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ORIGINAL PAPER

Role of Intravenous Omeprazole on Non-variceal Upper Gastrointestinal Bleeding After Endoscopic Treatment: a Comparative Study

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Aim: To evaluate and compare the clinical efficacy of intravenous omeprazole versus intravenous ranitidine therapy for the treatment of non-variceal upper gastrointestinal (UGI) bleeding after endoscopic therapy. **Methods:** 108 patients (72 males and 36 females) admitted with non-variceal UGI bleeding in the Intensive Care Unit of the University Hospital of Durres, Albania, from 2004 to 2008, were included in the study. Patients with gastro-duodenal malignancy and those who were previously receiving anti-secretory drugs were excluded. All patients were treated endoscopically by injecting epinephrine (diluted 1:10.000) followed by ethanol and subsequently were randomized to receive either intravenous omeprazole (with an initial dose of 80 mg, followed by 8 mg/h infusion [n = 54]), or intravenous ranitidine (100 mg bolus, followed by 100 mg boluses every 6 hours for the next 72 hours [n = 54]). **Results:** The re-bleeding rate 72 hours after endoscopic treatment was lower in the omeprazole group than in the ranitidine group (6 vs. 14 patients, respectively; OR=3.4; 95% CI =1.1 –7.2; P<0.01). Less volume of blood transfusion was needed for the omeprazole group than for the ranitidine one (1.1 ± 1.8 units vs. 2.3 ± 2.9 units, P=0.03). The hospitalization period was shorter among patients treated with omeprazole than among those treated with ranitidine (5.4 ± 2.6 days vs. 6.8 ± 3.3 days, respectively; P=0.04). The need for surgery and the mortality rate were not statistically different between the two groups. **Conclusion:** After endoscopic treatment of non-variceal UGI bleeding, intravenous omeprazole reduced the risk of recurrent bleeding, decreased the need for blood transfusion and shortened the period of hospitalization. Intravenous omeprazole should be used in patients with non-variceal UGI bleeding after effective endoscopic treatment. ***Key words:*** bleeding, omeprazole, peptic ulcer, ranitidine.

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1. INTRODUCTION

Non-variceal upper gastrointestinal (UGI) bleeding remains a major reason for hospitalization and mortality. Its overall incidence is approximately 150 hospital admissions per 100.000 inhabitants per year and the most common cause of UGI hemorrhage is peptic ulcer (1, 2). Most ulcers stop bleeding spontaneously as a result of intrinsic haemostatic mechanisms, but in one fifth of cases these mechanisms may fail, and the bleeding continues (2).

Endoscopic therapy for bleeding peptic ulcer is an important modality of treatment. A meta-analysis has shown that endoscopic treatment in such cases reduces the rates of recurrent bleeding, surgery and mortality (3). However bleeding recurs within 72 hours after endoscopic therapy in approximately 20% of patients and overall mortality of UGI bleeding remains around 10% (4, 5).

Pharmacological treatment is an attractive adjuvant to endoscopy therapy in UGI bleeding. The major goal of the medical therapy is the inhibition of gastric acid secretion. The studies have shown that a high intragastric pH could facilitate platelet aggregation and removal of proteolitic influence of pepsin on thrombus (2, 6, 7). The intragastric pH above 6.0 for a minimum period of 72 hours is necessarily for clot stability at the ulcer site (8).

The intravenous use of Histamine H2-receptor antagonists (H2RA) or Proton Pump Inhibitors (PPI) inhibits the gastric secretion but the intravenous infusion of PPI maintains in-

tragastric pH above 6.0, showing better effect than H2RA administration (6, 9). Thus, the intravenous use of PPI is theoretically superior in preventing recurrent bleeding.

Several studies have evaluated the effect of PPI on the non-variceal UGI bleeding (10-13). Unfortunately in some of them the results are not very clear because of including a heterogenic group of patients (10, 11), or not performing any endoscopic treatment (12, 13).

2. GOAL

The aim of our study was to evaluate the clinical effectivity of intravenous PPI therapy compared with intravenous H2RA for the treatment of non-variceal UGI bleeding after endoscopic therapy.

3. METHODS

Study population

Between June 2004 and August 2008, 173 patients with upper GI bleeding were admitted at the Intensive Care Unit of the University Hospital of Durres, Albania. All of them were diagnosed and eventually treated endoscopically. We included in our study the patients with non-variceal UGI bleeding older than 16 years in whom haemostatic endoscopy had been successful. We excluded patients with gastroduodenal malignancy and those previously treated with antisecretory drugs (H2RA or PPI).

