije i nakon tretmana.

Rezultati: Primjena terapije transkranijalne galvanske stimulacije uz konvencionalni rehabilitacioni tretman je imala za posljedicu statistički značajno umanjenje depresivnosti u našoj grupi pacijenata. Nije bilo statističke značajnosti u padu depresivnosti vezano za pol, lokaciju i tip moždanog udara

Zaključak: Studija ukazuje da primjena transkranijalne galvanske stimulacije na pacijente u toku rehabilitacije moždanog udara može umanjiti simptome depresivnosti.

Ključne riječi: Transkranijalna galvanska stimulacija, depresija nakon moždanog udara

ORIGINAL PAPER

doi: 10.18575/msrs.sm.e.18.03
UDC: 615.265.2
COBISS.RS-ID: 7316760

Physicochemical Equivalence Studies of Two Amlodipine Tablet Formulations

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ABSTRACT

Introduction: Based on the international drug regulatory requirements, all generic pharmaceutical manufacturers are obliged to ensure that their generic products are similar or equivalent to the innovative brand. The quality of generic medicines should be comparable with the innovator brand and therefore interchangeable with the innovator. Based on the Biopharmaceutical Classification System (BCS), dissolution tests can be used as a replacement for ***in vivo*** studies for drugs that belong to the BCS class I. Dissolution tests are considered the most sensitive ***in vitro*** parameters that can be with the highest probability of correlation with ***in vivo*** bioavailability. The comparison of in vitro dissolution tests using similarity factor (f2) is very often used as the most important parameter that can reflect the existence of bioavailability.

Aim of the Study: The aim of this study was to compare the physico-chemical characteristics of two amlodipine formulations made by the same manufacturer using the dissolution test and similarity factors to ascertain their in vitro similarity.

Material and methods: Two different generic copies of amlodipine 5 mg tablets produced by the same pharmaceutical manufacturer were evaluated using pharmaceutical parameters such as: uniformity of active ingredient test, weight uniformity text, disintegration test, hardness test, tablet friability test, and in vitro dissolution test.

Results: The results have shown that different salts and different manufacturing procedures do not have effect on in vitro equivalence of amlodipine tablets. The similarity factor (f2) at pH 4.5, 1.2 and 6.8 was 63.90, 53.87 and 57.57, respectively. Although these values demonstrated equivalence, statistically significant differences were found in the degree of dissolution rates of tablets formulation depending on time and pH values. The results of our study showed equivalence of dissolution profiles of different amlodipine formulations.

Conclusion: The results of our study have shown that the equivalence of dissolution profiles exists, although there were statistical differences in some pharmaceutical parameters.

Key words: amlodipine besylate, amlodipine mesylate, pharmaceutical formulation, dissolution

(Scr Med 2018:49:18-24)

Submitted: March 6th, 2018
Accepted: March 18th, 2018

Introduction

Amlodipine is a dihydropyridine calcium channel antagonists that inhibits the influx of extracellular calcium into vascular and cardiac cells via blockade of voltage-dependent L-type calcium channels.[1,2] This class of cardiovascular drugs lowers blood pressure through relaxation of vascular smooth muscles and vascular dilatation. It is the most frequently used calcium channel antagonist worldwide, indicated for the treatment of hypertension and coronary artery disease, well tolerated by the majority of patients with very moderate to mild side effects.[3] Amlodipine has slow elimination rate with prolonged half-life (t1/2 > 35 hours) resulting in long duration of action.[4]

Amlodipine was patented by Pfizer under the brand name Norvasc. After the patent right expired in late 2007, a number of generic versions of amlodipine became available.[5] Tablets of amlodipine from different or same producers may contain different salts. Based on internationally drug regulatory requirements, all generic pharmaceutical manufacturers are obliged to ensure that their generic products are similar or equivalent to the innovative brand. A generic medicine is defined as a faithful imitation of an original drug, which is not protected by a patent, and marketed with the chemical name of the active ingredient.[6] Quality of generic medicines should be comparable with the innovator brand and therefore interchangeable with the innovator.

Two different generic copies of amlodipine 5 mg tablets, produced by the same pharmaceutical manufacturer, were evaluated using pharmaceutical parameters such as: uniformity of active ingredient test, weight uniformity text, disintegration test, hardness test, tablet friability test, and in vitro dissolution test. These tests are required by most drug regulatory authorities to ascertain the claim of pharmaceutical equivalency. Based on the Biopharmaceutical Classification System (BCS), dissolution tests can be used as a replacement for in vivo studies for drugs that belong to the BCS class I.[7] Dissolution tests are considered the most sensitive *in vitro* parameters that can be with the highest probability of correlation with the in vivo bioavailability. Very often, comparison of dissolution tests *in vitro*, using similarity factor (f2) is used as the most important parameter that can reflect the existence of bioavailability.[8]

Aim of the Study

The aim of this study was to compare the physico-chemical characteristics of two amlodipine formulations made by the same manufacturer using the dissolution test and similarity factors to ascertain their in vitro similarity.

Material and methods

Materials

In order to assess physico-chemical equivalence, two generic brands of amlodipine from the EU market were used.

Two different formulations of amlodipine, with different salts of amlodipine 5 mg, amlodipine besylate (formulation 1), and amlodipine mesylate (formulation 2) were used.

Tablet formulation 1
The method used in preparation of formulation 1 was wet granulation. After mixing amlodipine besylate and starch, microcrystalline celullose and magnesium stearate were added in preparation for the tableting.

Tablet formulation 2
The method used in preparation of formulation 2 was dry mixing. After mixing amlodipine mesylate with calcium hydrogen phosphate, sodium starch glycolate microcrystalline celullose and magnesium stearate were added. The next step was tableting.

Chemicals
Chemicals used for these analyses were: potassium dihydrogen phosphate (KH_2PO_4) p.a, 1 M solution of sodium hydroxide p.a, concetrated hydrochloric acid (37% HCl) p.a, sodium acetate x 3 H_2O p.a, 2 N acetic acid p.a, purified water (HPLC grade), triethylamin p.a, phosphoric acid conc.p.a, methanol (HPLC grade), acetonitrile (HPLC grade), triethylamin buffer: disolve 7.0 ml triethylamine in 1000 ml water and adjusted pH on 3.0 ± 0.1 by phosphoric acid, ammonium acetate (HPLC grade) were used.

Apparatus

Apparatus used for analyses were: Friabilator, Erweka TAR 100; Erweka hardness tester, Erweka TBH 425; Apparatus II (USP paddle apparatus) Erweka DT 800; Scale, Sartorius Practum 213-1S; HPLC, Agilent 1100 Series.

In-process parameters

In-process parameters included measurement of tablets core weight (mg) and uniformity of mass using the method described in Ph. Eur. 2.9.5 and hardness (Ph. Eur.2.9.8), friability (Ph. Eur.2.9.7), disintegration time (Ph. Eur.2.9.1.). Analysis of final product is related to the following parameters: the content of amlodipine in tested formulations was determined by using the method of high pressure liquid chromatography (HPLC), and

dissolution profile were handled by using the paddle method (Method II, Paddle, Ph. Eur.).[9]

The content of amlodipine tablets

The content of amlodipine besylate in the tested formulation was determined by HPLC on column Zorbax Eclipse XBD-C-18.5µm, 150 x 4.6mm. The mixture of solution triethylene buffer pH 3.0: acetonitrile: methanol (500:150:350) was used as a mobile phase; flow rate 1.0 ml/min, temperature: 25 °C, detection: UV/VIS 237 nm; injection volume 10 µl. Referent solution was prepared by measurement of 35 mg amlodipine besylate as a reference substance and its disintegration in the mobile phase up to 50 ml. A sample of 5 ml of obtained solution was completed with a mobile phase up to 50 ml. The tested solution was prepared by measuring amlodipine tablets up to 5 mg, dissolved with 25 ml mobile phase. After 30 minutes of mixing in ultrasonic baths, solution was cooled up to 25 °C and combined with a mobile phase up to 500 ml, and after centrifuge the supernatant was filtrated through a membrane filter 45 µm. A sample of 5 ml was diluted with a mobile phase up to 100 ml. Evaluation and calculation of amlodipine besylate content in the tested formulations were performed according to the external standard with the use of peak heights / areas.

The content of amlodipine mesylate in the tested formulation was determined by HPLC on column Nucleosil RP- 18 HD/125 x 4 mm/5µm/ Macherey-Nagel. The mixture of ammonium acetate: water: acetonitrile (3.75:750:250) was used as a mobile phase A, titrated to pH 6.0 used with acetic acid, and acetonitrile (HPLC purity) was used as a mobile phase B; with flow rate of 1.0 ml/min, temperature: 40 °C, detection: U 240 nm, injection volume: 10 µl. Referent solution was prepared by measuring 24-26 ml amlodipine mesylate as a referent standard and mixing 15 min with 5 ml 1% acetic acid. The obtained solution was completed with a mobile phase A up to 50 ml. The solution was mixed for 2 minutes in ultrasonic baths. The tested solution was prepared by measurement of 10 tablets dissolved with 10 ml 1% acetic acid. After mixing for 15 min, the obtained solution was dissolved in the mobile phase B up to 50 ml and mixed in the ultrasonic baths for 5 minutes. After a centrifuge on 4000 rpm for 5 minutes, supernatant was used for injection.

Estimation/Evaluation and calculation of the amlodipine besylate and amlodipine mesylate content in the tested formulations were based on the external standards with the use of peak area. The value of the content of amlodipine in the tested tablets was calculated by using a software. Validation characteristics: specificity, accuracy, precision, linearity, range and reproducibility were tested.[10,11]

Dissolution profiles

Defining dissolution profile of both tested formulations was performed with 12 tablets each. Tests were handled by using the paddle method (Method II, Paddle, Ph.Eur.) 9 on spectrophotometer Agilent 8453 in three different media. Medium 1: phosphate buffer Ph 6.8 (Ph.Eur): 0.68% sodium hydrogen phosphate pH 6.8 with 1M sodium hydroxide. Medium 2: acetate buffer pH 4.5 (USP): 14 ml 2N of acetic acid was added in 2.99 g of sodium acetate trihydrate and dissolved with water up to 1000.0 ml. Medium 3 : hydrochloric acid 0.1 M: 8.5 ml concentrated hydrochloric acid (HCL 37%) completed in 1000.0 ml of water (pH 1.2). Media volume of 900 ml, at the rotation speed of 100 rpm and the temperature of 37°C ± 0.5 was used. Amlodipine besylate and amlodipine mesylate were used as the reference standard. The reference solution was prepared by dissolving 38 mg of referent substance in 500 ml of diluent, after that 5 ml of the obtained solution was combined with the 50 ml of diluent. The tested solutions, prepared in the same way, were filtrated through the membrane filter of 0.45 µm. Measurements were done by the spectrophotometric method at 239 nm. The average values of dissolution in all samples were obtained according to the calculation and expressed as a percentage of released active substance in defined time intervals. Obtained values were used for calculating similarity factors by formula:[8]

$$f_2 = 50 \times \log [\, [1 + (1/n) \Sigma\, t=1n\, (Rt-Tt)^2]^{-0,5} \times 100]$$

Similarity factor is a logarithmic reciprocal square root transformation of a sum of squared error and is a measurement of the similarity between the two curves, expressed in percentages (n - number of samples, Rt - dissolution value of formulation 1 at time t, Tt - dissolution value formulation 2 at time t).

Statistical analysis

Statistical analysis of the in-process communication parameters (IPC) as well as the content of amlodipine besylate were expressed using average values and standard deviations. The results were processed by t-test for IPC parameters and analysis of variance (ANOVA).

Results

In-process parameters

Analysis of IPC parameters showed a significant difference in average weight of tablet cores and disintegration time, but not in their hardness, friability and mass uniformity. The content of active substance was within the specification range in both formulations (table 1).

Table 1. Comparative data of pharmaceutical parameters for two amlodipine formulations

Tablets	Average weight (g)	Hardness	Friability (%)	Disintegration time (min.)	Uniformity of mass	Content (mg/ tbl):
Formulation 1	0.149 (0.148-0.153)	98.20 (93-104)	0.00 (max 0.1%)	0.53	–1.3% /+2%	4.87 (4.85-5.15)
Formulation 2	0.201 (0.198-0.204)*	103.5 (95-117)	0.02 (max 0.1%)	0.33*	–2% /+1%	5.02 (4.75-5.25)

*= *P<0.001*

Dissolution profiles of tested formulations and similarity factors

According to the World Health Organisation (WHO), quick release criteria will be satisfied if release of active substance is more than 85% in water media within 30 minutes, pH range 1.0 - 6.8. Release studies were conducted at pH 1.2, pH 4.5 and pH 6.8 buffer media . The dissolution rate of the formulation 2 was lower in all tested media during the first 30 minutes, but it increased in the following period and become higher than in the formulation 1. The more detailed data of dissolution values of tested formulations in different pH media are shown in figures 1-3.

Figure 1. Average dissolution values of tested samples (n=12) at defined time intervals at pH 6.8

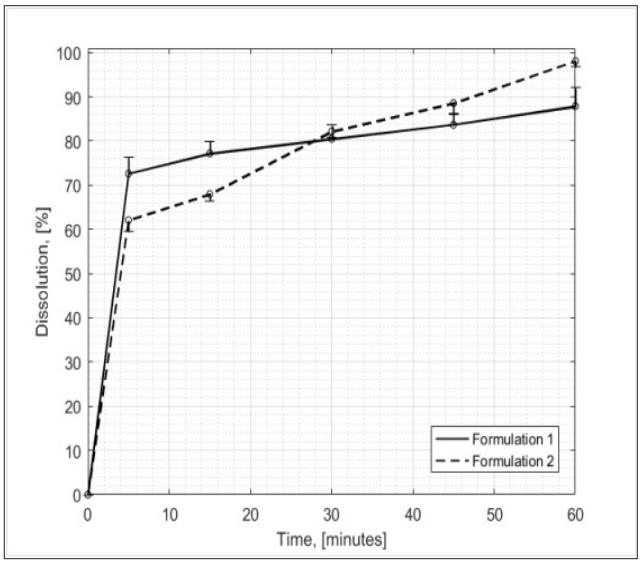
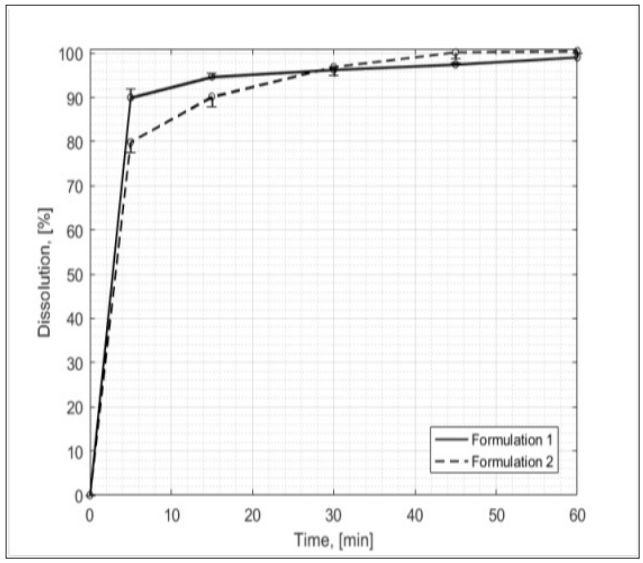


Figure 2. Average dissolution values of tested samples (n=12) at defined time intervals at pH 4.5



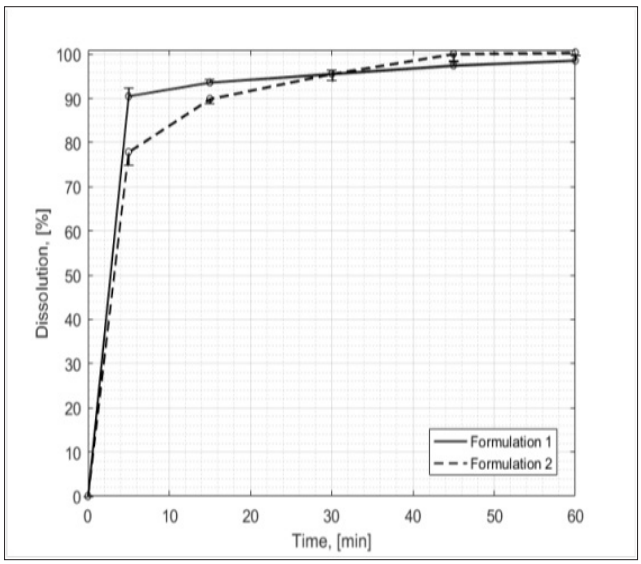
The value of the calculated similarity factor in in vitro conditions showed that the dissolution profiles of the tested formulations were equivalent at all tested conditions. Dissolution rate in lower pH values, in both formulations, was extremely fast, and after 5 minutes between 80% and 90 % of the active substances were released. The value of the obtained similarity factor (f2) at pH 4.5 was 63.90, while at pH 1.2 it was 53.87 (figures 2 and 3).

The dissolution rate at higher pH value (6.8) was lower in both formulation, so the dissolution profiles of tested formulation were similar (f2 = 57.57). Although the in vitro equivalence was confirmed at the tested pH, there

was a statistically significant difference in the values of the dissolutions for both formulations at all time intervals, except for the time of 30 minutes, which was confirmed by the analysis of variance (figures 1-3).

Further analysis showed statistically significant differences in dissolution rates of both formulations at pH 6.8 compared to pH 4.5 and pH 1.2, respectively, while these differences were not significant at pH values of 4.5 and 1.2.

Figure 3. Average dissolution values of tested samples (n=12) at defined time intervals at pH 1.2



Discussion

The comparison of two amlodipine formulations prepared by different manufacturing procedures showed that they were different in average weight and time of disintegration, but similar in dissolution profiles. In some studies that evaluated different brands of amlodipine tablets, the different disintegration time of tested tablets were observed, without having an impact on dissolution rate.[12,13]

In this study, the tablet formulation of amlodipine besylate showed slower dissolution rate (88 - 98%) in comparison with amlodipine mesilate (about 98 – 100 %) after 60 minutes, due to the different manufacturing procedures; wet granulation vs. dry mixing, respectively. Amlodipine mesylate prepared by dry mixing had higher proportion of small particles than amlodipine besylate prepared by wet granulation. For both amlodipine formulations dissolution rates were higher and faster in media with lower acidity (pH 1.2 and 4.5), but the dissolution rate was lower in less acide media (pH 6.8). All the above mentioned corresponds to the study performed by Akinleye et al. 12 and Shohin et al.[14]

The obtained results of the study, which confirm the equivalence of the tested formulations, are in accordance with studies of Shohin et al.[14] and Oyeniyi et al.[15] but in contrast with a similar study of Olusola et al.[7], where equivalence at pH 4.5 was not established in one of the tested formulations, even though it was equivalent at pH 1.2 and 6.8. In another study of Pant et al..[16] there where equivalence of tested formulations only at pH 1.2.

Problems related to the pharmaceutical equivalence are presented by a few authors, who dealt with different active substances such as tetracycline capsules,[17] nifedipine retard tablets[18] and metronidazole tablets.[19] The possible reasons for non-equivalence of pharmaceutical preparations in these studies could be attributed to variations of pharmaceutical parameters of the tested formulations. Therefore, the high dissolution rates of tested tablets do not automatically guarantee their *in vitro* equivalence.

Conclusion

In spite of the evident differences in disintegration times and dissolution rates of the formulations and media used, it can be considered that equivalence of both amlodipine formulations exists in in vitro conditions in all three media tested. Theoretically, there is a possibility that amlodipine besylate and amlodipine mesylate could be considered as bioequivalent, without performing classical bioequivalence studies.

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Ispitivanje fizičko-hemijske ekvivalencije dvije tabletne formulacije amlodipina

SAŽETAK

Uvod: Na osnovu međunarodnih regulatornih zahtjeva za lijekove, svi proizvođači generičkih lijekova su obavezni da obezbijede da njihovi generički proizvodi budu slični ili ekvivalentni ovom inovativnom brendu. Kvalitet generičkih lijekova bi trebalo da bude uporediv sa originalnim lijekom i stoga i zamjenjiv sa istim. Na osnovu Biofarmaceutskog sistema klasifikacije (BSC), ispitivanje brzine rastvaranja se može koristiti umjesto in vivo studija za lijekove koji pripadaju BSC klasi I. Testovi rastvaranja se smatraju najosjetljivijim in vitro parametrima koji mogu imati najviši nivo korelacije sa in vivo biološkom raspoloživošću. Veoma često se poređenje in vitro testova rastvaranja, uz određivanje faktora sličnosti (f2), koristi kao najvažniji parametar koji može da odražava postojanje biološke raspoloživosti.

Cilj rada: Cilj ove studije je bio da se uporede fizičko-hemijske karakteristike dvije formulacije amlodipina istog proizvođača i određivanjem faktora sličnosti utvrdi njihova farmaceutska ekvivalentnost.