Endoscopic therapy

Endoscopic examinations were performed using a video-endoscope (FUJINON 2200) within the first 24 hours of admission. Patients were treated endoscopically by injecting 10–25 cm^3 of adrenaline (epinephrine) (diluted 1:10 000) around the ulcer crater and absolute alcohol on the ulcer bed to stop the bleeding. Haemostasis was considered as established if bleeding had stopped and bleeding vessels were flattened or cavitated. In patients with non-bleeding visible vessels, haemostasis was considered as established when the vessel disappeared.

Data collection

After endoscopic treatment, patients were randomized to receive intravenous infusions of omeprazole or ranitidine for a period of 72 hours. They were divided into two groups according to the medical therapy: group I had received 80 mg intravenous omeprazole bolus, followed by an 8 mg/h infusion for 72 hours, and group II had received intravenous ranitidine 100 mg bolus, followed by 100 mg boluses every 6 hours for a period of 72 hours.

The following data were recorded on every patient: age, sex, location of the ulcer (stomach or duodenum), bleeding stigmata (visible vessel, oozing hemorrhage, spurting or clot), presence of shock, hemoglobin and hematocrit level, previous ulcer bleeding or ulcer disease, non-steroid anti-inflammatory drugs or aspirin use, and comorbid conditions. The Rockall scoring system was used to assess the severity of bleeding in both groups (14).

The primary end-point was 72-hours re-bleeding rate. Re-bleeding was defined as new hematemesis, melaena, or hypotension (< 100 mm Hg systolic blood pressure) associated with a drop in hemoglobin and/or endoscopic evidence of fresh re-bleeding. Volume of blood transfusion, hospital stay, need for surgery and mortality were considered as secondary end-points.

Statistical analysis

Data were entered into a personal computer and analyzed using the Statistical Package for the Social Sciences, version 12.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as means (± standard deviations). The results of the two treatment groups were compared by chi square ($\chi 2$) test (categorical variables), and Student's t test (numerical variables). To test the association between outcomes and clinical co-variables, we estimated risk ratios and 95% confidence intervals (95%CI). In all analyses, statistical significance was considered at $P \leq 0.05$.

4. RESULTS

During the study period, a total of 173 patients with upper GI bleeding were admitted to our Unit. We excluded

Variable	Omeprazole Group (N=54)	Ranitidine Group (N=54)
Sex (no. of patients) Male Female	 35 19	 37 17
Age (in years)	55.4 4 17.3†	55.8 4 16.9
Hemoglobin (g/dl)	8.24 4 1.4	8.29 4 1.5
Hematocrit level (%)	27.7 4 4.2	27.5 4 3.7
Shock at presentation (no. of patients)‡	7	6
Location of ulcer (no. of patients) Stomach Duodenum	 15 39	 16 38
Endoscopic signs of bleeding (no. of patients) Visible vessel Oozing hemorrhage Spurting hemorrhage Clot with underlying vessel	 16 20 4 15	 12 19 3 19
Size of ulcer (in cm.)	1.06 4 0.8	1.12 4 1.0
Previous ulcer disease (no. of patients)	11	12
Previous ulcer bleeding (no. of patients)	5	4
Risk factors for bleeding ulcer (no. of patients) Use of NSAID Use of aspirin	 10 18	 11 26
Rockall score	5.2 4 1.8	5.1 4 1.7
Coexisting illnesses (no. of patients) Ischemic heart diseases Cerebral stroke Diabetes mellitus Hypertension Other diseases	 8 3 3 4 2	 10 2 2 5 4

Table 1. Base-line characteristics of the 108 patients. There was no statistically significant difference between the two groups. † Means 4 standard deviations. ‡ Shock was defined as a systolic blood pressure of 90 mm Hg or less, or a pulse rate of 110 beats per minute or more.