Materijal i metode: Tokom studije izvršena je evaluacija dvije različite formulacije tableta amlodipina 5 mg proizvedene od strane istog proizvođača. Evaluacija je izvršena korištenjem farmaceutskih parametara poput: uniformnost sadržaja, uniformnosti mase, test raspadljivosti, test tvrdoće, test habanja tablete i test *in vitro* rastvorljivosti (disolucija).

Rezultati: Rezultati pokazuju da različite soli i različite proizvodne procedure ne utiču na ekvivalentnost tablete amlodipina in vitro. Faktori sličnosti (f2) pri pH 4,5, 1,2 i 6,8 su dobijeni 63,90, 53,87 i 57,57. Iako vrijednosti faktora sličnosti ukazuju na farmaceutsku ekvivalentnost, u stepenu rastvaranja utvrđene su statistički u tabletnim u zavisnosti od vremena i pH vrednosti. Rezultati našeg istraživanja pokazali su ekvivalenciju profila rastvaranja različitih formulacija amlodipina.

Zaključak: Rezultati ove studije su pokazali da postoji ekvivalentnost profila rastvaranja tabletnih formulacija amlodipina, iako je utvrđeno postojanje statističkih razlika u nekim farmaceutskim parametrima.

Ključne riječi: amlodipin besilat, amlodipin mesilat, farmaceutska formulacija, disolucija

ORIGINAL PAPER

doi: 10.18575/msrs.sm.e.18.04
UDC: 616.853-053.8
COBISS.RS-ID: 7317016

Status Epilepticus in Our Patients, a 15 Years Follow-Up Study

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ABSTRACT

Introduction: Status epilepticus (SE) is the second most frequent neurological emergency. The purpose of this study was to analyse clinical presentation, causes and outcome of SE.

Aim of the Study: The aim was to establish clinical characteristics, etiology and the outcome of status epilepticus as well as sex and age distribution in patients hospitalized at the Clinic of Neurology UCC RS in a 15-year follow-up.

Patients and Methods: In this prospective 15-year study, all patients with SE admitted to the University Clinical Center of Republic of Srpska, Clinic of Neurology, were treated in the period of 15 years (2003-2017). Demographic and clinical data were collected.

Results: In the aforesaid period, 124 patients with SE were treated, and there were 71 man (57%) with mean age of 59 years and 54 woman (43%), with mean age of 52.5 years. Primarily generalized tonic-clonic SE was identified in 70 (56%) and 44 (35.2%) patients, retrospectively. Simple partial SE occurred in 10 (8%) patients. 62% of the patients had previously had epilepsy while 38% had not. The main underlying causes were noncompliance to treatment in the first group (n=56; 72%) and cerebrovascular disease (n=36; 75%) in the second group. Overall mortality rate was 11.2% , which correlated with acute symptomatic etiology and patients of older age (mean: 73 years).

Conclusion: Epileptic patients are at greater risk to develop SE. However, in patients with no prior history of epilepsy and acute neurological problems SE may also occur. Cerebrovascular disease was the most common cause of SE in those with the initial seizure. Noncompliance to treatment was the major cause in patients with preexisting epilepsy.

Key words: epilepsy, status, etiology, clinical presentation, outcome

(Scr Med 2018:49:25-29)

Submitted: March 5th, 2018
Accepted: March 18th, 2018

Introduction

It is usual for status epilepticus not to last long and to have a tendency to spontaneously terminate. It is very rare for individual seizures to last longer than few minutes. However, in some cases, seizures do not terminate spontaneously na their tendency to continue present the essence of status epilepticus. Status epilepticus is the most urgent neurological state and reliability o diagnosis depends on the way the problem is defined.[1,2]

Overall definition indicates that that status epilepticus should be defined as an epileptic activity that is present for 30 minutes or longer as well as the presence of two or more seizures during which the patient does not return to baseline consciousness.[2,3] Contemporary papers tend to put under status epilepticus every expressed tendency to repeat epileptic seizures, regardless of their duration and without the full recover of consciousness or other functions affected by the seizure.

Basis for this perception is empirical and is based on the knowledge that epileptic seizures tipically last shorter than few minutes. In greater number of patients, secondary generalized tonic-clonic seizure will last between one and two minutes. Unlike that, most seizures that last longer than 5 minutes will last even longer that 30 minutes if not terminated with the use of medication.[3,4]

Status epilepticus is a medical and neurological emergency that has been associated with significant morbidity and mortality. SE is a major clinical concern in the adults and specially in the elderly population, both because it has increased incidence in the elderly compared with general population, and because of concurrent medical conditions that are mole likely to complicate therapy and worsen prognosis in elderly individuals.[4,5]

Many types of epileptic seizures have been described, and, therefore, it follows that there are many types of status epilepticus. This has led to complex classification of status epilepticus. However, using electroclinical features, status epilepticus may be classified simply by the presence of motor convulsions (convulsive status epilepticus) or their absence (nonconvulsive status epilepticus). They may be further divides into status epilepticus that affects the whole brain (generalized status epilepticus) or only part of the brain (partial status epilepticus). Status epilepticus may be initial (first epileptic manifestation) and intercurrent (in patients with prior history of epilepsy).[5]

Aim of the Study

The aim was to establish clinical characteristics, etiology and the outcome of status epilepticus as well as sex and age distribution in patients hospitalized at the Clinic of Neurology UCC RS in a 15-year follow-up.

Patients an Methods

In this prospective 15-year study, all patients with SE admitted to the University Clinical Center of Republic of Srpska, Clinic of Neurology, were treated in the period of 15 years (2003-2017).

We also analized demographic data (age, sex), status epilepticus types (generalized tonic-clonic; abans, partial, nonconvulsive, initial or intercurent), outcome of status epilepticus (survived or not), and after the diagnostic procedures, we analysed etiology of status epilepticus.

Results

In the fifteen-years period from 2003-2017. years, we had total of 125 patients with status epilepticus, 71 (57%) of them were male, and 54 (43%) were female.

Mean age of males was 59 years (with the range from 22 to 93 years), while the mean age of females was 52,5 years (with the range from 17 to 93 years).

14 patients died in that period, overall mortality was 11,2%. Deaths were correlated with acute symptomatice etiology due to cerebrovascular disease, and the mean age od those patients was 73 years.

Most of the patients had primarily generalized tonic-clonic status epilepticus (n=70; 56%), while the focal onset with secondarily generalized status epilepticus had 44 (35.2%) patients. Simple partial status epilepticus occurred in 10 (8%) patients, and one patient had nonconvulsive status epilepticus (o.8%). An absence of status epilepticus was not registered in our study.

Status epilepticus occurred in 77 (62%) patients with preexisting epilepsy, and in this subgroup of patients, noncompliance to treatment was the major cause in 56 (72%) patients with intercurrent SE.

Status epilepticus occurred in 48 (38%) patients as the first manifestation of disease, and cerebrovascular disease was the main cause in 36 (75%) patients.Etiology of status epilepticus is shown in Table 1.

The most common single cause of status epilepticus in whole group of patients was noncompliance to treatment in patients with preexisting epilepsy in 44.8% patients, followed by cerebrovascular disease in 28.8% patients. The third most common cause of status epilepticus was brain tumors and metastases in 5.6% patients..

Table 1. Etiology of status epilepticus

Etiology	n (%)
Noncompliance to treatment	56 (44.8)
Cerebrovascular disease	36 (28.8)
Tumors/metastases of brain	7 (5.6)
Alcohol intake	5 (4)
CNS infections	5 (4)
Infections with fever	5 (4)
Sequelae of brain injuries	3 (2.4)
Farmacoresistant epilepsy	3 (2.4)
Brain injuries	2 (1.6)
Metabolic causes	2 (1.6)
Idiopatic/criptogenic etiology	1 (0.8)
SUM:	125 (100)

There is a list of causes with incidence of 4% (alcohol intake, central nervous system infections, febrile systemic infections), followed by causes with the incidence of 2.4% (sequelae of brain injuries and patients with farmacoresistant epilepsy).

As a rare causes of status epilepticus we identified brain injuries and metabolic causes (renal and hepatic encephalopathy) in two patients, and in one patient the etiology remained idiopatic/criptogenic.

Discussion

According to International classification of epilepsy and epileptic syndromes the basic level of recognition of epilepsy and status epilepticus is regarding the etiology. So, we recognise symptomatic, idiopatic and criptogenic status epilepticus. Symptomatic etiologies could be acute or chronic. Idiopatic or criptogenc status epilepticus could have better prognosis than symptomatic ones.7 Criteria for classification depend on anamnesis, undertaken diagnostic procedures, observation and length of follow-up of the patients. Acute symptomatic etiologies correlated with poor outcome.[4] To underline the importance of acute symptomatic etiologies, some authors divide all etiologies on acute symptomatic in one hand and all others in another hand.[8]

In our study, the incidence of status epilepticus was higher for men compared with women (57% vs. 43%). The male patients were older compared with females (59 years vs. 52.5 years). Knake et all.[9] and Delanty et all.[11] reported in their studies a higher incidence of status epilepticus in men too. Božić et all.[12] reported in their study that status epilepticus occurred more often in male patients, and cerebrovascular disease was definitely the predominant cause.

Most of the previous studies suggest acute symptomatic etiology of status epilepticus.[4] Hui et. all.[7] reported that the most common underlying causes of status epilepticus were cerebrovascular disease, metabolic derangement, anti-convulsant withdrawal and alcohol intake.

Among the patients with status epilepticus as a first epileptic manifestation almost all studies found cerebrovascular disease as a leading underlying cause (Vignatelli et all.[11] 30%; Afsar et all.[13] 24.8%; Knake et all.[9] 33%; Darcel et all.[14] 37%; Delanty et all.[1] 41%; Govoni et all.[8] 45%) which correspondents with our results. Amare et all.[15] showed in their study with 119 Ethiopian patients that central nervous system infection was the most common cause of status epilepticus in the whole group, as well as in those with new onset seizure. We had 4% of patients with central nervous system infections in our study.

In previous studies, the proportion of patients with preexisting epilepsy was from 46% to 60%[1,9,10,11] and noncompliance to treatment was the major cause for status epilepticus in this group of patients, which correspondents with our results. Di Bonaventura et all.[2] reported that the predominant cause for status epilepticus were noncompliance, withdrawal or reduction of antiepileptc drugs.

In all previous studies, older age and underlying etiology were predictors of mortality. Reported mortalities in previous studies were from 1.9% to 40%.[16] Mortality in our study was 11.2% which is lower than reported in previous studies despite the similar clinical features of the patients (20.2%[15]; 15.6%[17]; 16%[7]; 19.8%[10]), and is very similarily reported in studies of Wu et all.[6] (10.7%), Govoni et all.[8] (5%), Vignateli et all.[11] (7%), and Chin et all.[4] (7.6%). Hui et all.[7] reported older age, delay in treatment and status epilepticus due to cerebrovascular disease as a predictors of poor outcome. Our deceased patients had a mean age of 73 years and status epilepticus due to cerebrovascular disease.

Renal or hepatric encephalopathy are reported in literature as individual causes of status epilepticus.[18,19]

Conclusion

Epileptic patients are at greater risk to develop SE. However, in patients with no prior history of epilepsy and acute neurological problems SE may also occur. Cerebrovascular disease was the most common cause of SE in those with the initial seizure. Noncompliance to treatment was the major cause in patients with preexisting epilepsy, which offers a good possibility for prevention. This study confirms the higher incidence of status epilepticus in male patients and in the elderly population. This may be due to a higher incidence of cerebrovascular disease in these subpopulations. Older age and acute symptomatic etiology were the major determinants of death.

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Epileptički status kod naših pacijenata, petnaest godina iskustva

SAŽETAK

Uvod: Epileptički status (SE) je drugo po učestalosti urgentno stanje u neurologiji. Cilj studije je analiza kliničkih manifestacija, uzroka i ishoda SE.

Cilj rada: Cilj rada je da se utvrde kliničke karakteristike, etiologija i ishod epileptičkog statusa kao i polna i starosna distribucija kod bolesnika hospitalizovanih na Klinici za neurologiji UKC RS u petnaestogodišnjem periodu praćenja.

Ispitanici i metode: Prospektivno su praćeni svi bolesnici koji su liječeni na Klinici za neurologiju Univerzitetskog kliničkog centra Republike Srpske pod dijagnozom epileptičkog statusa u periodu od 15 godina (2003-2017. godina). Prospektivno su praćeni demografski i klinički parametri.

Rezultati: U posmatranom periodu ukupno je liječeno 125 bolesnika zbog SE, od toga 71 (57%) muškaraca, prosječne starosti 59 godina, kao i 54 (43%) žene prosječne starosti 52,5 godina. Primarno generalizovani toničko klonički SE je imalo 70 (56%), dok su parcijalni SE sa sekundarnom generalizacijom imala 44 (35,2%) bolesnika, a 10 bolesnika (8%) je imalo prosti parcijalni SE. 62% bolesnika je prethodno bolovalo od epilepsije dok 38% nije. Najčešći uzrok SE u prvoj grupi je bilo neuzimanje lijekova (n=56; 72%), a cerebrovaskularna bolest u drugoj grupi (n=36; 75%). Ukupna smrtnost je bila 11,2%, što je bilo povezano sa akutnim simptomatskim uzrokom i starijim životnim dobom bolesnika (prosječna starost 73 godine).

Zaključak: Bolesnici sa epilepsijom su u višem riziku za dobijanje SE, ali i bolesnici bez prethodne epilepsije i akutnim neurološkim bolestima takođe mogu razviti SE. Cerebrovaskularne bolesti su bile najčešći uzrok SE kod bolesnika sa inicijalnim SE. Neuzimanje antiepileptičkih lijekova je bio najčešći uzrok SE kod bolesnika sa epilepsijom.

Ključne riječi: epilepsija, status, etiologija, kliničke manifestacije, ishod

ORIGINAL PAPER

doi: 10.18575/msrs.sm.e.18.05
UDC: 616.37-002.1-07
COBISS.RS-ID:7317272

Complications of Treatment of Acute Pancreatitis

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ABSTRACT

Introduction: Acute pancreatitis is non specific inflammation of the pancreas due to the intrapancreatic activation of its proteolytic and lipolytic enzymes - enzyme lesions. The enzymes normally excreted by the pancreas are activated in the pancreas and destroy its tissue, leading to an autolysis process that causes bleeding and damage to the blood vessels. Enzyme autodigestion begins with local inflammation, edema, bleeding and necrosis.

Aim of the Study: The aim of this paper is to determine the incidence and complications in patients with acute pancreatitis and on the basis of the results obtained define specific health care measures for prevention and suppression of complications.

Patients and Methods: This study included patients, suffering from acute pancreatitis, treated at the Clinic for General and Abdominal Surgery of UCCof the Republic of Srpska in Banja Luka, in the period from January 1st, 2015 until April 30th, 2017. The total number of patients treated in this period is 147. Diagnosis of the disease is based on a detailed anamnesis at the entrance (acute abdominal pain in all patients), laboratory examinations (complete blood images, C-reactive protein, amylase, and lipase) and diagnostic procedures (abdominal ultrasound examination, chest RTG, CT, ERCP, NMR and ECG). Based on the data obtained from the history of the disease, protocols and release lists, the following statistical analyses were performed: frequency of complications was established as well as mortality in billiary, alcoholic and idiopathic types of acute pancreatitis.

Results: The examinations performed determined the minimum number of laboratory and diagnostic procedures that confirm the acute pancreatitis diagnosis within a short period of time. The leading symptom of admission was a strong abdominal pain, present in all patients. Laboratory trials are dominated in elevated values of the total number leukocytes, C-reactive protein (CRP), and serum levels of amylase, lipase and bilirubin. Early diagnostic procedures, within the first 48 hours, significantly contribute to the reduction of acute pancreatitis complications. Out of a total of 147 patients with this diagnosis, 110 patients were treated conservatively and 27 operatively. Eight patients had a mortal outcome. By type of acute pancreatitis, billiary form is in the first, idiopathic second and alcoholic form in the third place. The mild clinical form of acute pancreatitis was present in 124 patients and severe in 23. Mortality rate was 5.44% in all three clinical forms.

Conclusion: Early confirmation of acute pancreatitis diagnosis is the basic prerequisite of disease progression, reduction of possible complications, and death as an outcome of the disease. Patients who were treated conservatively had a lower rate of complications, shorter hospital stay, faster recovery and better quality of life in the later period. Multidisciplinary approach to diagnosis and treatment patients suffering from acute pancreatitis significantly reduces morbidity and mortality. Quality and comprehensive health care, as part of multidisciplinary team work, contributes to reducing disease complications and faster recovery of the patient. The results of treatment of acute pancreatitis patients at UCC RS do not differ significantly from the results of treatment in similar institutions in the region and the world.

Key words: acute pancreatitis, therapy, complications

(Scr Med 2018:49:30-36)

Submitted: March 13th, 2018
Accepted: March 19th, 2018

Introduction

Acute pancreatitis is a growing problem in Europe and North America. Incidence of the acute pancreatitis is 40-102/100 000 in countries where alcohol is consumed intensively, particularly at weekends, such as in Finland. Incidence is different all over the world and due to various aetiological factors. It ranges from 5.4 to 73.4 per 100 000 inhabitants with a low incidence in England and the Netherlands, middle in Germany and Scotland, and exceptionally high in North America and Finland. The incidence of alcoholic pancreatitis is higher in males, and biliary type in females. In recent years, the incidence of diagnosed acute pancreatitis has increased in Western Europe countries. In developed countries, there are several reasons for these indicators about the increase in acute pancreatitis (AP). The main reason for this is the increase in diagnosed cholelitiasis syndrome as well as the increase in alcohol consumption and better diagnostic procedures (CT, endoscopic US, NMR and others). Although the incidence of disease increases, mortality is down due to improved diagnostic and therapeutic procedures. Based on some studies there was a fall in mortality in the last years between 2% and 11.4% .[1-3]

Acute pancreatitis is the autoimmune process caused by the activation of zymogens in the active proteolytic enzymes within the pancreas. The causes of the activation of this process are still unclear.[4]

The gold standard for diagnosing of AP is the determination of serum pancreatic enzymes (serum amylases and urine and lipase).[5,6] If lipase is 2.5-3 times higher than the physiological value it indicates alcoholic pancreatitis.[7] Other laboratory tests for the diagnoses of AP are important values: CRP (C-reactive protein), hemoglobin, hematocrit, leukocytes, platelets, bilirubin, creatinine, urea, glucose, cholesterol, albumin, potassium, sodium, coagulation factor, chloride, acid-base status, TNF- tumor necrosis factor), cytokines.[8]

Ultrasound (US) of the abdomena is the first line of search to determine the AP etiology and to track the development and course of the disease.[9] US is a non-invasive method, does not expose the patient to radiation, is fast and the first elementary indicator to assess the clinical image weight of AP.[10]

The second line of search is computerized tomography (CT). If the US could not confirm the diagnosis with certainty, because meteorism or adiposity of the patient, CT is the choice. A pancreatic presentation is provided and should be used in case of doubt in the severe form of AP as well as in all cases of unclear diagnosis.[11]

Based on the CT recordings, Baltazar and all. have developed the CT index of the weight of the image clinic, by which the morphological assessment of the AP.[12]

Nuclear magnetic resonance has several advantages over the CT to confirm the diagnosis and determine the complications. With NMR there is no risk of radiation, the contrast has little unwanted effects and is not nephrotoxic.[13,14]

ERCP (Endoscopic Retrograde Cholangio-Pancreatography) has a diagnostic and prophylactic purpose. This study visualises gallbladder stems, which can then be removed by papillotomy.[15] Severe forms of pancreatitis by ERCP reduce morbidity and mortality.[16]

Acute pancreatitis is non specific inflammation of the pancreas due to the intrapancreatic activation of its proteolytic and lipolytic enzymes - enzyme lesions. The enzymes normally excreted by the pancreas are activated in the pancreas and destroy its tissue, leading to an autolysis process that causes bleeding and damage to the blood vessels. Enzyme autodigestion begins with local inflammation, edema, bleeding and necrosis. The most common causes of acute pancreatitis are: gall bladder stones, viral infections (parotitis, coxsackie B virus), bacterial infections (Mycoplasma pneumoniae, Campylobacter), injuries, pancreatic or gall bladder operations, alcohol and some medications.

The severe form of acute pancreatitis is characterized by the development of local and systemic complications. Local complications include: pancreatic pseudocysts, necrosis, fistula development, and ascites formation, while systemic factors include: infection, hypotension, acute kidney failure, respiratory failure, cardiac insufficiency, gastrointestinal bleeding and the development of disseminated intravascular coagulation (DIC). Acute pancreatitis with multiple organic disorders ends with fatalities.[17]

Every year, a large number of papers on acute pancreatitis are published in the world, new conclusions are made and the papers are published in modern treatment, they are sharing experiences, which in itself speaks of the seriousness of this difficult problem which can often be an enigma. Based on these findings, today we distinguish two forms of acute pancreatitis: acute interstitial pancreatitis and acute necrotary pancreatitis. Despite early recognition and adequate treatment of acute pancreatitis and its complications, mortality remains very high. In late stages, patients die due to infections. The highest mortality in patients with infected necrosis of the pancreas is between 30 and 60%, while in sterile necrosis mortality ranges from 0 to 11% .[18]

Based on the clinical picture, laboratory, diagnostic and other parameters, the treatment is determined. There is a number of recommendations at the national and international level, as well as by gastroenterology associations, but there is still no specific causative therapy for this disease. Treatment begins with aggressive fluid replacement, correction of metabolic disorders, good analgesia and the treatment of local and systemic complications. Early and timely detection and recognition of complications is the key to proper treatment. AP requires treatment by multidisciplinary teams of doctors of various specialties as well as intervention and comprehensive health care by health professionals. On the basis of all relevant findings, a therapy that can be conservative and operative. These two therapies are mutually complementary.[19]

The mild to medium heavy form of the AP is treated at the surgical department, and is difficult in the intensive care unit of the surgery, with complete monitoring of the patient, which implies the establishment of a central venous pathway, measurement of central venous pressure (CVP), electrocardiography (ECG), arterial blood pressure (TA), diuresis, gas analyzes, breathing frequencies, blood count monitoring and biochemical analysis, temperature of the body. The mild and medium heavy forms have a mortality of 0-3%, uninfected necrotic pancreatitis up to 10%, and necrotic AP about 25-30%. The general mortality is 2-10%.[13]

The therapy of severe pancreatic disorders is largely surgical procedure.[17] Greenberg et al. states that serum lipase has a higher sensitivity to detect acute pancreatitis than serum amylase.[20] Values of antistreptolysin titre (AST), alanine transaminase (ALT), urea and bilirubin may be elevated, but are not significant for the detection of acute pancreatitis. Cholecystectomy is the most important of operative interventions.[21] The most common local complication is retroperitoneal abscesses, while the most common systemic complications are respiratory and cardiovascular.[22]

Aim of the Study

Determine the incidence of complications (morbidity) and mortality in the case of biliary, alcoholic and idiopathic types of acute pancreatitis and on the basis of the results, define specific health care measures for the prevention and suppression of the complications.

Patients and Methods

The study included patients with acute pancreatitis who were treated at the University Clinical Centre of the Republic of Srpska in Banja Luka, at the Clinic for General and Abdominal Surgery. The sample includes 147 patients who were treated in the period from January 1st, 2015 until May 1st, 2017. with the diagnosis of acute pancreatitis. Of the 147 patients analyzed, 94 (63.90%) were male and 53 (36.05%) female. Most patients had an mild-to-moderate form of acute pancreatitis, 124 patients (84.4%), while 23 patients (15.6%) had severe acute pancreatitis. The examination was conducted with respect to the Helsinki Declaration on Medical Research, with the prior consent of the Ethics Committee of the University Clinical Centre of the Republic of Srpska. The study was a retrospective-prospective study lasting 28 months, involving detailed data collection from the history of the disease and the protocols of the department. Evaluation of the obtained results, with all relevant parameters, was processed statistically and presented graphically.

Due to the way of processing, and with respect to the principles of credibility, all survey data were presented in electronic form. The obtained results, in accordance with the set objectives of the research, were statistically processed and analyzed using the appropriate standards and processing programs. When processing the data, each patient is provided with anonymity.

Different methods of interferential statistical processing tested and concluded implicit research hypotheses about the existence of differences between different methods of treatment of acute pancreatitis in relation to statistically credible research parameters.

During statistical processing, descriptive statistics of all patients by individual categories were first made, and then a comparison between two or more different categories according to the research objectives.

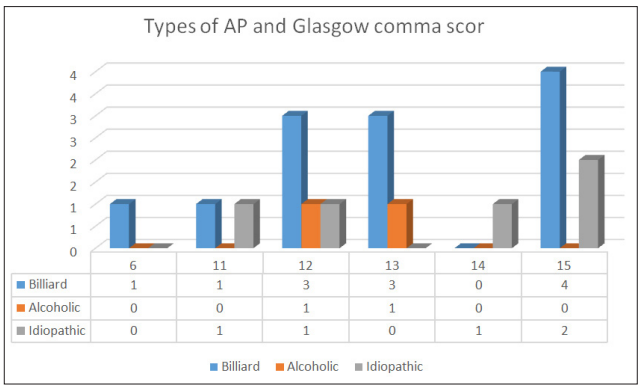
Results

Out of a total of 147 patients with AP, 124 or 84.4% had a mild to moderate clinical picture, while 23 or 15.6% had a severe clinical picture.

Of the 19 patients ranked according to the GLASGOW score scale, they were all in the range of 6 - 15. Most of them were biliary type (12) , out of which 1 patient was in a heavy coma, 4 in a middle difficulty coma and 3 patients in a shallow coma. Then there is an idiopathic type with 5 patients, of whom 2 were in the middle heavy coma and 3 in the shallow coma. In the end, the alcoholic type were two patients, of which 1 was in a medium heavy coma, and 1 in a shallow coma.

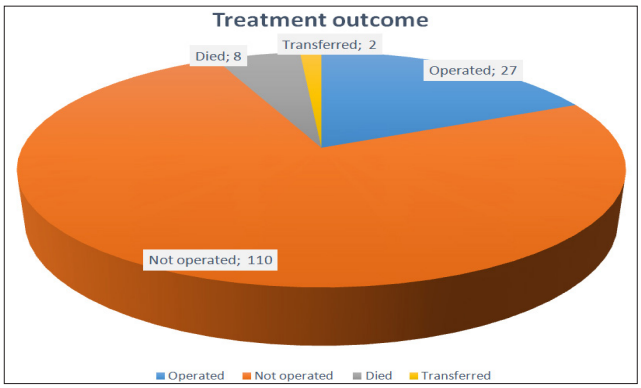
One patient was in a heavy coma, 7 patients in a middle-aged coma and 11 patients in a shallow coma. (Chart 1.)

Chart 1. Patients Ranked According to the Glasgow Comma Scores for Billiard, Alcoholic and Idiopathic AP Types



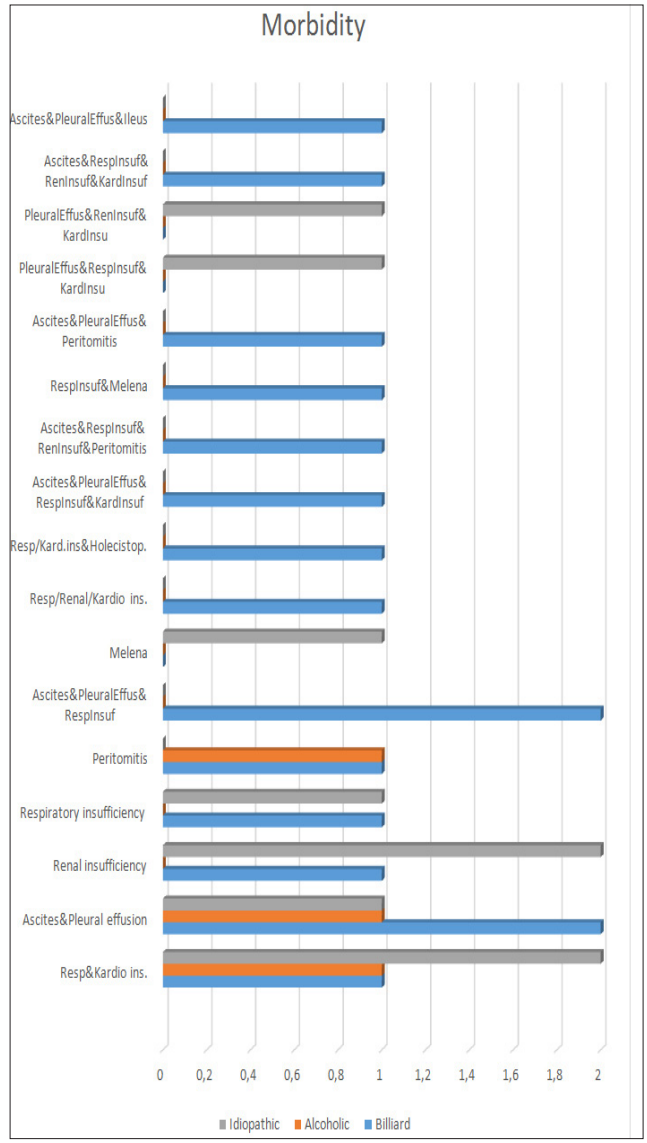
Out of the total analyzed 147 patients, 110 patients or 74.83% were treated conservatively, 27 or 18.37% were treated operatively, 8 patients or 5.44% were with death and 2 patients or 1.36% had been relocated to other departments. Of 8 patients with mortality, 5 were treated conservatively and 3 patients operatively. Three patients scheduled for surgery failed to give written consent and were not operated. (Chart 2.)

Chart 2. Outcome Treatment of Patients with Patients Exposed Treatment Conservative and Operative Procedures



The most complications are in the biliary type AP (12.24%), followed by idiopathic type AP (10.20%) and alcohol type AP (2.04%). Out of a total of 147 patients with AP, 66 were biliary (18 with complications, 48 without complications), 25 alcoholic (3 with complications, 22 without any complications), 56 idiopathic (15 with complications, 41 without any complications). The most common complications are ascites, pleural effusion, renal insufficiency, respiratory failure, cardiac insufficiency and combinations of combined complications in systemic failure of vital organs. (Chart 3.)

Chart 3. Frequency of Complications (Morbidity) in Biliary, Alcoholic and Idiopathic AP types

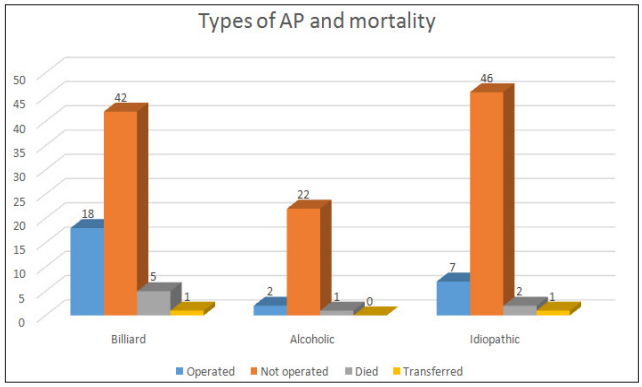


Out of the 66 (44.90%) patients of the biliary type, the structure was as follows: 18 (12.24%) were treated surgically, 42 (28.57%) conservatively, 5 (3.40%) fatal outcomes, 1 (0.68%) patient was transferred to another department.

There were 25 (17.01%) patients with alcohol type of AP, and the structure was as follows: 2 (1.36%) were treated surgically, 22 (14.97%) conservatively, 1 (0.68%) death outcome. Of 56 (38.10%) of patients with idiopathic type AP, the structure was as follows: 7 (4.76%) were treated surgically, 46 (31.29%) conservatively, 2 (1.36%) had a fatal outcome and 1 0.68%) patient was transferred to

another department. (Chart 4)

Chart 4. Mortality in Billiard, Alcoholic and Idiopathic AP types



Discussion

Acute pancreatitis is a disease that requires a quick anamnestic and diagnostic assessment of the state of the disease's severity to predict the course and outcome of the disease as early as possible. Treatment can be conservative and operative. According to the protocol, it begins with the conservative measures that give the best results. In cases of failure through conservative treatment or complications, treatment with hepatic injury is considered.[1] Indications for an operation are: progressive clinical deterioration, in addition to intensive conservative therapy, pancreatic abscess, uncertainty in clinical diagnosis, correction of the simultaneous hepatobiliary tract disease.[2]

Out of a total of 147 patients treated with acute pancreatitis diagnosed during the period from January 1st 2015 until May 1st 2017. at the Clinic for General and Abdominal Surgery, 110 (74.83%) were treated conservatively, 27 (18.37%) operatively, 8 (5.44%) patients had a mortality outcome, another 2 (1.36%) patients were treated conservatively and moved to further treatment, to the second division. The obtained statistical results are comparable with the data from available literature. Clinical centers in the European Union, according to modern treatment protocols, also have the largest number of conservatively treated patients. The relationship between conservatively treated and treated patients varies depending on the number of patients involved in the study and varies from country to country.[19,23]

The frequency of complications is most pronounced in the billiary type (12.24%) followed by idiopathic type (10.20%) and alcohol type (2.04%). Out of a total of 147 patients, 66 were billiary (18 with complications, 48 without any complications), 25 alcoholic type (3 with complications, 22 without any complications), 56 idiopathic type (15 with complications, 41 without any complications). The most common complications were: ascites, pleural effusion, renal insufficiency, respiratory insufficiency, cardiac insufficiency and a combination of joint complications in systemic vital organs. According to larger, randomized studies, regardless of whether they are multicentric type or not, the most complications are described in the billiary type, but the type of complications and their duration differ.[22-25] These facts are explained by a greater degree and the development of health care in the countries of Western Europe. Studies showed a small incidence of complications such as renal and respiratory insufficiency, especially in younger patients.[24-27]

Conclusion

Patients with biliary type of AP are most common. Of the total number of patients analyzed, the majority of them were treated conservatively, with fewer incidences of the complications and deaths. The most common complications were: ascites, pleural effusion, respiratory and renal insufficiency, as well as a combination of associated complications in the systemic failure of vital organs. Early diagnosis and adequate therapy are crucial for both the outcome of the disease and the financial point of view.

A multidisciplinary approach in the diagnosis and treatment of patients suffering from acute pancreatitis significantly reduces morbidity and mortality. The results of treating patients suffering from acute pancreatitis in the University Clinical centre of the Republic of Srpska in Banja Luka do not deviate significantly from the results of treatment in similar institutions in our region and in the world.

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Komplikacije liječenja akutnog pankreatitisa

SAŽETAK

Uvod: Akutni pankreatitis je nespecifično zapaljenje pankreasa koje nastaje zbog intrapankreatične aktivacije njegovih proteolitičkih i lipolitičkih enzima - enzimska lezija. Enzimi koje pankreas normalno izlučuje se aktiviraju u pankreasu i razaraju njegovo tkivo, dovodeći do procesa autolize koji uzrokuje krvarenja i oštećenje krvnih sudova. Enzimska autodigestija počinje lokalnom inflamacijom, edemom, krvarenjem i nekrozom.

Cilj rada: Cilj ovog rada je utvrđivanje učestalosti i komplikacije kod pacijenata oboljelih od akutnog pankreatitisa i na osnovu dobijenih rezultata definisati specifične mjere zdravstvene njege za prevenciju i suzbijanje komplikacija.

Ispitanici i metode: Ovim radom obuhvaćeni su pacijenti oboljeli od akutnog pankreatitisa, liječeni na Klinici za opštu i abdominalnu hirurgiju UKC Republike Srpske u Banjaluci, u periodu od 01.01.2015. do 30.04.2017. Ukupan broj pacijenata liječenih u ovom periodu je 147. Dijagnoza bolesti postavljena je na osnovu iscrpne anamneze pri prijemu (akutni abdominalni bol kod svih pacijenata), laboratorijskih pretraga (kompletne krvne slike, C reaktivni protein, amilaze, lipaza) i dijagnostičkih procedura (ultrazvučnog pregleda abdomena, RTG-a grudnog koša, EKG-a, ERCP-a CT-a i NMR-a). Na osnovu dobijenih podataka iz istorija bolesti, protokola i otpusnih lista izvršene su slijedeće statističke analize: utvrđena je učestalost komplikacija i smrtnost kod bilijarnih, alkoholnih i idiopatskih tipova akutnog pankreatitisa.

Rezultati: Učinjenom obradom utvrđen je najmanji broj laboratorijskih i dijagnostičkih procedura koji uz anamnestičke podatke u kratkom vremenskom roku potvrđuju dijagnozu akutnog pankreatitisa. Vodeći simptom na prijemu bio je jak abdominalni-pojasni bol, kod svih ispitanika. U laboratorijskim pretragama dominaraju povišene vrijednosti ukupnog broja leukocita, C reaktivnog proteina (CRP), te serumske vrijednosti amilaze, lipaze i bilirubina. Rane dijagnostičke procedure, u prvih 48 sati, značajno doprinose smanjenju komplikacija akutnog pankreatitisa. Od ukupno 147 pacijenata sa navedenom dijagnozom, 110 pacijenata je liječeno konzervativno, a 27 operativno. Osam pacijenata je imalo smrtni ishod. Po tipu akutnog pankreatitisa na prvom mjestu je bilijarni oblik, zatim idiopatski i na trećem mjestu alkoholni oblik. Lakša klinička forma akutnog pankreatitisa bila je zastupljena kod 124 pacijenta, a teška kod njih 23. Stopa smrtnosti je 5,44% kod sva tri klinička oblika.

Zaključak: Rana potvrda dijagnoze akutnog pankreatitisa je osnovni preduslov toka bolesti, smanjenja nastanka mogućih komplikacija i smrtnog ishoda bolesti. Pacijenti koji su liječeni konzervativno imali su manji procenat komplikacija, kraću hospitalizaciju, brži oporavak i bolji kvalitet života u kasnijem periodu. Multidisciplinarni pristup u dijagnostici i liječenju pacijenata oboljelih od akutnog pankreatitisa značajno je smanjio morbiditet i mortalitet. Kvalitetna i sveobuhvatna zdravstvena njega, kao dio multidisciplinarnog timskog rada, doprinosi smanjenju komplikacija bolesti i bržem oporavku pacijenta. Rezultati liječenja pacijenata oboljelih od akutnog pankreatitisa na UKC RS ne odstupaju bitnije od rezultata liječenja u sličnim ustanovama u regionu i svijetu.

Ključne riječi: akutni pankreatitis, liječenje, komplikacije.

ORIGINAL PAPER

doi: 10.18575/msrs.sm.e.18.06
UDC: 616.33:316.728
COBISS.RS-ID: 7317528

Quality of Life after Gastrectomy

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ABSTRACT

Introduction: Until recently, gastric cancer represented the most common visceral neoplasm. In Japan, the prevalence of disease is 58.4 per 100,000 inhabitants for men and 29.9 for women. Here, the incidence is lower. Gastrectomy is the most common surgical method of treating carcinomas of the stomach.

Aim of the Study: To determine which method of reconstruction after gastrectomy improves the quality of life optimally.

Patients and Methods: We analyzed 221 patient operated on for gastric cancer at the Surgical Clinic of the University Clinical Center in Banja Luka, and the subject of a detailed analysis of the 111 patients who were operated with the intention of achieving curability.

Results: Reflux esophagitis is dominant modality in reconstruction wth omega loop ($p < 0.05$). Analyzing GIQLI, we found dominant modality GIQLI II in the total gastrectomy and reconstruction options RY, while predominantly GIQLI III was registered in HLR reservoir reconstruction method ($p < 0.01$). And two hours after the ingestion of a meal labeled with a radioisotope Tc99m in artificial gastric reservoir (HLR) showed signs of radioactivity (about 10% amount). "H0 performance" (AJCC / UICC) was the most frequently recorded in subtotal gastrectomy, while there was significant appearance of "H1" and "H2" modalities with the total gastrectomy statistically. In RY reconstruction, statistically significant was participation modalities "H1", while "H1" performance (AJCC / UICC) was the dominant modality at the HLR options reconstruction with statistically significant frequency of occurrence ($p < 0.01$).

Conclusion: The results of the assessment of quality of life are comparable with the results of other statistical series. They confirm antireflux component Roux en Y reconstructions and its intestinoplications and highlight the advantage of the nutritional components loop modifications (creation pouch-a).

Keywords: gastrectomy, quality of life

(Scr Med 2018:49:37-42)

Submitted: March 17th, 2018
Accepted: March 25th, 2018

Introduction

Until recently, gastric cancer represented the most common visceral neoplasm. In Japan, the prevalence of disease is 58.4 per 100,000 inhabitants for men and 29.9 for women. In the United States of America, it ranks eighth on the list of causes of death related to malignancy. The five-year survival rate in Western countries is approximately 20% on the average, while in Japan it reaches up to 50% (for early gastric cancer – EGC even up to 90%).[1-5] The concept of extensive surgery for visceral neoplasms is currently topical and it further actualized the problem of restoration of digestive continuity, as the reduction of surgical radicality in an attempt to reduce the intensity of postoperative suquelae is unjustified.[6-11]

Aim of the Study

Aim of the study is to determine whether the construction of a gastric pouch has a beneficial effect on the nutritional status, i.e. whether it improves the quality of life of those who underwent surgery.