Variables	Omeprazole Group (N=54)	Ranitidine Group (N=54)	Relative Risk (95% CI)	P value
Recurrent bleeding (%)	6 (11.1)	14 (25.9)	3.4 (1.1-7.2)	<0.05
Volume of blood transfusion (units)	1.1 4 1.8*	2.3 4 2.9	___	<0.05
Hospital stay (days)	5.4 4 2.6*	6.8 4 3.3	___	<0.05
Surgery (%)	2	5	0.5 (0.09-2.8)	NS†
Death (%)	1	2	1.9 (1.5-2.3)	NS

Table 2. Clinical outcomes after endoscopic therapy and medical treatment * Means 4 standard deviations.† Not statistically significant (P>0.05).

from the study 28 patients with other gastro duodenal lesions who were not treated endoscopically or underwent surgery because of profuse bleeding, 23 patients with esophageal varices, 6 patients with gastric tumors, and 8 patients who had previously received antisecretory drugs, H2RA or PPI. Only 108 patients fulfilled the criteria to be included in our study. The mean age of the patients was 55.6 years (range: 17 – 85 years). We had 54 patients in group I (taking intravenous omeprazole) and 54 patients in group II (taking intravenous ranitidine).

There were no statistically significant differences between the two study groups on regard of age, the severity of bleeding at presentation, the location of ulcer, endoscopic signs of bleeding, risk factors for ulcers, and coexisting illnesses (table 1).

Table 2 shows the clinical outcomes of this study. The re-bleeding rate after 72 hours of endoscopic treatment was lower in the omeprazole group than in the ranitidine group (6 vs. 14 patients, respectively; OR=3.4; 95% CI =1.1 –7.2; P=0.003). The mean (±SD) number of units of blood transfused after endoscopy and medical treatment was significantly smaller in the omeprazole group than in the ranitidine group (1.1 ± 1.8 vs. 2.3 ± 2.9 units, P=0.03). The difference was probably related to treatment, since the mean number of units transfused before endoscopic treatment was similar in the two groups (0.9 ± 1.2 and 1.0 ± 1.4 units, respectively; P=0.45). The hospitalization period was shorter among patients treated with intravenous omeprazole than those treated with intravenous ranitidine (5.4 ± 2.6 days vs. 6.8 ± 3.3 days, respectively; P=0.04). Twenty patients (6 in the omeprazole group and 14 in the ranitidine group) who had recurrent bleeding underwent a second endoscopy. The endoscopic retreatment stopped the bleeding in 67% of the patients in omeprazole group (4/6), and in 64% of the patients in ranitidine group (9/14). The need for surgery was lower in the omeprazole group (two vs. five), but the difference was not significant (P=0.17). Also, the mortality rate was not statistically different between the two groups of the study. One patient (1.8%) died in the omeprazole group compared with 2 (3.7%) in ranitidine group (P=0.14). All the patients died because of coexisting illnesses.

5. DISCUSSION

The main findings of our study indicate that aggressive acid suppression with intravenous omeprazole significantly reduces the rate of recurrent bleeding, if compared with intravenous ranitidine in patients with non-variceal UGI bleeding after endoscopic schlerotherapy. Patients who were treated with intravenous omeprazole required fewer blood transfusions and had significantly shorter period of hospital stay. The need for surgery and the mortality rate were also lower in the omeprazole group, but these differences were not significant.

Several studies have evaluated the use of PPI in patients with non-variceal UGI bleeding. These studies have shown that patients who received intravenous PPI had significantly lower rate of recurrent bleeding than those who received H2RA or placebo (10, 15, 16). PPI also decreases the need for blood transfusions, the need for surgery, the mortality rate, and shortens the time of hospitalization (9, 17).

In second reports, the use of intravenous omeprazole is shown ineffective in patients with upper gastrointestinal haemorrhage either with (18) or without endoscopic therapy (12). The study of Daneshmend et al. included patients with variceal bleeding, tumours, and peptic ulcers, but in these two studies, the authors used an 80 mg intravenous bolus of omeprazole followed by 40 mg every 8 hours. Two other studies found that intravenous omeprazole reduced the need for surgery if it was accompanied with endoscopic therapy, but they did not show if it reduced the rate of recurrent bleeding or mortality (19, 20)

In our study, we enrolled patients with gastro-duodenal bleeding ulcers. All the patients were treated with endoscopic epinephrine and ethanol injection within the first 24 hours of admission. Adrenaline in doses of 20 ml solution 1: 10 000 leads to about 85-90% suppression of non-variceal UGI bleeding (21, 22).