Patients and Methods

We analysed 221 patients surgically treated for gastric cancer at the Surgery Clinic of the Clinical Centre in Banja Luka, while 111 patients who were operated with the intention of achieving curability were the subject of a detailed analysis. In the study, documentation of the Surgery Clinic and the Institute for Pathology of the University Clinical Centre in Banja Luka was used. The patients were classified based on gender and age, while gastric malignancy was classified based on the macroscopic and microscopic appearance, tumor location and stage of the disease. The study covered 64 male patients (57.7%) and 47 female patients (42.3%). Most patients belonged to the age group between 60 and 70 years (36%). The dominant type of cancer was adenocarcinoma (92%), while 5% of these were lymphoma and 3% were sarcoma. There were 5% patients who underwent surgery of limited extensiveness, 43% of them underwent subtotal resection, 46% total gastrectomy and 6% of patients underwent extended total gastrectomy. For total gastrectomy, in 52.63% of cases the reconstruction was done with the RY method, in 43.86% of cases an HLR pouch was made, and in 2 patients (3.51%) an omega loop was made.

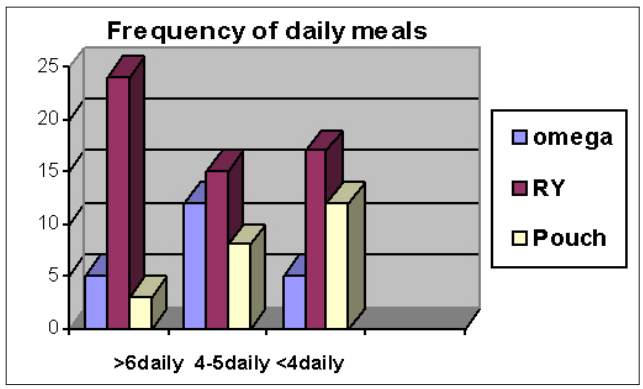
Results

1. Reflux oesophagitis - *in certain gastric substitution options: (a sample of 53 patients who underwent gastroscopy and reflux was confirmed.*

Based on the calculated value of Fisher test (Fisher: p=0.030), in the overall sample of those included in the analysis, there was a statistically significant difference ($p < 0.05$) in the occurrence of reflux gastritis and oesophagitis in patients with respected to certain gastric substitution options, with grade 1 reflux being the dominant modality. Among the different reflux modalities, grade 2 reflux and grade 3 reflux were significant in omega-loop reconstruction.

2. Meal frequency - *in certain gastric substitution options*

Chart 1. Daily Meal Frequency in Different Reconstruction Methods



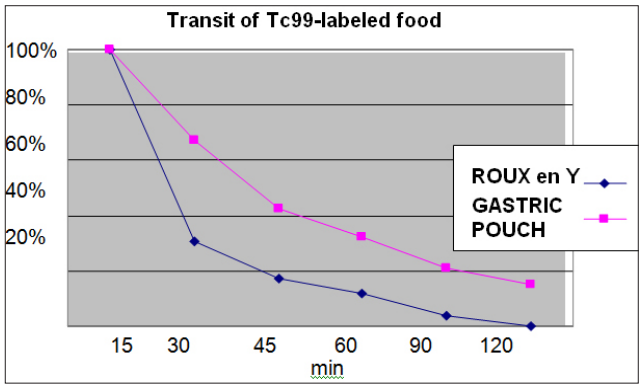
Based on the calculated value of $\chi 2$ test ($\chi 2 = 12.103$; $p = 0.0166$), in accordance with the established contingency table, in the overall sample of those included in the analysis, there was a statistically significant difference ($p < 0.05$) in the daily meal frequencies in patients with different gastric substitution options, with 4 to 5 meals per day being the dominant modality. (Chart 1.)

3. Food transit (food clearance) - *in certain gastric substitution options*

Food transit was monitored using a SOPHA gamma camera, made in France.

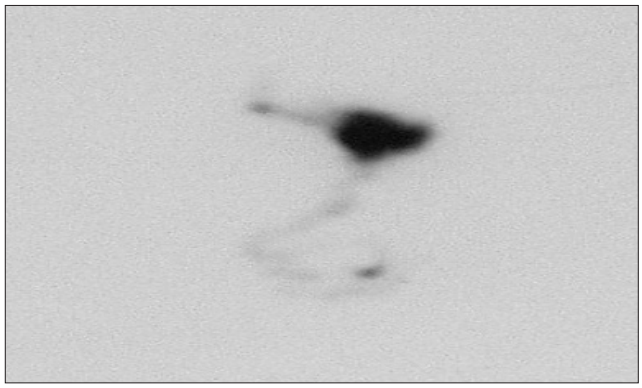
A radiopharmaceutical (isotope) Tc99 sulfur colloid was given perorally, at a dose of 2-3 mCi (74-111 kBq), with a small amount of water. A comparison was made between RY reconstruction option and Hunt-Lawrence-Rodino pouch reconstruction. For Roux-en-Y method, rapid emptying of food labeled with radioactive Tc99 was registered. After 30 minutes, only about 30% of the total amount of food was registered in the Roux-Y loop region and after 45 minutes about 18%, while after 60 minutes signs of radioactivity were barely displayed (about 10%). For HLR pouch reconstruction, over 60% of the total amount of food was registered in the pouch after 30 minutes and about 35% after 60 minutes. (Chart 2.)

Chart 2. Food Transit (emptying time)



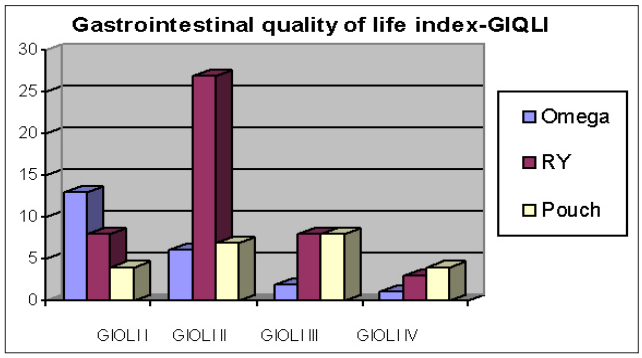
Even after two hours, the artificial gastric pouch showed signs of radioactivity (about 10% of the total amount). (Figure 1.)

Figure 1. Food transit (food clearance) – scintigraphy with radioactive colloid Tc^{99}; Transit after 30 min (HLR pouch)



4. Gastrointestinal quality of life index- GIQLI - *in certain gastric substitution options* To estimate the postoperative quality of life , we used questionnaire of index quality of life by Eypasch, Williams , Troidl - in 36 questions (Gastrointestinal Quality of Life Index - GIQLI).[1-4]

Chart 3. Gastrointestinal Quality of Life Index (giqli)



Based on the calculated value of $\chi 2$ test ($\chi 2 = 21.858$; $p = 0.0013$), in accordance with the established contingency table, in the overall sample of those included in the analysis there was a statistically highly significant difference ($p < 0.01$) in the GIQLI in patients with different gastric substitution options, with GIQLI II being the dominant modality. (Chart 3.)

5. »H performance« (AJCC/UICC) - *in certain gastric substitution options* Based on the calculated value of $\chi 2$ test, for omega loop reconstruction method ($\chi 2 = 1.455$; $p = 0.4831$), there was no statistically significant difference ($p > 0.05$) in the share of the "H2 performance status" modality. For Roux-en-Y reconstruction option ($\chi 2 = 7.087$; $p = 0.0289$), there was a statistically significant difference ($p < 0.05$) in the share of the "H1 performance" modality. For Hunt-Lawrence-Rodino pouch reconstruction option ($z = 6.572$; $p = 0.0000$), there was a statistically highly significant difference ($p < 0.01$) in the share of the "H1 performance" modality. Based on the calculated value of $\chi 2$ test ($\chi 2 = 30.171$; $p = 0.0000$), in accordance with the established contingency table, in the total number of analysed patients there was a statistically highly significant difference ($p < 0.01$) in the "H performance status" between different gastric substitution options. The share of the "H1 performance status" modality was dominant.

Discussion

Despite the declining incidence, gastric cancer remains in the focus of attention of medical experts due to its high mortality rate. From the surgical perspective, only radical resection of the primary tumor lesion, including lymphatic drainage, while achieving safe resection margins (tumor-free margins) offers a realistic hope for an adequate control of the disease. Standardisation of luminal resection levels has already been achieved, while the surgical research is dominated by the still unresolved question of which level of lymph node dissection should be performed for what stage of the disease.[1-3] The rate of late morbidity is high, as more than two thirds of those who underwent surgery failed to reach the preoperative body weight. Most frequent were patients for whom the modality of moderate malnutrition (loss up to 10 kg of body weight) was most commonly recorded. Statistically significant moderate to severe malnutrition was observed for total gastrectomy and the reconstruction option involving Roux-en-Y method. Reflux gastritis and oesophagitis is a sequela that is registered in 28.3% of patients who underwent surgery, most frequently for the option of reconstructing the digestive tract with omega loop. Disordered eating occurring due to the loss of gastric reservoir results in an increase in number of meals and a decrease in quantity of meals. Different

methods of substituting lost gastric reservoir (so far, over 60 options are known) are the subject of numerous studies nowadays, with the aim of improving the quality of postoperative life. The authors generally agree the quality of life assessment must be multidimensional and include, according to some of them, three dimensions: psychological, social and emotional (Cella and Tulsky), or even more than 10 categories, as advocated by Spitzer, Troidl and Kusche (psychological status, functional status, family and emotional well-being, spirituality, satisfaction with treatment, orientation towards the future, sexuality, social and occupational functions).4-10 To assess the postoperative quality of life, the Gastrointestinal Quality of Life Index (GIQLI) Questionnaire by Eypasch, Williams and Troidl, consisting of 36 questions required for the assessment of the postoperative state of the patient, was used in the study. Each question referred to the patient's state for the last 15 days and there were five options to be chosen from in the answer: always, mostly, sometimes, rarely, never. The variants of the answer to each question were: a) never-4 points, b) rarely-3 points, c) sometimes - 2 points, d) mostly-1 point, e) always-0 points.

The most favourable option is 4 points, while the least favourable one is 0 points. Points are added to obtain the result which is calculated in the result scale.[11- 17]

In accordance with the American Joint Committee on Cancer/Union Internationale Contre le Cancer (AJCC/ UICC) Classification, "H performance" was applied as follows:

A)"H0" - asymptomatic, normally active patient;
B)"H1" – moderate-intensity symptoms, requiring no treatment;
C)"H2" – patients requiring ambulatory treatment more than 50% of time;
D)"H3" – patients requiring medical care more than 50% of time;
E)"H4" – patients who need hospitalisation or are bedridden.[13,14]

The ratio of current and ideal body weight (Blackburn) served to assess the postoperative nutritional status of the patient.15 It was applied as follows:

1. Blackburn <1 ----- malnutrition;
2. Blackburn 1-1,2 – optimal nutrition;
3. Blackburn >1,2 – adiposity.

An analysis of the quality of life is an integral part of most statistical series. K. Buhl et al. from the University of Heidelberg, analysing the quality of life after gastric substitution, find the highest prevalence of heartburn after the reconstruction without a pouch, which is confirmed by the endoscopic findings of symptoms of reflux oesophagitis.15-17.Similar findings resulted from the quantification of the severity of postprandial dumping syndrome with dominant symptoms in patients who underwent the reconstruction without a pouch. The daily meal frequency was highest in the gastric substitution option with Hunt-Lawrence-Rodino pouch, while the quantity of meals was slightly higher in the same option of digestive continuity reconstruction (Hunt-Lawrence-Rodino). Nutritional status was assessed based on the ratio of current and optimal body weight (Blackburn); the best results were recorded for the reconstruction option with a pouch.18,19 Visick grade, Karnofsky Performance Scale Index, Spitzer Index, Troidl scoring system were the parameters used and they indicate more optimal postoperative results achieved by creating a gastric pouch with an antireflux and nutritive component. Fass J. Et al. from the Department of Surgery in Aachen, Germany, performing a conversion of omega loop into Roux-en-Y option in 4 patients due to reflux oesophagitis, reported complete resolution of reflux symptoms immediately after surgical treatment.20,21The current Visick grading was 1, 2, 2, 3. Korenaga assessing the quality of life using the Visick scale in 40 patients who underwent surgery due to gastric atony, found a significant improvement in comparison with the values of the Visick scale preoperatively.22 A.C. Takiguchi assessed the quality of life for certain gastric substitution options, coming to the following results: patients with omega loop (Braun) had heartburn, and grade 2 reflux oesophagitis was endoscopically confirmed. In two patients omega loop was converted into antireflux Roux-en-Y option (Schloffer reconstruction), resulting in a complete remission of symptoms. "H performance status" (AJCC/UICC) indicates that the best results are achieved by creating Roux-en-Y option ("H0", "H1").23 In the analysed sample of patients who underwent surgery, in terms of the daily meal frequency, there is a significant difference for certain reconstruction options. For the reconstruction method with a pouch, less than 4 meals per day is the dominant modality, while for Roux-en-Y reconstruction method the most common modality is more than 6 meals per day. In terms of quantity, the largest meal was consumed by patients who underwent reconstruction with a pouch; one third provided data about approximately the same quantity of food consumed per one meal as before the surgery. Comparing the food emptying time from the artificial gastric pouch and simple Roux-en-Y reconstruction method, we came to results that indicate that Roux-en-Y method was characterised by rapid emptying of food labeled with radioactive Tc99. After 30 minutes, only about 30% of the total amount of food was registered in the Roux-Y loop region, after 45 minutes about 18%, and after 60 minutes about 10%. For the pouch reconstruction, over

60% of the total amount of food was registered in the pouch after 30 minutes and about 35% after 60 minutes. Even after two hours, the artificial gastric pouch showed signs of radioactivity (about 10% of the total amount). Analysing the Gastrointestinal Quality of Life Index (GIQLI), we found that the GIQLI II modality was dominant for total gastrectomy and RY reconstruction option, while GIQLI III was dominant for HLR pouch reconstruction method. Karnofsky Performance Scale Index 60-100% appeared to a statistically significant extent for total gastrectomy, while HLR reconstruction option had a statistically highly significant share of the same value index. "H0 performance" (AJCC/UICC) was most commonly recorded for subtotal gastrectomy, while total gastrectomy had a statistically highly significant occurrence of "H1" and "H2" modalities. For RY reconstruction option, there was a statistically significant share of "H1" modality, while "H1 performance" (AJCC/UICC) was the dominant modality for HLR reconstruction option, with a statistically highly significant frequency of occurrence.

Conclusion

Results of the quality of life assessment are comparable with results of other statistical series. They confirm the antireflux component of Roux-en-Y loop and its intestinoplasty, emphasising the advantage of the nutritional component of loop modification (creation of a pouch).

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Kvalitet života nakon gastrektomije

SAŽETAK

Uvod: Karcinom želuca je jedna od najučestalijih visceralnih neoplazmi. U Japanu je učestalost obolijevanja 58,4 na 100 000 stanovnika za muškarce i 29,9 za žene. Kod nas je incidencija nešto niža. Gastrektomija je najčešća hirurška metoda liječenja kacinoma želuca.

Cilj rada: Utvrditi koja metoda rekonstrukcije nakon gastrektomije optimalno poboljšava kvalitet života operisanih.

Ispitanici i metode: Analiziran je 221 pacijent operisan zbog malignoma želuca na Hirurškoj klinici Univerzitetskog Kliničkog centra u Banjaluci, a predmet detaljne analize je 111 pacijenata koji su operisani sa namjerom postizanja kurabilnosti.

Rezultati: Refluks ezofagitis je dominantni modalitet morbiditeta kod rekonstrukcije omega vijugom ($p < 0.05$). Analizirajući GIQLI, dominiralo je učešće modaliteta GIQLI II kod totalne gastrektomije i opcije rekonstrukcije RY, dok je GIQLI III najčešće registrovan kod metode rekonstrukcije HLR rezervoarom ($p < 0.01$). I nakon dva sata nakon ingestije obroka obilježenog radioaktivnim izotopom Tc99 arteficijelni želudac (HLR) je pokazivao znake radioaktivnosti (oko 10% unijete količine). „H0 performance" (AJCC/UICC) je najčešće zabilježen kod subtotalne gastrektomije, dok je kod totalne gastrektomije statistički visoko značajno pojavljivanje "H1" i "H2" modaliteta. Kod RY opcije rekonstrukcije, statistički značajno je učešće modaliteta "H1", dok je "H1" performance (AJCC/UICC) dominantan modalitet kod HLR opcije rekonstrukcije sa statistički visoko značajnom učestalošću ($p < 0.01$).

Zaključak: Dobijeni rezultati procjene kvaliteta života su komparabilni sa rezultatima drugih statističkih serija. Oni potvrđuju antirefluksnu komponentu Roux en Y vijuge i njene intestinoplikacije i naglašavaju prednost nutritivne komponente loop modifikacije (kreacije pouch-a).

Ključne riječi: gastrektomija, kvalitet života

ORIGINAL PAPER

doi: 10.18575/msrs.sm.e.18.07
UDC: 616.683-006-033.2
COBISS.RS-ID:7317784

Testicular Tumors – Occurrence of Retroperitoneal Lymphadenomegaly at the Time of Diagnosis

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ABSTRACT

Introduction: Testicular tumors account for approximately 1% of all malignancies in men, but the age of patients and its increasing incidence make this malignancy one of the leading oncological problems. In spite of the fact that the testicles are organs accessible for self-examination and the accessibility of ultrasound examination as the method of choice in diagnostics, these tumors are often detected in an advanced stage of the disease.

Aim of the Study: The aim of this study is to evaluate the occurrence of advanced disease at the time of diagnosis of testicular germ cell tumors, through retrospective analysis.

Patients and Methods: Our study examines patients with testicular germ cell tumor (seminomatous and non-seminomatous) according to numerous parameters – anamnesis with special emphasis on risk factors, clinical examination, laboratory analyses with tumor markers, and diagnostic imaging examinations (thorax, abdomen and pelvis CT scan). Before the specific treatment, spermiogram and semen cryopreservation were done for most patients, while in some cases additional diagnostics (MRI of the endocranium, skeletal scintigraphy) was indicated as well.

Results: During the observation period, 132 patients with testicular germ cell tumor were treated and observed, of which 58 patients (44%) with seminomatous tumor type and 74 patients (56%) with non-seminomatous tumors. Of the total number of patients, at the time of disease diagnosis, there were 41 patients (31%) with N1-N3 status of retroperitoneal lymph nodes and 17 patients (12.8%) with M1a-M1b metastatic status.

Conclusion: A large number of newly detected testicular tumors are diagnosed in an advanced stage of the disease. It is necessary to raise awareness of the general population about this malignancy, emphasise the importance of self-examination in younger men, and promote the possibility of routine ultrasound examinations with the aim of early detection of the disease.

Key words: testicular germ cell tumor, advanced disease

(Scr Med 2018:49:43-48)

Sumbitted: March 19th, 2018
Accepted: April 2nd, 2018

Introduction

Testicular tumors represent the most common solid tumors in male population aged between 18 and 35 years. They account for 1% of malignancies in men, that is, for 5% of all urological malignancies.[1] In the last decades, there has been a continuous increase in the number of patients, with significant geographical variations. In Denmark, the incidence is 13.4/100,000 men per year, in Switzerland 12.7/100,000, in Norway 12.7/100,000, while in Egypt the incidence is 0.5/100,000.[2] Since 2001, when Registry of Malignant Diseases was founded in the Republic of Srpska, 422 patients with malignant testicular tumors have been registered, and 61 have died.[3] Approximately 95% of all malignant testicular tumors are germinal epithelium tumors, which are classified into seminoma and non-seminomatous tumors. Non-seminomatous tumors include choriocarcinoma, embryonal carcinoma, yolk sac tumor and teratoma (mature and immature). Seminoma has better prognosis than non-seminomatous tumors.[4] Most often, seminomatous tumors occur between the ages of 30 and 40, while non-seminomatous tumors in most cases occur between 20 and 30 years of age.

Cryptochidism is considered the most important risk factor, along with Klinefelter syndrome and a positive family history. Gynecomastia in young males requires additional diagnostic treatment.

Data from family cancer databases have shown that sons whose fathers have testicular cancer have four times the risk of testicular cancer, and brothers of patients with testicular cancer have eight times the risk of having testicular cancer.[5] Genetic changes have been described in patients with testicular cancer. A specific genetic marker (an isochromosome of the short arm of chromosome 12 - i(12p) - has been described in all histological types of germ cell tumors and in testicular intraepithelial neoplasia (TIN). Alterations in the p53 locus have been identified in 66% of cases of testicular TIN. A deregulation in the pluripotent programme of foetal germ cells (identified by specific markers, M2A, C-KIT and OCT4/NANOG) is likely responsible for the development of TIN and germ cell neoplasia. There is an overlap in the development to seminoma and embryonal carcinoma as shown by genome-wide expression analysis and detection of alpha-fetoprotein (AFP) mRNA in some atypical seminoma.[6]

A history of testicular germ cell tumor represents a significant risk factor for contralateral testicular cancer, which has to be taken into account in the restaging and follow up of the patient once the specific oncological treatment is completed. Infertility and gonadal dysgenesis, with pathological spermiogram findings, are often associated with the onset of testicular cancer. The role of previous testicular trauma and the association with microlithiasis are being examined.[7]

Pathological prognostic factors in metastatic disease:

- seminoma
  - Tumor larger than 4 cm,
  - *rete testis* invasion,
- non-seminomatous tumors
  - vascular/lymphatic or peritumoral invasion,
  - *proliferation rate* (MIB-1) higher than 70%,
  - percentage of embryonal carcinoma higher than 50%.

Clinical prognostic factors in metastatic disease:

- primary location,
- elevated tumor marker levels,
- presence of non-pulmonary visceral metastases.

International Germ Cell Cancer Collaborative Group (IGCCCG) has defined prognostic factors for the staging system for metastasis germ cell tumors (mGCT), including a good and intermediate prognosis for seminoma, and a good, moderate and poor prognosis for NSGCT (non-seminomatous germ cell tumors). Depending on the clinical stage of the disease and prognostic factors, expected five-year survival is different.[8]

Testicular germ cell tumors are highly curable - 100% in stage 1 and up to 80% for metastatic disease.

Aim of the Study

The aim of this study is to evaluate the occurrence of advanced disease at the time of diagnosis of testicular germ cell tumors, through retrospective analysis.

Patients and Methods

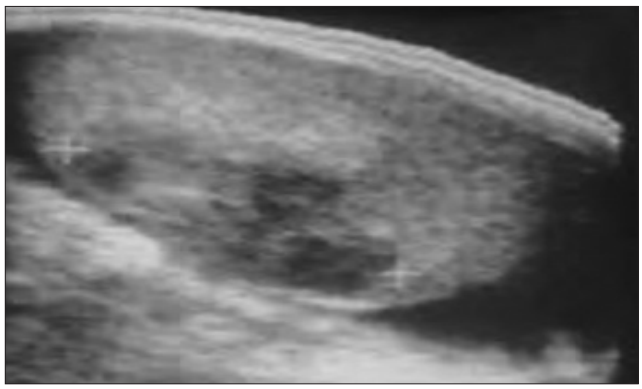
The study examines 132 patients with testicular germ cell tumor (seminomatous and non-seminomatous), who were treated at the Oncology Clinic of the University Clinical Centre in Banja Luka and the Healthcare Institution Hospital for Surgical and Internal Medicine "S.tetik", in the period between 2009 and 2014. After a radical orchiectomy and an examination of the pathohistological (PH) finding, at the first oncologist examination, a detailed

anamnesis was taken from all the patients and they all underwent an oncological clinical examination. Further treatment in accordance with ESMO (European Society for Medical Oncology), EAU (European Association of Urology) and NCCN (National Comprehensive Cancer Network) recommendations was indicated - laboratory analyses, including postoperative tumor markers - category S (alpha-fetoprotein – AFP, human chorionic gonadotropin – HCG and lactate dehydrogenase – LDH), as well as a thorax, abdomen and pelvis CT scan, which represents standard diagnostic treatment for this histological type of tumor. Before the specific treatment, spermiogram and semen cryopreservation were done for most patients, while in some cases additional diagnostics (MRI of the endocranium, skeletal scintigraphy) was indicated as well. The research represents a retrospective study.

Results

During the observation period encompassing six years, 132 patients (22 patients per year on the average) were treated and observed. There were 58 patients (44%) with seminomatous tumor type, of which 52 (90%) with classical seminoma, and 74 patients (56%) with non-seminomatous tumors. In all of patients, it was gonadal primary tumor localization. Primary tumor was in most cases diagnosed by ultrasound imaging (Figure 1).

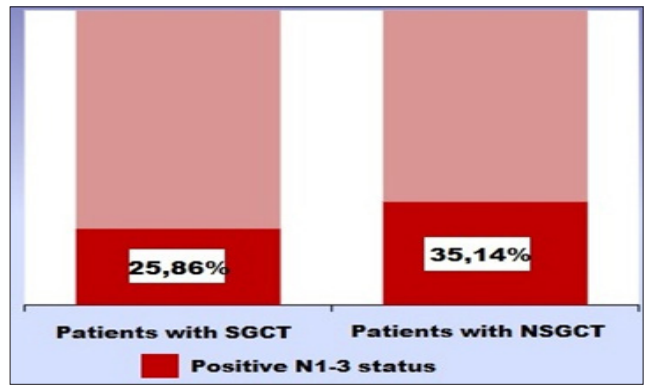
Figure 1. Testicular Ultrasound – Non-Homogenous Hypoechoic Change Corresponds to a Testicular Tumor



The average age of patients with seminoma was 38 years, while the average age of patients with non-seminomatous tumor was 30 years. Of the total number of patients, at the time of disease diagnosis, there were 41 patients (31%) with N1-N3 status of retroperitoneal lymph nodes and 17 patients (12.8%) with M1a-M1b metastatic status. M1a status indicates the presence of metastases in nonregional lymph nodes and lungs, and M1b refers to metastases in other organs.

Of 41 patients with a positive N status, there were 15 patients with seminoma (25.8% of the total number of patients with seminoma) and 26 patients with non-seminomatous tumor (35.1% of the total number of patients with NSGCT). These results are shown in Figure 2. Difference in representation of patients with positive N status and patients with seminomatous tumor and patients with non-seminomatous tumor was not statistically significant . (Pearson's $\chi 2$ test of contingency: p=0.253).

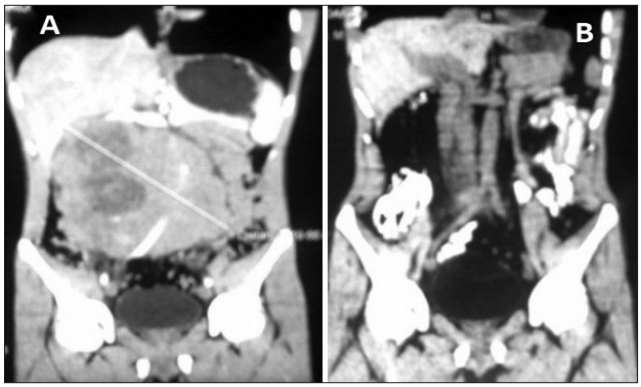
Figure 2. Percentage Representation of Patients with Positive N Status by Type of Germinative Tumor



At the time of disease diagnosis, when it comes to patients with seminoma, N1 status was found in 6 patients (metastasis in the lymph node 2 cm or smaller in the largest diameter, or multiple metastases in the lymph nodes, none exceeding 2 cm), N2 status (metastasis in the lymph nodes 2-5 cm, or multiple metastases, none exceeding 5 cm) in 7 patients, and N3 status (lymph node larger than 5 cm) in 3 patients. Non-seminomatous tumors were mainly combined (mixed) tumors, consisting of varying percentages of embryonal carcinoma, choriocarcinoma, seminoma, teratoma and yolk sac tumor. The study also included 2 cases with pure embryonal carcinoma, 1 case with pure choriocarcinoma and 1 case with pure yolk sac tumor with initial hematogenous hepatic metastasis. At the time of disease diagnosis, when it comes to patients with non-seminomatous tumor, N1 status of lymph nodes was found in 10 patients, N2 status in 9 patients and N3 status in 7 patients. Conglomerate retroperitoneal lymph nodes were found in a patient with NSGCT, with the largest diameter of 20 cm at the time of disease diagnosis (Figure 3a). The patient consulted a doctor due to pain in the lumbar region. After systemic chemotherapy, there was a great regression of lymphadenomegaly in a large number of patients, which once again demonstrated the efficacy of cisplatin-based chemotherapy in the treatment of metastatic germ cell tumors (the same patient – Figure 3b). The status of tumor marker values – category S, which is required along with the TNM classification for

determining the clinical stage of the disease), was not the subject of our analysis in this study.

Figure 3. a) - Abdomen CT Scan – 20 cm Conglomerate Retroperitoneal Lymph Nodes in a Patient Aged 24 (NSCGT)) b) - Abdomen CT Scan – Full Regression of Retroperitoneal Lymphadenomegaly after Chemotherapy

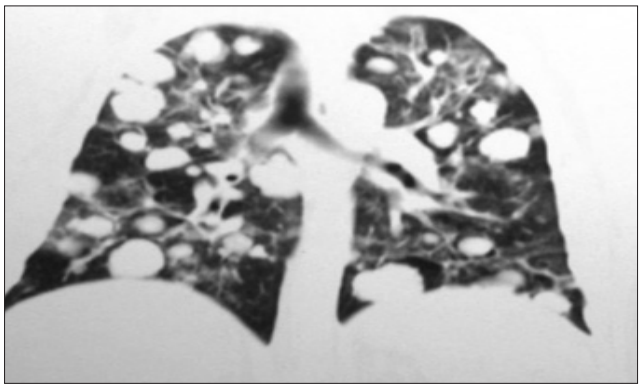


Of 15 patients with seminoma with N1-N3 status, there were 3 patients with M1a distant disease category. Of 14 patients with non-seminomatous tumor, M1a was indicated in 4 patients (nonregional lymph nodes or lungs) (Figure 3) and M1b was indicated in 10 patients (bone, brain, liver).

Of the total number of patients with seminoma (58), M1a was indicated in 3 patients (5.1%).

Of the total number of patients with non-seminomatous testicular tumor (74), M1 was indicated in 8 patients (10.8%) and M1b was indicated in 10 patients (13.5%) (8 patients with associated secondary deposits in lungs and 2 patients with extrapulmonal metastasis).

Figure 4. Thorax CT Scan – Multiple Meta-Changes in the Lungs in a patient with Non-Seminomatous Testicular Tumor



An analysis of the anamnestic data has shown that 72% of the patients have never performed self-examination, 32% of them provided information about previous testicular trauma during sport activities, 3.7% reported cryptochism, and 3% reported ginaecomastia. In addition, 15% of the patients reported positive family history. The first symptom in 15% of the patients was retroperitoneal pain. In 39% of the patients, numerous anomalies were found in spermiogram findings, ranging from reduced mobility of spermatozoa and reduced sperm count, to total absence of spermatozoa (azoospermia) in 9 patients (6.8%). No significant incidence of the pathological spermiogram findings was observed for the histological type of tumor.

Discussion

According to world literature data, around 11% of testicular cancers are diagnosed in N+ stadium.[9]

Albers and al. published that 10% out of all patients suffered with metastatic disease in the moment of diagnosing it. The most common hematogenic place of tumor expansion were lungs. Impressive surviving has been proved in treating patients with combined specific oncological therapy (Surgical intervention led by chemotherapy based on cisplatina). [10]

In research which analized patients with bad performance status - ECOG 3, Gillesen and al. proved that NSGCT with bad prognosis was in 90% of patients, of which 80% had N1-N3 status and 75% M1 status. According to frequency other viscelar organs were liver, bones and brain (M1b).[11]

In our examination, the middle age of patients with seminoma was 38 years, and the ones with nonseminoma 30 years. According to data, seminomatous tumors occur between the ages of 30 and 40, while non-seminomatous tumors in most cases occur between 20 and 30 years of age.[12]

Seminoma tends to be less aggressive, to be diagnosed at an earlier stage, and to spread predictably along lymphatic channels to the retroperitoneum before spreading hematogenously to the lung or other organs. Seminoma is also associated with a lower incidence of occult metastasis and a lower risk of systemic relapse. According to some research the retroperitoneal lymph node size is the most important factor for predicted recurrence.[13]

Our research showed that 15 patients (25.8% of all patients with seminom) had N1-N3 status and 26 nonseminous tumours (35.1% of all patients with NSGCT). In patients with seminoma (58), M1a status was proved in 3 patients (5.1%). In the ones with nonseminous tumour(74), 8 had

M1a status (10,8%) and 10 had M1b status (13,5%).

In comparison with other literature data, our patients had more frequently advanced disease in case of retroperitoneal lymfadenomegaly and hematogenic spread in distant organs.

Conclusion

Regardless of the fact that the testicles are accessible for self-examination and expert clinical examination and the fact that ultrasound diagnostics of the testicles is simple, harmless, painless and available, a large number of patients consult a doctor once the disease has advanced, when the treatment is very complex and the outcome is uncertain. It is necessary to increase the level of education in this regard, in order to raise awareness and improve knowledge of the general population about this problem. In addition, organised programmes and activities of experts and volunteers should serve to work towards the early detection of this malignant disease.

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Tumori testisa – učestalost retroperitonealne limfadenomegalije u trenutku dijagnostikovanja bolesti

SAŽETAK

Uvod: Tumori testisa ukupno čine oko 1% svih maligniteta kod muškaraca, ali životna dob oboljelih i sve veća učestalost, čine ovaj malignitet jednim od vodećih onkoloških problema. Bez obzira na činjenicu da testisi spadaju u organe dostupne samopregledu, te pristupačnost ultrazvučnog pregleda koji predstavlja metodu izbora u dijagnostici, ovi tumori se često otkrivaju u uznapredovalom stadijumu bolesti.

Cilj rada: Cilj rada je retrospektivnom analizom zaključiti kolika je učestalost uznapredovale bolesti u trenutku dijagnostikovanja germinativnih tumora testisa.

Ispitanici i metode: U našem radu obradili smo pacijente sa germinativnim tumorom testisa (seminomskim i neseminomskim) po brojnim parametrima - anamneza sa posebnim osvrtom na faktore rizika, klinički pregled, laboratorijske analize sa tumorskim markerima, te slikovne dijagnotičke pretrage (CT toraksa, abdomena i karlice). Većini pacijenata je prije specifičnog tretmana urađen spermiogram i krioprezervacija sperme, a u nekim slučajevima je indikovana i dodatna dijagnostika (MR endokranijuma, scintigrafija skeleta).

Rezultati: U analiziranom periodu liječena su i praćena 132 pacijenta sa germinativnim tumorima testisa, od čega je bilo 58 pacijenata (44 %) sa seminomskim tipom tumora i 74 pacijenta (56%) sa neseminomskim tumorom. Od ukupnog broja pacijenata u trenutku dijagnostikovanja bolesti, 41 pacijent (31%) je bio sa statusom retroperitonealnih limfnih čvorova N1 – N3, te 17 (12,8%) pacijenata sa statusom metastatske bolesti M1a –M1b.

Zaključak: Veliki broj novootkrivenih tumora testisa se dijagnostikuje u uznapredovaloj fazi bolesti. Neophodno je povećati informisanost opšte populacije o ovom malignitetu, naglasiti značaj samopregleda kod mlađih muškaraca, te mogućnosti rutinskih UZV pregleda u ranom otkrivanju bolesti.

Ključne riječi: germinativni tumor testisa, uznapredovala bolest

REVIEW ARTICLE

doi: 10.18575/msrs.sm.e.18.08
UDC: 615.2.076:616-056.7
COBISS.RS-ID: 7318040

Clinical Trials and the Importance of Biobanks in Rare Diseases

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ABSTRACT

Rare diseases ("*orphan diseases*") (RDs) count for 5000-8000 diseases with low prevalence and most commonly of genetic origin. Although most of rare diseases are manifested in early childhood, many are diagnosed in adults, even in elderly. Common characteristics, such as severity, debilitating and life-threatening features, with the lack of a specific drugs, make the treatment of RD a significant public-health problem. Even though randomized controlled trials (RCTs) are the most ideal design for evaluating new drugs, the aim of this review was to present the aggravating circumstances that development of so-called *orphan drugs* faces in context of RD. We searched the PubMed/Medline for publications on studies and ethics in RDs and applying of „omics" technologies in analysing tissue samples at biobanks published between 2010 and 2017. In this review, we presented the most significant obstacles in conducting clinical trials in RD as well as main alternative clinical trial designs aiming to decrease the number of patients recruited with increased access to innovative medicines as many as possible. Furthermore, we have presented the possibility of accessing innovative drugs outside of clinical trials as well as ethics violations by the involvement of the subject in clinical trial. Modern technologies in molecular biology will enable the development of „precision medicine" aimed at identifying the best therapeutic goal, depending on the genetic and epigenetic factors in the affected person. That is why RD biobanks have great significance in the preservation and distribution of tissue samples, in the research of diagnostic biomarkers and the drug development.

Key words: rare diseases, "orphan drugs", ethics/ethical, biobanks

(Scr Med 2018:49:49-56)

Submitted: March 2nd, 2018
Accepted: March 11th, 2018

Introduction

Today, it is known between 5000 and 8000 different rare diseases (RDs), which affect 6-8% of the population. According to the definition of the European Organization for rare diseases (EURORDIS), a RD has a prevalence of at least 1 affected to 2000 persons.[1,2] Occasionally the term "orphan" is used instead of "rare", to emphasize the public's attention and scientific community to RDs. Based on their common characteristics (Table 1),[1,2] RDs represent a complex challenge in the treatment, research and drug development ("orphan drugs").

As RDs are recognized as public health problem, The Ordinance on rare diseases, issued by European Medicines Agency (EMA) (European Parliament, EC 141/2000, 847/2000) and the 1983 Medicines

Act for rare diseases in the United States, intensively support development of innovative drugs for RD through various projects (eg. Framework programs, FP 6-7, Horizon2020) and support pharmaceutical companies.[3-5] These initiatives enable development of new drugs and give opportunities to treat RDs based on scientific evidence (evidence-based medicine), instead of "eminence-based medicine" treatments so far.[6] However, drug development for RDs in comparison to other clinical trials faces additional specific challenges and barriers. The aim of this manuscript was to present the characteristics and the most common obstacles in conducting clinical trials with "orphan drugs", proposed new designs these clinical trials, and availability of biological samples for the research of rare diseases. In our study, we considered scientific publications in PubMed/Medline (2010-2017 period) with the chosen keywords: "rare diseases", "orphan drugs", "clinical trials", "ethics / ethics issues", "biobanks".

Table 1. Common Characteristics of Rare Diseases[1,2]

Low disease prevalence	< 1 patient/2000 inhabitants
Diverse etiological causes	80% genetic origin.
	Other rare disease are not entirely caused by gene mutation, such as follows: metabolic, autoimmune,. neuromuscular, neurodegenerative, congenital anomalies, dysmorphia, rare carcinoma.
	Not preventable.
	Screening programmes can be used in identification risk and probability of rare disease inheritance.
Manifestation in across different age groups	Most (approx. 75%) are manifested in early childhood.
	(4-5% newborns and infants).
	Others can be manifested in adult or elder patients.
Delayed diagnosis	Insufficient knowledge about a particular rare disease.
	Required multidisciplinary approach and coordination within health system.
	Unavailable specific diagnostics for the most of rare disease (70%).
	Expensive and unavailable diagnostics in low-income countries.
Various disease course	Chronic, progressive diseases, various clinical forms, various prognosis.
	Disease course can be fulminant.
	Impaired quality of life
	(limited daily activities, disability, cognitive decline).
Disease complexity	Affects organ and/or entire organ system.
	Progress and affects several organ systems.
	Life-threatening.
	Incurable diseases.

An overview of characteristics and obstacles in conducting clinical trials of drugs in rare diseases

In general, conduction of randomized, placebo-controlled clinical trials as a "gold standard" in drug development, faces great difficulties in RDs (Table 2).[2,5,7,10]

A small sample size of patients distributed worldwide (eg, a few to 100 patients in the world) prevents the implementation of multi-centric studies that provide strong scientific evidence. Furthermore, RDs may be slow progressive with a wide spectrum of phenotypic manifestations (clinical symptoms), which make difficult to form a group of participants with a similar clinical form, monitor course a disease, define and measure endpoints.

Rare diseases are most commonly diagnosed in childhood, which, depending on the type of disease, increase ethical issues for participation in the trial (giving assent or consent for participation). In addition, use of placebo is ethically unacceptable neither in parallel design of clinical trials in life-threatening diseases, nor in *cross-over*, in a trial arm without investigated or standard treatment (non-drug period).[2,5,7-10] For a large number of RDs, there are not adequate experimental models of disease that results in insufficient data of efficacy and

drug safety originated in preclinical research (e.g. acute, chronic, reproductive toxicity and carcinogenicity), and consequently presents a certain risk in the selection of the first dose for clinical clinical trials.

Table 2. The Most Frequent Issues in Conducting Randomized Clinical Trials in Rare Diseases[2,5]

Lack of preclinical disease model	Lack/incomplete preclinical data of investigational drug efficacy and safety Risk in selection of„*first-dose in human*“ dose in clinical trials
Feasibility	Low number of participants/patients and wide geographical distribution that complicate enrollment in clinical trials
Heterogeneity in participants` sample	Diversity in clinical forms and diseases stage. Participants/patients are of different age group. Variability of genuine disease course and prognosis.
Lack of reliable parameters/endpoints for disease monitoring	Lack of specific diagnostic tests to monitor disease course. Diversity of diseases clinical manifestations of diseases and eligible patients, complicate defining and assessment of „*endpoints*“ in clinical trials.
Ethical issues	Limited possibilities in conducting randomized, placebo control trials, or „*cross-over*“ studies with placebo arm. Vulnerable population of patients.