After endoscopic therapy we used 80 mg intravenous omeprazole bolus, followed by an 8 mg/h infusion for the next 72 hours. PPI are continuously being generated, and the half-life of omeprazole in the circulation is short (50 minutes), therefore it needs to be given more frequently (e.g. every 3 hours) or continuously (23). Recommended dose of PPI for prevention of non-variceal bleeding recurrences is 80 mg in bolus and subsequently through next 72 hours dosage of 8mg/hour (7, 8). We used intravenous omeprazole because oral omeprazole may suppress acid production to a similar degree, but it may take several days before the pH is consistently above 6.0.

Omeprazole acts on K^+-H^+-ATPases pump situated in parietal cells and outside gastric sites, in renal and vascular smooth muscles (23, 25). This can result in decreased renal function and vasoconstriction in blood vessels. In our patients the mortality rate was not significant between the two groups and the deaths were caused only by co-morbid conditions.

Our study had some limitations. We did not measure intra-gastric pH in our patients because the high dose of omeprazole, like the one we used, can maintain intra-gastric pH above 6.0 (6). Our patients were not examined for Helicobacter pylori presence. The prevalence of H. Pylori in Albanian population is very high (26, 27) and therefore

we did not examine for this bacteria in this group of peptic ulcer patients.

6. CONCLUSION

We found that intravenous omeprazole reduce the risk of recurrent bleeding, decreased the need for blood transfusion and shortened the hospital stay in patients with non-variceal UGI bleeding after endoscopic epinephrine injection. It should be used in these patients after effective endoscopic treatment.

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ORIGINAL PAPER

Evaluation of Medical and Surgical Management of Critical Extremity Ischemia Caused by Atherothrombosis

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Aim: To assess efficacy of surgical and medical (conservative) treatment of acute exacerbation of chronic extremity ischemia by evaluating their early therapeutic outcomes in terms of mortality, extremity amputation and reamputation rate, limb salvage rate and length of hospitalization period. **Patients and methods**: Patients were divided into two groups based on method used for the treatment of critical ischemia. Group A consisted of 40 patients that were subjected to surgical treatment of critical extremity ischemia during period 2004-2009. All patients were subjected to thrombectomy in local anesthesia (2% lidocaine) as initial step of treatment protocol. Urgent Seldinger angiography was performed for all patients that have undergone thrombectomy regardless of successfulness of thrombectomy. Based on angiography findings decision was made about further definitive treatment. It consisted of either using antiaggregating drugs (acetyl salicylic acid; 150 mg/day) if no significant postthrombectomy stenotic lesion was found or subjecting patients to further surgical revascularization in the form of bypass were significant stenosis or occlusion was identified. Group B consisted of 40 patients; all of them received conventional heparin anticoagulation therapy supplemented with vasoactive infusion treatment (Pentoxyohylline 300 mg/day) during period 1998-2004. On the third day of hospitalization oral anticoagulation (Sintrom) was included in the therapy protocol using dosage 2-8mg/day in order to achieve INR 2-4, once therapeutic INR was obtained heparin was withdrawn. Study was clinical, designed as retrospective prospective and was conducted at the Clinic for vascular surgery in Sarajevo. **Results**: Mean age in group A was 66,5 years and in group B it was 65,78 years. Lenght of hospital stay in group A was 13,78 days while in group B it was 34,25 days (P value <0,001). Limb salvage rate was 70% in group A and 17,5% in group B (P value < 0,001). In group A , nine amputations were performed (22,5%) while in group B we had to perform 38 amputations (95%), P value <0,001. Only one reamputation was performed in group A (2,5% of patients) while in group B ten reamputations were performed (25% of patients). Mortality rate between groups was not statistically significant (P value <0,077). **Conclusion**: Surgical thrombectomy as introduction to definitive treatment of critical limb ischemia caused by atherothrombosis gives statistically superior results in comparison to conservative treatment. Key words:

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1. INTRODUCTION

Acute exacerbation of chronic extremity ischemia is caused by thrombus formation in the artery on its atherosclerotic plaque, the process also known as atherothrombosis. In 60% of cases it is responsible for acute limb ischemia. Clinically this phenomenon is recognizable as preterminal ischemia or critical limb ischemia which has been defined as degree of ischemia that would in the absence of timely provision of adequate revascularization lead to amputation of limb[1].Besides atherothrombosis, thromboembolism may also lead to acute limb ischemia and it is considered to be responsible factor in 30% of cases. Other causes of acute ischemia are trauma, thrombosis of arterial aneurysm, dissection of aorta etc. When thrombus occludes artery affected by atherosclerosis, vascular segment that is located distally from the site of arterial occlusion undergoes spasm, reaction that is deemed to have protective role in terms of prevention of thrombus propagation into distal arterial tree[2]. There is also retrograde deposition of thrombus in the artery with resultant complete covering or masking of potential culprit stenosis in the atherothrombosed artery. Distal arterial spasm persists about 8 hours and then it