Observational studies, such as cohort studies, can only contribute to simple research questions such as epidemiology and natural course of a disease, or in identification of risk factors of disease deterioration. Herewith, cohort studies help in evaluation of *off-label* drug use (only when no other treatment options available) or symptomatic therapies (e.g. perception of patients and physician regarding the use of symptomatic drugs in amyotrophic lateral sclerosis (ALS), or off-label application of lithium in ALS). However, often the impossibility to form other, un-exposed cohort; then the variable course of a disease, make results of cohort studies scientifically less important.[2,11]

Case-control studies may be a possibility for drug development, only in those RDs that have long latent period or where the study endpoints are sporadic (eg. rare acute disease).[2,11]

Alternative designs of clinical trials in rare diseases

Although conventional clinical trials provide the strongest scientific evidence, in RDs research, an alternative (non-conventional) design is being employed to ensure “proof of concept” trial with a small study sample and enhanced participants recruitment in an treatment arm (Table 3). Additionally, in successful conduction of research in a small number of participants, selection of surrogate endopoints is of great importance. A surrogate endopoints refer to biomarkers that substitute some clinical parameters (e.g. the frequency of epileptic attacks), and which are expected to have the ability to predict benefit (or damage) of the applied intervention.[2, 7, 8]

Trials with historical controls need approximately four-fold fewer participants compared with a traditional two-arm trial with a concurrent control group.

Although the problem of recruitment is overcome in this design, this approach remains biassed quality and reliability of the results with respect to the confusing variables (e.g. different treatment in observed periods, lack of blindness, blinization). These contribute to the the incorrect assessment of interventional effects of investigated drugs.[2]

Cross-over design are controlled studies in which each participants receives study medications (tested and comparable / standard medicine without placebo), in different consecutive periods, with an appropriate wash-out period. Cross-over studies are probably the best design for studying chronic diseases, particularly as they are feasible in a small number of patients that serve as their own controls, along with ethical justification, as patients receive all study medications throughout the study. However, lack of blindness in the study may lead to bias in evaluating the drug investigated, while a long “wash-out” period may expose the participants to worsening of the disease.[2,7,8,11]

N-of-1 design is a variant of a single cross-over (only one patient) trial. In this trial, the only one patient is included and exposed to experimental and control treatments, several times (N number), with “wash- out “periods. The

main purpose of this study is the individual assessment of investigated drug, and in terms of RD, there are obstacles in the requirement for a certain number of patients. However, this design requires stable state at the beginning of each investigational/treatment period. Although, these designs do not provide statistical power, multiple *N-of-1 trials* are in fact case studies.[2,7,8,11]

Table 3. Alternative Designs to Conventional, Randomized, Clinical Trials in Rare Diseases[2]

Study design	Description	Purpose
Use of historical controls (instead of a concurrent control group)	"Artificial" control group obtained from data of patients databases or registries	Minimize sample size
"*Cross over*" design	Use of participants as their own controls. Access to standard (if any) or investigational drug throughout study.	Minimize sample size Maximize participants recruitment due to increased access of receiving treatments
N-of-1 design	Trial of a single patient randomized to alternately receive different treatments at different (N) times.	Minimize sample size Assessment of therapeutic response for individual patients
Adaptive design	Modifications of trial protocol (e.g., sample size, randomization ratio, number of treatment arms), based on interim analyses.	Minimize sample size Maximize recruitment of participants receiving potential effective treatment Adapted randomization in accordance to treatment response and/or probabilities to patient characteristics.
Delayed start design	Patients are continuously enrolled in trial, starting a different time points, until a conclusion, positive or negative, about the investigational drug is reached.	Minimize sample size Time and cost saving

A *delayed start design* is also known as a "*placebo-phase*" or "*open ended*" randomized clinical study, and is conducted when participation in control group are unacceptable for patients and treating. Participants are recruited during the study at different time points starting either with investigational drug (one group receives drug as soon as they are enrolled (*early start group*), while the other (*delayed start group*) gets the placebo and after a certain period switch to the investigational drug). All participants are enrolled in the study until a positive or negative results are reached, and an assessment of drug efficacy and safety can be performed. However, large variations in the length of drug administration affect the statistical power of study results.[2,12]

Adaptive (flexible, Bayesian design) study design involves the modification of key study protocol features (sample size, randomization, length of drug administration) that depends on interim analyzes (data analysis during the test). These analyzes are particulary important in studies for RDs, as they can lead to an increased number of participants receiving investigational drug (response-adaptive randomization), or provide evidence for a premature interruption the trial due unacceptable drug safety.[2,13]

In conclusion, the number of participants, duration of study, clinical symptoms and fluctuation of disease course will influence on selected study design. In many RDs trials, more than one design can be employed taking into account all previously gained data that improve the statistical strength of the study results.

Compassionate drug use in rare diseases

In the context of the development of drugs for RDs, it is necessary to mark the compassionate use program (CUP). According to the EU Regulation 726/2004, Article 83.2, the CUP is defined as a procedure for medicinal product in treating chronic and/or serious, life-threatening

disease that cannot be treated with approved medicines; administered drug is undergoing clinical trials or is in the process of obtaining a marketing authorization (*early access program*).[14] Most common, compassionate drug use is considered in later phases of clinical trials (Phase III), although is possible even earlier, in order to "bridge" the period between completion of trial and approval for marketing authorization by regulatory agencie.[15] Only patients who do not meet defined criteria for participation in a clinical trial may receive a drug within the CUP without exposing them, for example, to a placebo group.[16] It is important to emphasize that compassionate drug use in RDs can be carried out along to the clinical trials, but investigational drug within CUP is not intended for testing in patients (does not use placebo, or comparative drugs). Nevertheless, CUP represents a source of data on efficacy and drug safety in "real life". Besides, CUP does not represent "*off-label*" drug use (approved drug for another indication/age group), it is not a humanitarian or financial aid of pharmaceutical companies; nor marketing promotion is allowed to reach faster marketing authorisation for given drug.[17]

Similar to CUP, there is an additional possibility in the European Union (EU) for development a drug outside the clinical trial. This approach is intended for a single patient (*named patient program*), on the basis of a doctor's request to a pharmaceutical company. Although EMA has issued the EU Regulation 726/2004, and member states can develop their own CUP, this program is not obligatory. Thus, for example, Britain, Ireland and Sweden do not have a formal, while Hungary does not have a CUP at all. It is therefore necessary for doctors, patient associations, pharmaceutical companies and policy makers to participate in the creation of the CUP in order to provide access to innovative therapies. According to the EMA data, since 2006, 50 applications for CUP were registered, of which 17 were for RDs. A positive example illustrates activities of European and national associations patients with Gaucher's disease, which provided treatment even to the patients outside the EU, such was the case in Bosnia and Herzegovina.[14,17,18]

Ethical considerations of clinical trials of drugs for rare diseases

Although clinical trials are one of the best regulated areas of research, regulation that determines ethics principles in drug development for RDs is still insufficient. For the assessment of efficacy and safety of an "*orphan drug*", optimal approach would be benefit/risk analysis, instead of additional cost/benefit analysis claimed by pharmaceutical companies that invest in drug research. This can partially explain reduced interest in the investment to drug development for RDs.[19,20] In addition, RDs studies often question the basic principles of ethics: nonmaleficence (do no harm), beneficence, autonomy and dignity, and justice.

The principle of *well-being and nonmaleficence (do no harm)* is endangered in these studies for the following reasons: pharmacological active substances are often administered to participants even their efficacy and safety are not proved in preclinical studies (lack of an adequate model of disease), or participants consent to use drug within CUP. Secondly, low prevalence, or progressive course of some RDs, make impossible carrying out, and ethically unacceptable to have a placebo-controlled group of participants.[21,22]

The principle of *autonomy and dignity* is questioned in a community where treatment cost is high, and participation in clinical trials is the only way to access a potential drug. The fact that most of RDs occur in early childhood and that patients are unable to decide for their interest (the inability to give consent to participate in the study) makes them vulnerable. The vulnerability of these participants is particularly empahisized if cognitive impairment of children, adults and the elderly develop due to disease progression, which then may be relatively or absolutely incapable to consent to participate in the study.

The principle of *justice* is most often endangered because the criteria for participation in clinical study are strictly defined and without the possibility to adapt to respondents needs that prevents inclusion of seriously ill or patients with progressive disease.[21,22]

Herewith, ethical dilemmas raise genome research in patients` tissue samples obtained during clinical trial that requires access to genetic material and information. Therefore, carriers of a gene mutation for a particular diseases or patients are faced with the potential violated privacy of their relatives by disclosure their genetic information. The rationale for disclosure of genetic information is only for recessive gene carriers for a particular disease, in their reproductive period and in offspring planning.[19]

The importance of biobanks the development of drugs for rare diseases

Biobanks (biorepository) are one of the most important parts in the development of translation research in predictive, personalized and precision medicine (PPPM). Biobanks that meet quality and safety criteria represent an infrastructure that assures a link between biological samples, registries of patients and clinical data.[23,24] Today, biobanks networks have a significant role

worldwide, out of them pan-european platforms such as European Research Infrastructure Consortiums (ERICs) and Biobanking and BioMolecular Resources Research Infrastructure (BBMRI-ERIC) are the most important. These networks create guidelines for good practise in biobanks, ethical, legal and social issues (Ethical, Legal, Social Issues, ELSI) in order to facilitate exchange of samples and of research results across Europe.[5,25,26]

According to Orphanet database (www.orpha.net), today there are 120 biobanks for RDs worldwide. These RDs biobanks may be foucus only on one disease such as the Progeria Research Foundation Cell and Tissue Bank, brain developmental anomalies of the National Institute of Child Health and Human Development Brain and Tissue Bank, or on tissue culture "Munich Tissue Culture Collection ", or to be connected within a network.[5,26] For RDs in Europe, the most important network is EuroBioBank, consisting of 22 countries, which contains approximately half a million samples of 500 diseases, with an annual increase of 1300 samples. EuroBioBank provides samples in a wide geographic region and enables genetic research, gene therapy and drug toxicity testing, or development of diagnostic and therapeutic biomarkers. Recently, EuroBiobank has joined to RD-Connect platform, a European research project, whose ultimate goal is to link patients registers, biorepositions and clinical data to RDs.[27]

Pharmaceutical companies also use biobanks in the development of drugs for RDs. As an example is Rare Disease Hub (RD-HUB), the central repository database of RDs that provide access to samples and associated clinical data of patients. This kind of co-operation has been the backbone for 30 years, and have resulted in the development and marketing authorisations for more than 400 drugs for RDs. In clinical trials of RDs, DNA samples are used to explore genetic polymorphism, genotype/ phenotype relations, then serum and plasma to identify new biomarkers drug efficacy monitoring, while cell and tissue culture make investigation of pharmacodynamics possible.[5,24,26,27]

However, to overcome the problem in conducting clinical trials due to the small number of patients and their samples, "omic" technology (genomics, proteomics, transcripts, metabolomics) are employed on high quality samples of biological material. The "omic" technologies in RDs make possible genome analysis, determination of proteins and metabolites profiles in a particular tissue / cell, detection of diagnostic and therapeutic biomarkers.[28]

Based on the aforementioned, biobanks for RDs are facing with a number of challenges, additionally to required quality of biological material. In the future there must be developed system that will connect with patient registers and their clinical data to facilitate location and exchange of research samples, and secure patient privacy in accordance according to ethical and legal provisions in different countries.[27]

Conclusion

Clinical trials in RDs around the world face problems of feasibility, constraints in patients recruitment, different regulatory requirements, and ethical issues. The design of clinical trials for RDs therefore are adapted to the specific indication and use of surrogate markers for outcomes assessment. One of the opportunities to access to drugs for RDs is within CUPs, when patients who do not meet defined criteria for participation in a clinical trial may receive a treatment. The promising option for the development of drugs for RDs includes research of diagnostic and therapeutic biomarkers in tissue samples stored in biobanks.

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Klinička ispitivanja lijekova i značaj banaka biološkog materijala u rijetkim bolestima

SAŽETAK

Rijetke bolesti (“*orphan diseases*”) predstavljaju 5000-8000 oboljenja, niske prevalence i najčešće genetski uslovljene etiologije. Iako se većina ovih bolesti manifestuje u ranom djetinjstvu, mnoge se dijagnostikuju kod odraslih, čak i kod osoba starije životne dobi. Zajedničke karakteristike, kao što su ozbiljnost kliničke slike, to da su onesposobljavajuća i životno-ugrožavajuća stanja, uz nedostatak specifičnog lijeka, čini liječenje rijetke bolesti značajnim javno-zdravstvenim problemom. Premda randomizovana, kontrolisana klinička ispitivanja predstavljaju najidealniji dizajn istraživanja novih lijekova i cilj ovog rada je bio da u kontekstu rijetkih bolesti prikažemo otežavajuće okolnosti sa kojima se suočava razvoj tzv. *orphan drugs*. U obzir smo uzeli pregled naučnih publikacija objavljenih u PubMed/Medline, za period 2010. do 2017. godina, a koje se tiču kliničkih ispitivanja i etičnosti u rijetkim bolestima, te primjeni *“omics”* tehnologija u istraživanju uzoraka tkiva deponovanih u bankama biološkog materijala. U ovom preglednom radu smo prikazali najznačajnije barijere u provođenju ispitivanja lijekova za rijetke bolesti, kao i glavne, alternativne dizajne kliničkih ispitivanja, a koja imaju za cilj smanjenje broja regrutovanih pacijenata, uz povećanu mogućnost dobijanja inovativnih lijekova što većeg broja ispitanika. Dalje, prikazali smo mogućnost pristupa inovativnim lijekovima van kliničkih ispitivanja, kao i načela etičnosti koja bivaju ugrožena učešćem oboljelog u ispitivanju. Savremene tehonologije u molekularnoj biologiji će omogućiti razvoj precizne medicine (*“precise medicine”*), usmjerene na identifikaciju najboljeg terapijskog cilja, zavisno od genetskih i epigentskih faktora kod oboljelog. Upravo zbog toga banke biološkog materijala za rijetke bolesti (biorepozitorijumi) imaju veliku značaj u čuvanju i distribuciji uzoraka tkiva, u istraživanjima dijagnostičkih biomarkera i razvoju novih lijekova.

Ključne riječi: rijetke bolesti, “*orphan drugs*”, klinička ispitivanja, etika/etičnost, biobanke

CASE REPORT

doi: 10.18575/msrs.sm.e.18.09
UDC: 616.12-008.315-071
COBISS.RS-ID: 7318296

Surgical Treatment of the Left Ventricular Assist Device Drive Line Infection with Abscess Formation

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ABSTRACT

Specific left ventricular assist device infections are the leading cause of morbidity and second most common cause of death in patients who survive the first six months after implanting device, and also they are the most common cause of readmissions to hospital. The patient is a 63-year-old who received LVAD HeartMate II. The patient was readmitted to the hospital due to a driveline exit site infection and a developed abscess formation at 4 cm from the DL exit site. After reducing infection with antibiotics therapy, he was successfully operated by creating new exit site while removing the driveline from the infected region of the subcutaneous tissue. Repositioning of the driveline to a new exit site with mandatory removal of part of the driveline from the subcutaneous tissue in the region of infection, with extensive debridement of the wound is appropriate therapeutic option for patients with driveline infection.

Key words: drive line infection, LVAD, C shaped

(Scr Med 2018:49:57-60)

Submitted: February 1st, 2018
Accepted: February 18th, 2018

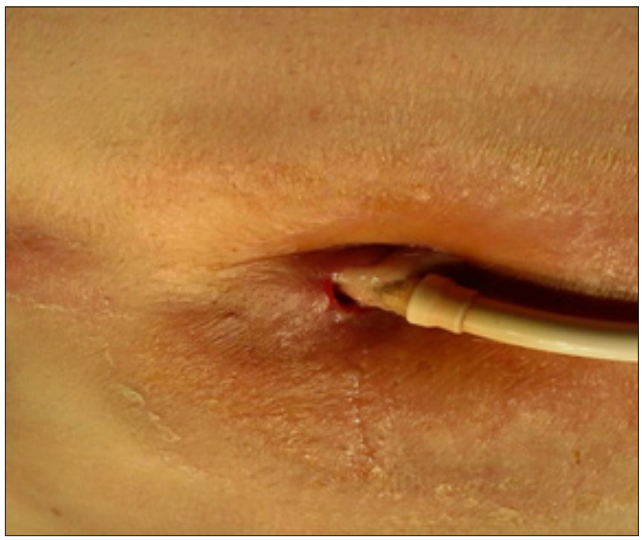
Introduction

Specific LVAD infections, among which infections of driveline exit site as the most frequent, are the leading cause of morbidity and second most common cause of death in patients who survive the first six months after implanting the LVAD. LVAD infections are also the most common cause of readmissions to hospital. Given the specific clinical condition in terms of having a foreign body and the forming of bacterial or fungal biofilm that prevents an effective antibiotic therapy, the treatment of these infections is a serious therapeutic challenge. By developing surgical techniques for treating driveline exit site infections, it is possible to increase the survival rate and reduce morbidity in patients with the inserted LVAD. [1,2]

Case Report

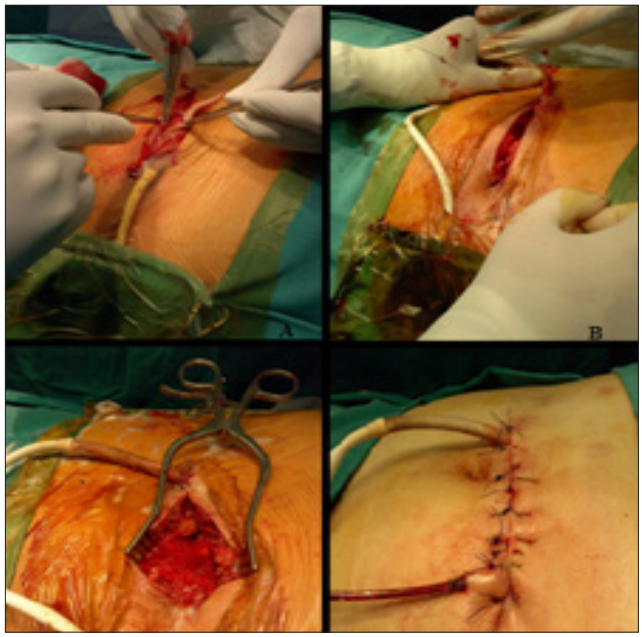
The patient in question is a 63-year-old who had the pump for mechanical circulatory support of left ventricular HeartMate II implanted ten months earlier as bridge to transplant. The patient was admitted to hospital due to a driveline exit site infection and a developed abscess formation at 4 cm from the DL exit site. On reception, the skin around the exit driveline was red, swollen, sensitive and painful, with purulent secretion. An abscess formation with the surrounding cellulitis was formed at 4 cm from the exit site DL. (Figure 1.)

Figure 1. Drive-line Exit Site Infection and a Developed Abscess Formation



During the first hospitalization, when the pump HeartMate II was implanted, the operative and postoperative period passed regularly. In the operative procedure, the exit driveline was inserted through the skin in the "C shaped- doubled DL tunneling" form. At discharge from hospital, the skin around the driveline exit site healed well, with no signs of erythema, soreness, drainage, or other signs of infection.

Figure 2. P Repositing DL and Creating New Exit Site

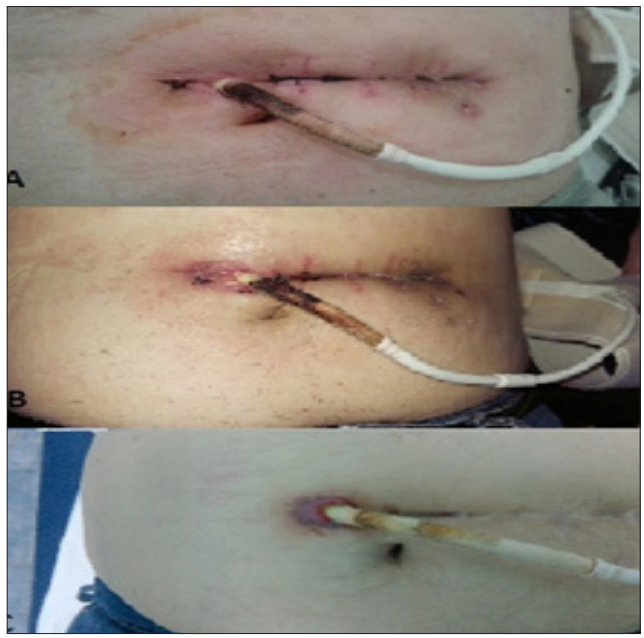


At hospital reception ten months after the implantation, the patient complained of burning and 'piercing' sensation in the driveline exit area with abscess formation 4 cm from DL exit site. Patient was without systemic signs of infection, blood stream tests were without bacteriological findings. *Pseudomonas aeruginosa spp.* was isolated from the swab taken around the driveline exit site of LVAD. Adequate antimicrobial therapy (Meropenem 3x1 g) was introduced according to antibiogram followed by intensive toilet of the wound three times a day.

On the eleventh day after the admission, after initial antibiotic therapy, the patient was operated. Incision in the driveline projection to a length of 8 cm was performed, part of the driveline outside subcutaneous structures was removed with an extensive debridement of the wound and abscess formation. Finally, the exit driveline was repositioned and fixed (without its returning to the subcutaneous adipose tissue), that is, a new exit site of DL was formed (Figure 2.). A swab was taken during the operation (which later confirmed *Pseudomonas spp*).

In the postoperative period, the patient was daily bandaged and adequate antibiotic therapy according to antibiogram was administered. The wound healed regularly. The stitches were removed on the twentieth postoperative day (Figure 3,a).

Figure 3 a,b,c. Wound Healing and Checkup



The patient was dismissed with the regularly healed wound, with no signs of erythema or soreness, and without secretion. A careful inspection of the outside of LVAD driveline showed no signs indicating disruption of the driveline's integrity. The checkup after three months (Figure 3,b), shows completely healed wound with no

signs of infection. After one year, the checkup shows a small amount of granulation tissue around the exit site (Figure 3,c).

Discussion

High incidence of infectious syndromes in patients with implanted devices for mechanical circulatory support significantly affects the efficiency, increasing the rate of morbidity, mortality, length of hospitalization and treatment costs. Since there is a serious issue with the lack of donors, the necessity arises to develop various clinical modalities to treat DL infections in both BTT and DT group of patients.[3]

In the presented case, due to a specific DL infection in terms of the presence of a foreign body, constant irritation of the skin at the exit DL and consequent formation of bacterial biofilms by Pseudomonas spp., the use of antibiotics and frequent bandaging of the wound after the initial occurrence of the infection seven months after LVAD implant contributed to reduced symptoms (reduction of infection). However, a complete eradication of the infection has not been possible.[4] In the given period, there were no adequate donors and the patient had met the requirements for heart transplant. Two months after discharge, the patients had recurrence of substantial secretion with an abscess formation at 4 cm from the DL exit site. Repeated antibiotic treatment partially alleviated symptoms after which the surgical treatment followed. The surgical treatment aimed to completely remove from the body a part of the driveline that was in infected region and reposition it to another spot. Removing the driveline from an infectious region included an extensive debridement of the wound. Antibiotic treatment was continued. DL primary placed in the form of C shaped- doubled DL tunneling, enabled the incision along the DL projection through the skin to be far enough from the infected area, as well as far enough from the mediastinum region.[5] After hospital discharge, the patient is regularly bandaged once a day and ten months after there were no signs of an infectious process.

Conclusion

Repositioning of the driveline to a new exit site with mandatory removal of part of the driveline from the subcutaneous tissue that had previously been positioned in the region of infection, with extensive debridement of the wound can be an appropriate therapeutic option for patients with driveline exit site infection with or without possible abscess formations. Placing the driveline in the form of "C shaped" in the initial LVAD implant facilitates, this treatment provides wider opportunities and greater safety for patients.

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Hirurško liječenje infekcije sa apscesnom formacijom izlaznog mjesta kabla za napajanje uređaja za potporu rada lijeve komore

SAŽETAK

LVAD specifične infekcije, a među njima infekcije izlaznog mesta kabla kao najfrekventnije, predstavljaju vodeći uzrok morbiditeta i drugi najčešći uzrok smrti kod bolesnika koji prežive prvih šest meseci od ugradnje uređaja, a takođe su i najčešći uzrok ponovnih prijema u bolnicu. Naš pacijent je 63-godišnjak kojem je implantirana pumpa za mehaničku potporu cirkulacije leve komore HeartMate II. Pacijent je ponovo primljen u bolnicu zbog infekcije izlaznog mesta kabla LVAD-a i razvoja apscesne formacije na 4 cm od izlaznog mesta kabla za napajanje. Nakon redukcije infekcije antibiotskom terapijom, pacijent je uspješno operisan kreiranjem novog izlaznog mjesta i otklanjanjem izlaznog kabla iz inficiranog područja subkutanog tkiva. Repozicija kabla na novo izlazno mesto uz obavezno uklanjanje dijela kabla za napajanje potkožnog tkiva koji je prethodno bio pozicioniran u infektivnoj regiji, sa opsežnim debridmanom rane, a može biti adekvatan terapijski izbor kod bolesnika sa infekcijom izlaznog mjesta kabla za napajanje.

Ključne riječi: infekcija izlaznog kabla za napajanje, LVAD, C shaped forma

CASE STUDY

doi: 10.18575/msrs.sm.e.18.10
UDC: 616.13-007.64/.141
COBISS.RS-ID: 7318552

Right Pulmonary Artery Aneurysm Mimicking Tumor on Chest X-Ray in Patient with Eisenmenger Syndrome

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Submitted: February 8th, 2018
Accepted February 28th, 2018

ABSTRACT

A 66-year-old patient with previously diagnosed largeventricular septal defect and Eisenmenger syndrome (ES) performed a preoperative(planned inguinal hernioplasty)chest x-ray that showed a tumor-like lung mass,which led to a chestCT scan. The ChestCT scan showed an extremely dilated right pulmonary artery which mimicked tumor with rarely described atherosclerotic changes in the right blood flow with calcified plaques and thrombotic masses. Since pulmonary artery thrombosis is common in adults with ES,it is our belief that anticoagulation should be considered in this group of patients.

Key words: Eisenmenger syndrome, ventricular septal defect, pulmonary artery aneurysm

(Scr Med 2018:49:61-64)

Introduction

Eisenmenger syndrome (ES) is defined as pulmonary vascular obstructive disease that develops as a consequence of large preexisting left-to-right shunt. In ES, pulmonary artery pressures approach systemic levels and the direction of the flow becomes bidirectional or right-to-left. Lesions in Eisenmenger's syndrome, such as large septal defect, are characterized by high pulmonary pressure, high pulmonary vascular resistance and/or a high pulmonary flow state, and they are associated with pulmonary vascular disease. ES is rarely described in the elderly because congenital heart defects such as ventricular septal defect(VSD) are usually treated in childhood.[1] Recent studies have demonstrated some hypotheses about possible etiologies of pulmonary artery thrombosis in ES. In these studies are listed pathophysiological mechanisms that are considered most likely to lead to thrombosis: local vascular injury from progressive pulmonary hypertension,hypercoagulability and sluggish flow in the pulmonary artery, which promote red cellaggregation.Some of them suggest that the pulmonary artery atherosclerosis is responsible for thrombosis.[2]

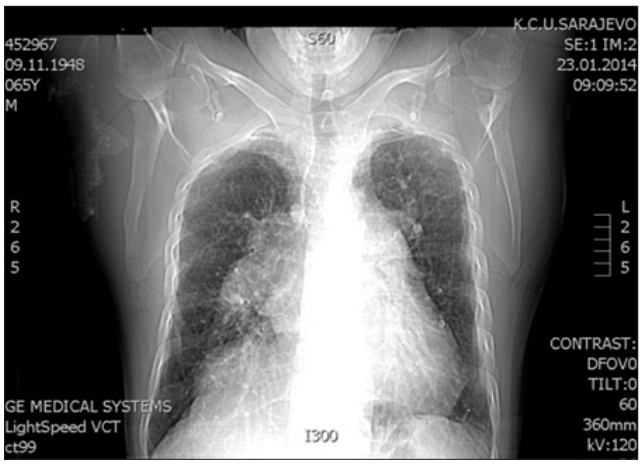
Case Study

A 66 year-old man with previous cardiac disease (VSD andES) was referred to our hospital for detailed diagnostic evaluation of huge right hilar lung mass found on routine chest X-ray during preoperative evaluation foringuinal hernioplasty.(Fig.1.)

Patient had a 1-year history of dyspnea.Physical findings include dyspnea, central cyanosis and systolic mild murmur in left parasternal intercostal space. Laboratory

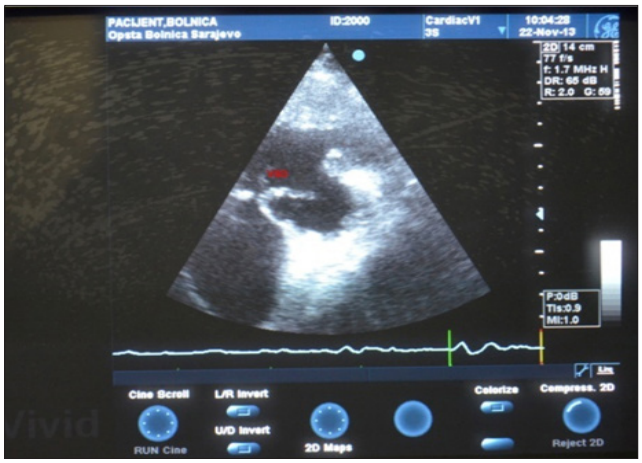
findings showed secondary polycythemia (Red blood cell level - 8.66 x109/L,Hemoglobin level - 222 g/L, Hematocrit level - 0.70, Erythrocyte sedimentation rate – 2 mm,Potassium 3.32 mmol/L, Ferrum level 10.10μmol/L, cholesterol 7.30 mmol/L).Arterial blood gases analysis showed extreme hypoxia (pH 7.383, pCO2 5.62, pO2 5.52, sO2 75.8).

Figure 1. Chest CT Scan



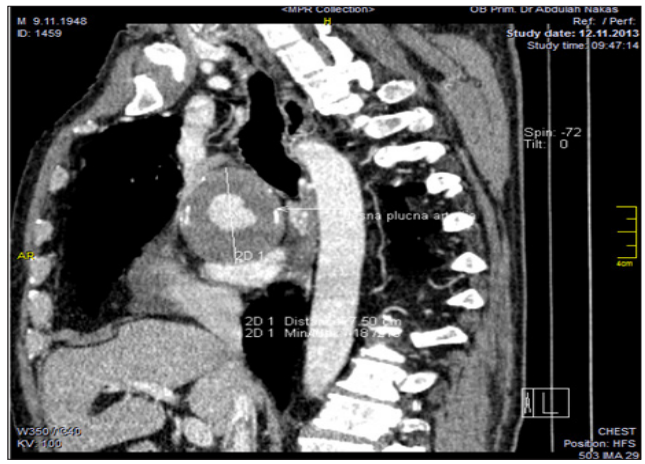
ECG showed signs of right axis with incomplete right bundle branch block and posterior left hemiblock, inverted T wave in lead II and III, aVF, and right precordial leads - V2, V3 withST segment depression in leads V4-V6.(Fig.2.)

Figure 2. Transtorocal Echocardiography showing VSD



Echocardiogram verified extreme hypertrophy of both right and left ventricular walls, paradox moving of interventricular septum with calculated RYSP over 120 mm Hg, large muscularseptal defect (23 mm) associated with bidirectional dominantly right–to-left shunt and severe pulmonary hypertension with PAPS over 120 mm Hg. Transesophageal echocardiography was not performed due to poor transesophageal window and insufficient view of cardiac structures.(Fig.3.)

Figure 3. Chest CT scan showing right tumor-like lung mass



Contrast-Enhanced Computed Tomography (CT) of heart confirmed the existence of ventricular septal defect and also showed extremely dilated right pulmonary artery (56 mm in diameter) with large intraluminal thrombus, which incompletely obturated lumen,and laminar calcifications (75mm). Lobar branches of right pulmonary artery for superior and middle lobe were completely obturated with the thrombotic mass. CT scan also showed strong bronchial collateral circulation.

Discussion

We described the case of older patient with ES secondary to large VSD and giant thrombosed right pulmonary artery aneurism(PAA) which initially presented on chest X-ray as large paracardial right tumorous lesion. Further investigation (chest CT with contrast) showed, apart from previously diagnosed VSD, atherosclerotic changes in pulmonary circulation with extremely dilated right pulmonary artery in which large thrombotic mass obturated lumen of lobar branches for the upper and middle lobe of the right lung. These findings (atherosclerotic changes in pulmonary circulation with secondary thrombosis) have showed us that, in this case, pulmonary vessels mimic systemic circulation, which makes it very interesting. Pulmonary artery aneurysm is an infrequent disease of the pulmonary vasculature; and in more than 50% of cases is caused by congenital heart disease.[3] Patient history and clinical clues are essential for the recognition of PAA, since it is rare and unlikely cause of suspected lung mass.[4] In our patient,VSD with left-to-right shunt increased the volume and pressure

load on the pulmonary artery circulation; then secondary pulmonary hypertension increased hemodynamic shear stress on the vessel walls and promoted aneurysm formation in the right pulmonary artery. PAA is associated with severe complications such as pulmonary artery dissection and rupture, bronchial pressure and thrombus formation as seen in our case. About 20-30% of the patients with ES present with pulmonary artery thrombus.[5] Predictors of pulmonary thrombus formation in patients with ES are not known. In the study of Silverside et al. pulmonary artery calcifications were seen more frequently in patients with pulmonary thrombosis. Patients with ES have bleeding and clotting tendencies, as well as the labile INR, therefore it is difficult to make recommendations regarding anticoagulation in these patient.[6] Since pulmonary arterial thrombosis among adults with ES is common and relates to older age, biventricular dysfunction, and slow pulmonary artery blood flow, it is our belief that oral anticoagulation should be administrated to this group of patients.[2]

Conclusion

In cases when the chest CT scan shows tumor-like hilar mass, extremely dilated right pulmonary artery mimicking tumor, it is necessary to perform a complete cardiology procedure.

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Aneurizma desne plućne arterije koja imitira tumor na radiografiji grudnog koša kod pacijenta sa Eisenmengerovim sindromom

SAŽETAK

Pacijent, 66godina, sa ranije dijagnostikovanim velikim ventrikularnim septalnim defektom i Eismengerovim sindromom (ES) je obavio preoperativno obradu radi planirane operacije ingvinalne hernije. RTG grudnog koša koji je pokazao tumorozno izmijenjen desni hilus što je indiciralo CT grudnog koša.CT grudnog koša je pokazao ekstremno dilatiranu desnu plućnu arteriju koja imitira tumor uz rijetko opisane aterosklerotske promjene desnog krvotoka sa kalcificiranim plakovima i trombotskim masama. S obziromna to da je tromboza plućne arterije uobičajena kod odraslih sa ES, smatramo da je kod ove grupe pacijenata potrebno razmotriti i antikoagulantnu terapiju.

Ključne riječi: Eisenmenger-ov sindrom, ventrikularni septalni defekt, aneurizma plućne arterije

CASE STUDY

doi: 10.18575/msrs.sm.e.18.11
UDC: 616.36-004-06
COBISS.RS-ID: 7318808

Surgical Treatment of Spontaneous Spleen Rupture in Patients with Splenomegalia

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ABSTRACT

Spontaneous spleen rupture rarely occurs, and is primarily present in patients with splenomegaly. This is a life-threatening condition that, without adequate surgical treatment, always ends lethally. The very etiology of spontaneous atriumatic spleen rupture is not known, but it can often be associated with neoplastic diseases, liver cirrhosis, and some infectious diseases. Diagnosis is made by non-invasive methods (findings of red blood cell elements, ultrasonography, computerized tomography of abdominal CT, magnetic resonance NMR). The therapy consists of laparotomy, evacuation of the haemorrhagic content and removal of the spleen. Surgical treatment is successful, and as a postoperative complication, bleeding may occur as a result of inadequate care of the laryngeal artery and vein, and short gastric blood vessels. Here we presented a 58- year- old male patient who, due to a marked abdominal pain, low blood pressure, and low blood cell counts, was taken to hospital and successfully surgically treated at the Clinic for General and Abdominal Surgery.

Key words: splenomegaly, spleen rupture, haemorrhagic shock, splenectomy.

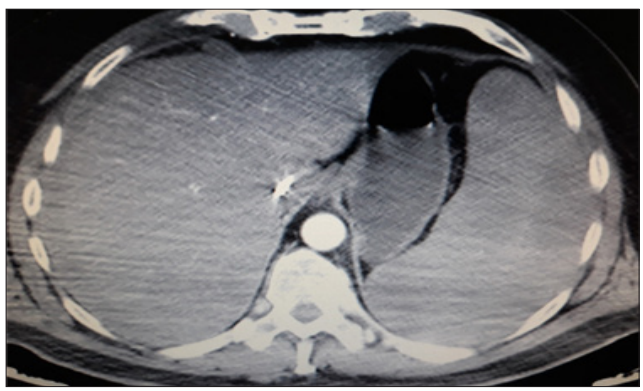
(Scr Med 2018:49:65-68)

Submitted: March 15th, 2018
Accepted: March 25th, 2018

Introduction

The destruction of parenchyma, capsules, or blood vessels is a spleen condition called rupture. Spleen may rupture spontaneously, but spontaneous rupture of the spleen is very rare and is most common in malaria, mononucleosis, lymphoma, leukemia and other conditions followed by enlargement of the spleen.1 In recent times, fewer spontaneous ruptures occur in patients on anticoagulation-antiagregation therapy.2 The exact mechanism of spontaneous spleen rupture is unknown, and the clinical picture may vary from severe hypovolemic shock to minimal symptoms. In the earlier period, the mortality of these patients was very high due to complications and difficult diagnosis, and the main cause of mortality was hypovolemic shock due to the loss of large amounts of blood.

Figure 1. CT Image of Enlarged Spleen



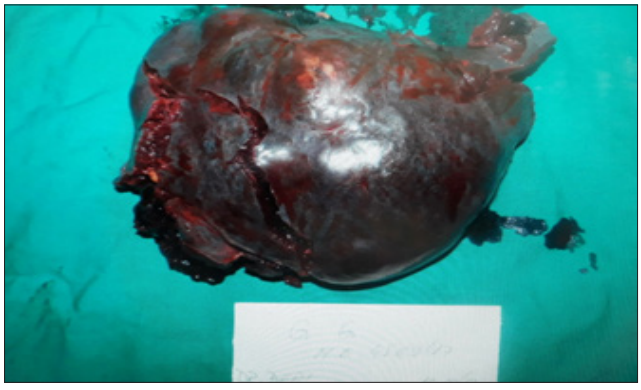
Today, due to significant advances in diagnostic

procedures, primarily by the introduction of CT and NMR abdominal (Fig. 1), mortality has been significantly reduced.[3] Disposing of a patient with rupture may require surgical or non-operative treatment, which is assessed on the basis of general condition, vital parameters and clinical picture.

Case report

In the intensive care unit (ICU), a 58-year-old patient was admitted due to anxiety pain, pain in the upper abdomen and weaknesses. Until that moment, the patient was suffering from anxiety and did not use the therapy. Insights into the medical records of the patient did not establish the existence of any cardiological or chronic illness. Also, the patient denied any kind of trauma. By physical examination, a pulse of 110 beats per minute was established and a blood pressure value of 115 / 70mmHg. Peripheral blood results showed the value of red blood cell (Er) 3.1, hemoglobin (Hgb) 95g / l, platelets (PLT) 58x109. The patient was given an IV solution therapy and he underwent detailed diagnostic treatment. An emergency CT of abdominal and chest bone was performed in the patient. The enlarged spleen with the capsules lesions and the presence of free fluid in the abdominal density of the blood were found. According to the findings, the patient was appointed to surgery, where a patient in a conscious but poor general condition, is admitted into an intensive care unit. The patient repeated the peripheral blood analyses, which showed results of decreasing values and the same was administered with two doses of blood. Based on the insight into the medical documentation and the general condition of the patient, a decision for surgical treatment was made.

Figure 2. Removed Raptured Spleen



The patient was introduced into the general endotracheal anesthesia, and then the upper medial laparatomy was made, the abdominal cavity was entered, where the enlarged spleen with rupture was noted as well as higher amount of free blood that filled the upper and lower part of the abdominal cavity. (Fig. 2)

Evacuation of blood from the abdominal cavity was done, and arteries and venous lienalis were reconverted, ligated and then resected. Then, the preparation and treatment of short gastric blood vessels was done, and this kind of uncompressed and released spleen was removed from the abdominal cavity. After the evacuation of the spleen, the abdominal cavity was rinsed, and the adhesive hemostase and drainage with two abdominal drains were done. One of the drains was placed in the place of the removed spleen and the other in the Douglas tread. The abdomen was sealed in anatomical layers and the patient was transferred the Intensive Care Unit (ICU) for further treatment. After 24 hours, the patient's condition was stable with stable blood references, on the abdominal drains a smaller amount of bloody rinsing was present and the patient was transferred to the General Surgery Clinic for further treatment. The patient situated in the ward was examined by a hematologist who, on the basis of a clinical examination and obtained blood tests, excluded the existence of a hematological disorder. An early postoperative course passed neatly, the control findings of the blood tests were regular and the patient was released home in good general condition.