is followed by relaxation of arterial wall with consequent deposition of thrombus in arterial segment located distally from the site of occlusion that in turn leads to occlusion of collateral vessels with exacerbation of ischemia[2].Skeletal muscles and nerves tolerate ischemia for about 8 hours without irreversible damage. Skin marmorization due to appearance of reticular cyanosis takes place. Skin can tolerate ischemia for about 24 hours. When period of ischemia tolerance is used up, irreversible phase of ischemia sets in[3]. Primary aim of treatment is prevention of mortality and limb loss. Five year mortality in patients with critical limb ischemia reaches up to 70%. Desirable outcome is survival without limb loss[4]. Treatment options are aimed at removal of thrombus by surgical or pharmacological means. Then angiographic mapping of affected artery and radiological insight into position, extent and degree of stenotic atherosclerotic lesion is done with subsequent planning of reconstructive procedure. The aim of this study was to assess efficacy of surgical and medical (conservative) treatment of acute exacerbation of chronic extremity ischemia by evaluating their early therapeutic outcomes on basis of following parameters:

- Length of hospitalization period
- Efficacy of limb salvage between analyzed groups
- Number of amputation procedures
- Number of reamputation procedures
- Mortality rate.

In addition primary, patency of revascularization procedure will be determined.

Current management of this condition is based on urgent thrombolytic treatment followed by additional endovascular or surgical revascularisation of arterial stenotic lesion. In our setting, instead of active thrombolysis we attempted to remove thrombus with Fogarty catheter and then based on angiographic findings we decided about further definitive treatment.

2. PATIENTS AND METHODS

Patients were divided into two groups based on method used for the treatment of critical ischemia. Inclusion criteria were: rest pain, confirmed positive history of previous intermittent claudication, positive risk factors for atherosclerosis. Exclusion criteria were: absolute arrhythmia, extremity rest pain after myocardial infarction, thromboangitis obliterans and thrombosis of arterial aneurysm.

Group A consisted of 40 patients that were subjected to surgical treatment of critical extremity ischemia during period 2004-2009. After confirming diagnosis of atherothrombosis, patients were subjected to urgent thrombectomy of affected artery. Thrombectomy was made in local anesthesia (2% lidocaine). Approach to occluded arterial segment was made via arteritomy on common femoral artery in case of lower extremity ischemia or through arteriotomy made on brachial or cubital artery in case of ischemia of upper extremity. Fogarty embolectomy catheters Ch 4 or 6 (depending on the size of artery) were used for extraction of thrombus from the artery exploiting technique of anterograde or retrograde Fogarty thrombectomy. Urgent Seldinger angiography was performed for all patients that have undergone thrombectomy regardless of successfulness of thrombectomy. Based on angiography findings that might have revealed the cause of atherothrombosis decision was made about definitive treatment. It consisted of further therapy using antiaggregating drugs (acetyl salicylic acid 150 mg/day) or subjecting patients to further surgical revascularization in the form of bypass.

APTT	HEPARIN
40-60 sec	10000 IU
60-80 sec	5000 IU
80-100 sec	-
Over 100 sec	Protamine suphate

Table 1 Bolus dosage according to APTT

Group B consisted of 40 patients; all of them received conventional heparin anticoagulation therapy supplemented with vasoactive infusion treatment (Pentoxyohylline 300 mg/day) during period 1998-2004. Heparin was used as part of a standard protocol for treatment of extremity atherothrombosis at our Clinic until year 2004. On admission, patient received heparin solution intravenously during 6 hour period (20000 IU in 500 ml of Normal Saline) and then every 6 hours bolus intravenous heparin supplementation was administered depending on APTT value according to the following scheme (see table 1).