Discussion

Spontaneous atraumatic spleen rupture is a rare, but serious clinical event requiring urgent surgical intervention to save the patient's life. However, in a small number of cases where the patient's condition is stable and there is no deterioration of vital parameters, treatment can be conservative.[4] Although spontaneous spleen rupture rarely occurs, it is mainly associated with a neoplastic process (30%), an infectious process (27%), an inflammatory non-infectious process (20%) but can also occur in a fully healthy spleen (6%).[5] In a study published by Kapan and authors, it was found that the use of anticoagulant-anti-aggregation therapy in 33% of cases was the cause of spontaneous spleen rupture.[6]

In our patient's presentation, no histological change or an etiological factor was found to be the cause of spontaneous spleen rupture. Also in the study conducted by Koceal and authors, there were examples of spontaneous spleen rupture that occurred without the established cause of rupture with a representation of 8% of cases. Such cases of spontaneous rupture are considered idiopathic.[7] However, despite all the known causes of spontaneous spleen rupture, the mechanism of spontaneous rupture itself has not been fully clarified.

It is believed that there are three possible mechanisms of rupture formation, namely distension due to enlargement

of the spleen and spraying of the capsule, spleen infarction with consequent rupture and defect of blood coagulation with rupture. The main clinical symptoms of spleen rupture are abdominal pain, hypotension, nausea, dizziness. Also well-known are the Kehr's sign (left diaphragmatic irritation with the spread of pain in the left shoulder) and Balance's sign (tangible mass in the left upper quadrant of the abdomen.[8] Nevertheless, despite these clinical symptoms, a definite diagnosis of spleen rupture can only be made on the basis of findings from the US and CT abdomens.[9] In our case, based on the clinical picture and laboratory diagnosis, it was suspected of cardiac disease, but the definitive diagnosis was based on the CT abdomen and chest.

After the diagnosis of spontaneous rupture of the spleen and assessment of the general condition of patients, it is approached to the treatment. The treatment of haemodynamically stable patients with minor rupture caused by infectious diseases is generally conservative, and the success of conservative treatment ranges up to 80%.[5] In addition to conservative treatment in haemodynamically stable patients, arterial embolization10 has been used with recent success. However, in all haemodynamically unstable patients, with whom general conditions are aggravated, an emergency surgical treatment involving splenectomy, is indicated. Splenectomy is a classic treatment because it removes the source of bleeding and allows exploration of the abdominal cavity. Surgery, splenectomy, ranges from 84% to 91% in numerous studies.[11] In our case, due to the deterioration of general conditions of the patient and further decline of the blood test, an emergency splenectomy was reported, after which a successful recovery of the patient occurred. Mortality in patients with spontaneous rupture of the spleen ranged to 12.2%, and it was found that mortality was increasing in patients with neoplastic diseases and in patients over 40 years of age.[5]

Conclusion

Based on all previously said, it follows that spontaneous rupture of the spleen is rare but life-threatening condition, with a high mortality rate if complete diagnosis and adequate therapy is not performed. In most cases, surgical treatment involving spleen removal is the main therapeutic procedure.

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Hirurško zbrinjavanje spontane rupture slezene kod pacijenta sa splenomegalijom

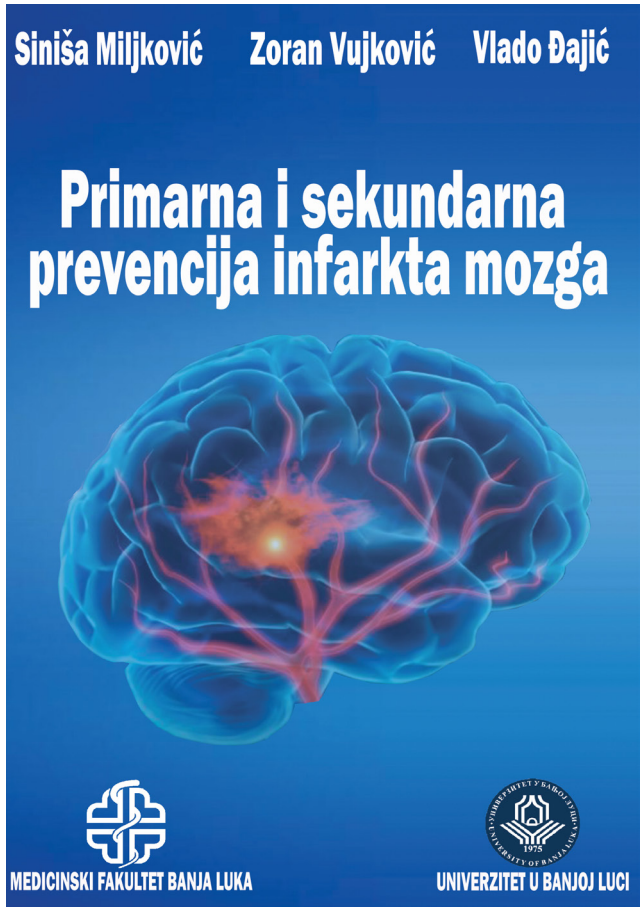
SAŽETAK

Spontana ruptura slezene se rijetko javlja i prvenstveno je zastupljena kod pacijenata sa splenomegalijom. To je po život opasno stanje koje se bez adekvatnog hirurškog tretmana uvijek završava letalno. Sama etiologija spontane atraumatske rupture slezene nije poznata, ali se ona često može povezati sa neoplastičnim oboljenjima, cirozom jetre i nekim infektivnim oboljenjima. Dijagnoza se postavlja neinvazivnim metodama (nalazima elemenata crvene krvne loze, ultrasonografija, kompjuterizovana tomografija abdomena CT, magnetna rezonanca NMR). Terapija se sastoji od laparatomije, evakuacije hemoragičnog sadržaja i uklanjanja slezene. Hirurško liječenje je uspješno, a kao postoperativna komplikacija se može javiti krvarenje kao posljedica neadekvatnog zbrinjavanja lijenalne arterije i vene, te kratkih gastričnih krvnih sudova. Ovdje smo prikazali 58-ogodišnjeg pacijenta muškog pola, koji je zbog izraženog abdominalnog bola, malaksalosti, te niske vrijednosti krvne slike primljen i uspješno hirurški zbrinut na Klinici za opštu i abdominalnu hirurgiju.

Ključne riječi: Splenomegalija, ruptura slezene, hemoragijski šok, splenektomija

BOOK REVIEW

Primary and Secondary Stroke Prevention



Faculty of Medicine of the University of Banja Luka published the book "Primary and Secondary Stroke Prevention" by Dr. Siniša Miljković, Prof. Dr. Zoran Vujković and Prof. Dr. Vlado Đajić. The idea for writing this book came from the fact that we live in the time of explosion of cerebrovascular diseases and stroke epidemic with a high degree of disability and mortality. The authors' intention was to indicate the most significant risk factors for stroke, the importance of primary prevention and the necessity of secondary prevention in patients who already had a stroke in order to prevent relapse. Treatment of stroke alone is a costly, long-term and of uncertain outcome, and this monograph is the first step in launching a general actions to reduce the number of people affected by this severe illness. The book is written on 537 pages, and the theme is divided into three parts.

In the first part *The Ischemic Stroke*, data from its history are given as well as the current situation in the world and in our country regarding epidemiological data such as incidence and prevalence, morbidity and mortality, and costs of treatment of stroke. The basic classification of stroke is also highlighted. A special review of the transient ischemic attack as a preinfarction condition is made. Diagnostic methods for the diagnosis of stroke are also described.

The Primary Prevention of Brain Infections is described in the second part, where detailed guidelines for primary prevention, risk assessment tools from the first stroke, and unchangeable and variable risk factors described in details and each individually processed. Strategies for improving prevention are also elaborated. At the very end of this chapter, recommendations for antiaggregation therapy are given.

The third part describes *Measures for Secondary Stroke Prevention*, which include measures and therapeutic procedures that should be applied after the onset of the first transient ischemic attack, or brain infarction, in order to prevent relapse. Given that risk factors for the occurrence of the first TIA and brain infarction are also risk factors for the recurrence, this chapter presents some of the most common risk factors and recommendations for their control and therapy. The treatment of patients with cardiogenic embolization in the field of atrial fibrillation is also described as well as recommendations for the introduction of oral anticoagulant therapy after hemorrhagic stroke.

This monograph was created as a result of many years of practical work performed by its authors with patients suffering from stroke and based on the systematization of various recommendations of European and world associations with the latest opinions on the prevention of stroke.

Prof. Dr Milorad Žikić

Instructions for Authors

Scripta Medica (SM) is a peer-reviewed international journal published under the auspices of the Medical Society of the Republic of Srpska. The journal publishes original biomedical studies, including those addressing ethical and social issues. As a general medical journal, SM gives preference to clinically oriented studies over those on experimental animals. It publishes peer-reviewed original research papers, case reports, review articles, essays, special articles, clinical problem-solving, images in clinical medicine only in English. Book reviews and news are published only in Serbian. The full text of SM is available, free of charge, online at www.scriptamedica.com.

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1. Manuscripts should be submitted in the .DOC format (MicrosoftWord), using the Times New Roman font. The text should be single spaced in 11 point. The main heading should be 12 point **bold**. Subheadings should be 11 point **bold**. Tables must be in 10 point, single spaced; headings within tables should be in 10 point **bold**; the main table heading should be in 12 point **bold**; legends should be single spaced in 11 point. Illustrations can be submitted in either JPG or TIFF format (300 dpi or higher resolution).

2. Drugs and chemicals should be indicated by generic names. Instruments, apparatus or other devices are indicated by trade names, with the producer's name and place of production indicated in brackets.

3. Numbers in text and tables should be provided if expressed as %; means should be accompanied by SDs, and medians by interquartile range (IQR). In text, use following rule: spell out numbers up to ten and then use numerical designation for 10 and above.

4. All images must have minimum resolution of 300 dpi. The main figure heading should be in 10 point **bold**; legends should be single spaced in 10 point.

5. References should be indicated in the text sequentially in the Vancouver numbering style, as superscripted numbers after any punctuation mark.

6. Units of measurement, length, height, weight and volume are to be expressed in metric units (e.g., meter—m, kilogram—kg, liter—l) or subunits. Temperature should be in degrees Celsius (oC); quantities of substances are given in moles (mol), and blood pressure is expressed as millimeters of mercury (mm Hg). All values of hematological, clinical and biochemical measurements use the metric system according to the International System of Units (SI units).

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8. Authorship statement. To qualify for authorship, one must made substantial intellectual contributions to the study on which the article is based (WAME.com, Policy Statements—Authorship). The author should participate at least in one of these three categories:

a. research question, conception and design, data acquisition and analysis,

b. statistical analysis, interpretation of data, provision of funding, technical or material support, overall supervision of the project.

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In some research projects may participate experts (such as biostatisticians or epidemiologists) that may not be equally familiar with all aspects of the work (for example, some clinical variables or laboratory measurements), but they may be qualified as the authors. A statement acknowledging contribution to the manuscript should be signed by all the authors. It will be published in the section "Author Contributions." The corresponding author is responsible for the integrity of the work as a whole. It is dishonest to omit mentioning the investigator who had important engagement with some aspects of the work.

9. Financial disclosure. A disclosure statement declaring any potential conflict of interest must be signed by each author. (See the policy statement on conflict of interest issued by the World Association of Medical Editors, WAME, www.wame.org or ICMJE uniform disclosure form for potential conflicts of interest, www.icmje.org.) This disclosure includes all affiliations or financial involvement (e.g., employment, consulting fee or honorarium, gifts, stock ownership or options, travel/accomodations expenses, grants or patents received or pending, and royalties) with any organization having a financial interest in or financial conf ict with the subject

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The majority of these instructions are in accordance with "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (www.icmje.org).

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a. A statement that the paper has not been previously published, nor is it concurrently submitted to any other journal,

b. A statement that the manuscript has been read and approved by all authors.

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13. Submission of manuscripts. Manuscripts and all enclosures (cover letter, authorship statement and financial disclosures) should be sent by e-mail to editor@scriptamedica.com, preferably in one file. Signed copies of the cover letter and various statements may be faxed to +387 (51) 329-100. Submissions that do not comply with these instructions will be returned, unread.

14. Editorial process. Manuscripts deemed suitable for publication by in-house assessment will be reviewed by two or more outside experts. Contributors are encouraged to provide names of two or more qualified reviewers with experience in the subject of the submitted manuscript, but this is not mandatory. Page proofs of accepted articles will be sent to the corresponding author, and the corrected proofs should be returned within three days. The entire process, from the initial submission of the manuscript to the final review, including the sending and receiving of page proofs, can be completed online.

15. Review procedure. Manuscripts suitable for peer review will be sent to two outside reviewers. Some manuscripts may be accepted without revision, but if revision is required, the corresponding author must address each question, criticism and suggestion from the reviewers and editor. These topics can be addressed in a letter to the editor along with a revised manuscript. The acceptance rate for SM is around 60%.

16. For further information, please contact us at the following address:

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Specific instructions for a manuscript

Title page. The title page of the manuscript contains the title of the article, the full name of each author (without titles), and the departments and institutions of the author(s) in the order they are listed. The title page must also include the name of the corresponding author, (along with address, phone and fax numbers and e-mail address) to which the work should be attributed. A short running title should have no more than 40 characters, including spaces. The word count should be indicated as well. Original articles may have up to 2.500 words, excluding references and abstract.

The title should identify the main topic or the message of the paper. The standard title of a research paper is a phrase (rarely a sentence) that identifies the topic of the paper; it should be concise and precise, informative and descriptive.

The title of a descriptive paper should include the necessary description, function, purpose, animal species or population. When a method is described, the title should indicate whether it is new or improved.

Abstract and key words. Structured abstracts should be included in papers that report original research. Abstracts are limited to 250 words in four labeled paragraphs: Introduction, Materials and Methods, Results, and Conclusion. The abstract should state concisely the question that was asked or the objectives of the study, the methods that were used, the results obtained, and adequately answer the question posed in the introduc-

tion. The abstract should provide pertinent information when read alone. Below the abstract, authors should provide 3-6 key words or short phrases, according to terms from the Medical Subject Headings—MeSH (www.nlm.nih.gov/mesh).

Introduction. Generally, this section provides the motivation for the paper (i.e., what is missing or unknown in the research literature at this time), an overview of the scientific theory or conceptual models on which the research was based, and the purpose of the study and why it is important. Cite only relevant references.

Materials and methods. This section accurately describes the procedures used to carry out the study; it should be complete enough to permit others to replicate the study. Describe the methodological design, subjects, data sources, data collection methods, and any statistical and analytical procedures. These five parts may not be needed in all papers. Short papers may include these details in different paragraphs, but titled subsections may be used in longer papers. The Methods section should describe how the research was structured, how subjects or groups of subjects (defined by sex, age, and other characteristics) and how the subjects were chosen and assigned to these groups. Identify all drugs and chemicals by generic names, exact drug dosages and routes of administration. Variability should be expressed in terms of means and standard deviations (SD). Because SD and SEM are positive numbers, we recommend elimination of a +/- sign; instead, the SD may be given in brackets. For example, "systolic blood pressure in group of healthy students was 129 mm Hg [SD = 6, n = 87]." A p-value can be used to disprove the null hypothesis, but the authors should also give an estimate of the power of the study and state the exact tests used for statistical analysis.

Results. This section presents findings in logical sequence using the text, tables and illustrations. This section should show how the results of the study answer the research question. This may be shortest part of the entire paper. Details may be presented concisely in one or more tables or figures. Do not repeat the data presented in tables or illustrations in the text. Emphasize or summarize only important observations and how these answer the question posed in the introduction.

Tables. Each table (4 tables or figures are permitted) with its legends, should be self-explanatory and numbered in Arabic numerals in order of their mentioning in the text. The title should be typed above the table, and any explanatory text, including definitions of abbreviations, is placed below the table.

Illustrations (Figures). All figures (photographs, graphs, or schemes) should be numbered with Arabic numerals in the order of their mentioning in the text (a maximum of 4 figures or tables may be submitted). All lettering should be dark against a white background and of sufficient size to be legible when reduced for publication. Do not send original artwork, x-ray films, or ECG tracings but rather photographs of such material. Images need to be at least 300 DPI (JPG or TIF fi les). Figure legends should be typed double-spaced on a separate page with Arabic numerals corresponding to the figure. All symbols, arrows, numbers, or letters should be explained in the legend. An internal scale should appear on photomicrographs, and methods of staining should be described in the legend.

Discussion. Briefly state the principal finding that relates to the purpose or research question posed in the Introduction and follow the interpretation of the results obtained. Compare your findings with work reported previously by others. Discuss the implications of your findings and their limitations with respect to the methods used.

Acknowledgments. List all persons as well as financial and material supporters who helped to realize the project, even if they did not meet the criteria for authorship.

References. The reference list is the responsibility of the authors. List all the papers or other sources cited in describing previous or related research. Cite references in the text sequentially in the Vancouver numbering style, as superscripted number after any punctuation mark. For example: ...as reported by Vulić and colleagues.12 When two references are cited, they should be separated by comma, with no space. Three or more consequtive references are given as a range with an en rule. References in tables and figures should be in numerical order according to where the item is cited in the text. For citations according to the Vancouver style, see Uniform Requirements for Manuscripts Submitted to Biomedical Journals; this source gives the rules and formats established by the International Committee of Medical Journal Editors (www.icmje.org). If there are six authors or fewer, list all six by last name, space, initials, comma. If there are seven or more, list the first three in the same way, followed by et al. For a book, list the editors and the publisher, the city of publication, and year of publication. For a chapter or section of a book, give the authors and title of the section, and the page numbes. For online material, please cite the URL and the date you accessed the website.. Online journal articles can be cited using the DOI number. Do not put references within the Abstract section. All titles should be in English (the name of the original language should appear in brackets). See exam-

ples below that conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals:

De Lacey G, Record C, Wade J. How accurate are quotations and references in medical journals. BMJ 1985; 291:884-6.

International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Croat Med J 2003; 44:770-83.

Huth EJ. How to write and publish papers in the medical sciences. Philadelphia: ISI Press, 1982.

Davidović L, Marković M, Čolić M, et al. Treatment of traumatic rupture of the thoracic aorta. Srp Arh Celok Lek 2008; 136: 498-504.

Curtis MJ, Shattock MJ. The role of the manuscript assessor. In: Hall GM, ed. How to write a paper. London: BMJ Publishing Group; 1994: 89-95.

Electronic publications:

International Society of Scientometrics and Informatics Web site. Available at: http://www.issi-society.info Accessed March 20, 2012.

Lock SP. Journalology: are the quotes needed? CBE Views. 1989:1257-9. Available at: http://garfi eld.libraryupenn. edu/ essays/v13p019y1990.pdf. Accessed April 25, 2012.

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Case reports are most likely to be published if they describe any of the following: an unreported drug side effects (adverse or benefi cial), drug interactions; a new, unexpected, or unusual manifestation of a disease; previously unsuspected causal association between two diseases; presentations, diagnosis and/ or management of new and emerging diseases; an unexpected association between diseases or symptoms; an unexpected event in the course of observing or treating a patient, fi ndings that shed new light on the possible pathogenesis of a disease or an adverse effect; a previously unknown disease. *Scripta Medica* does not publish instructive case reports, that is, presentations that make important teaching point of what is already well known but often forgotten.

Case reports (no longer than 750 words) should include the following: title, case presentation (including up to three illustrations) and discussion, references (up to six), and an unstructured abstract in English or Serbian. The abstract may be a single paragraph containing no more than 100 words, and followed by key words. Title should facilitate retrieval with electronic searching. Case presentation should include the history, examination and investigations adequately, description of treatments, all available therapeutic options that have been considered and outcomes related to treatments. Discussion includes the following: statement an unusual diagnosis, prognosis, therapy; report of a literature review of other similar cases; explain rationale for reporting the case; what is unusual about the case; could things be done differently in a similar case?

Case reports may have as many as five authors. A very short case, about a particular disease can be submitted as a Letter to the Editor. Consent for publication must be obtained from the patients involved; if this is not possible, permission from a close relative or guardian must be obtained before submission.

In a cover letter authors should indicate how the case report contributes to the medical literature. Submissions that do not include this information will be returned to authors prior to peer review. For all case reports, informed written consent is required; the cover letter should state that consent was obtained. Authorship statement and financial disclosure should be presented.

Images in clinical medicine

The editors will consider original, clear and interesting images that depict new or “classic” clinical pictures submitted along with a descriptive paragraph of up to 200 words. The report may include two authors and three references. The authors must obtain a signed, informed consent from the patient or from a close relative or guardian. The cover letter from the corresponding author should state that written consent was obtained.

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Solutions for various clinical problems, including certain clinical studies, should include the following sections: Abstract, Introduction, Methods or Case(s) Presentation, up to four tables or illustrations, Discussion, References

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To minimize delays, we advise that you prepare signed copies of all statements before submitting the manuscript.

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- Authorship statement
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