On the third day of hospitalization oral anticoagulation (Sintrom) was included in the therapy protocol and once value of INR 2-4 was achieved, heparin was withdrawn. In case of favorable response patients continued to receive Sintrom, maintaining INR in therapeutical range (for maximum of 6 months when they would replace Sintrom with Aspirin-100 mg /day indefinitely). Concomitantly with heparin, pentoxyphilline infusion was administered to patients with favorable clinical response for 10 days in total. After that period patients would receive pentoxiphylline per os (400 mg, tid). Discrepancies in anticoagulation response are based on individual differences in heparin clearance as well as to the value of APTT on administered quantity of heparin.[5] Study

Analyzed group	Mean	T test	P value	Mean difference	Standard error difference
Group A	66,65				
Group B	65,78	0,368	<0,714	0,875	2,376

Table 2. Age difference between analyzed groups (in years) and statistical significance

Analyzed group	Mean	T test	P value	Mean difference	Standard error difference
Group A	13,78				
Group B	34,25	-7,488	<0,001	-20,478	2,734

Table 3. Length of hospital stay between analyzed groups (in days) and statistical significance

Analyzed group	Procenat	T test	P value	Mean difference	Standard error difference
Group A	70%	5,508	<0,001	0,525	0,095
Group B	17,5%				

Table 4. Percentage of limb salvage between analyzed groups and statistical significance

Analyzed group	Amputation	Chi square test	P value
Group A	9	43,378	<0,001
Group B	38		

Table 5. Number of patients with amputations and statistical significance

Analyzed group	Reamputated extremities	Chi square test	P value
Group A	1	8,538	<0,003
Group B	10		

Table 6. Number of patients with reamputations and statistical significance

Analyzed group	Mortality	Chi square test	P value
Group A	3	3,117	<0,077
Group B	0		

Table 7. Number of lethal outcomes and statistical significance

was clinical, designed as retrospective prospective and was conducted at the Clinic for vascular surgery in Sarajevo.

3. RESULTS

Mean age in group A was 66,5 years and in group B it was 65,78 years. (Table 2). Lenght of hospital stay in group A was 13,78 days while in group B it was 34,25 days, P value <0,001, (Table 3, Figure 1). Limb salvage rate in group A was 70% and in group B it was 17,5%, P value <0,001.(Table 4, Figure 2). In group A , nine amputations were performed (22,5%) while in group B we had to perform 38 amputations (95%), 33 major amputations and 5 minor amputations; major amputation stands for amputation performed above ankle joint and minor for amputations at the level of foot-below ankle joint. (Table 5 and Figure 3). Only one reamputation was performed in group A (2,5% of patients). In group B, 10 reamputations were performed (25% of patients), difference in reamputation rate was statistically significant (Table 6, Figure 4). Mortality rate between groups was not statistically significant , P value <0,077, though in group A we had three cases with death outcome. In group B mortality rate was zero. (Table 7)

4. DISCUSSION

Mean age for group A was 66.65 years while for the group B it was 65.78. Difference was not statistically significant and it was similar to the mean age in other relevant studies[6]. Age is important determinant of peripheral arterial disease (PAD) and with advancing age prevalence of PAD increases.

Length of hospital stay is expressed in days and it varies significantly between analyzed groups, (group A= 13,78 days, group B= 34,25; p<0,001). Mean patient hospital stay in surgical group is below mean hospital stay mentioned in Report of National Survey of Great Britain and Ireland[6]. 679 patients were included in that study and 70% of them received revascularization treatment; mean hospital stay in that study was 25 days. Length of hospital stay of patients in the group B was longer due to obviously ineffective therapeutical response in terms of failure to improve oxygen delivery to limb periphery and consequently it required higher rate of extremity amputation and reamputation treatments.

Limb salvage rate in group A was successful in 28 out of 40 patients. In group B it was significantly less, it was achieved only in case of 7 out of 40 patients (70 vs. 17,5 %; p<0,001). Although some studies[7,8] report certain therapuetical effect of pentoxifylline in the treatment of chronic critical ischemia in our study its effect was obviously inferior when compared to the results obtained by surgical intervention. Lapentalo et Matzke also noticed significant reduction of limb salvage percentage in the absence of reconstruction for the treatment of chronic critical limb ischemia[9].

In the group that received conservative treatment (group B), 33 amputations were done above ankle joint (major amputations), 5 patients had amputations of digits and 2 patients did not require amputation treatment at all. In summary, conservative therapy was effective in the case of 7 patients (2 patients did not required amputation treatment at all, while 5 patients after minor amputations of digits had successful wound healing and their walking function of foot was undisturbed)

In surgically treated group (group A) thrombectomy was successfully achieved in 29 out of 40 patients. In remaining 11 patients tip of Fogarty catheter came across hard intraluminal resistance that could not be traversed without danger of penetrating

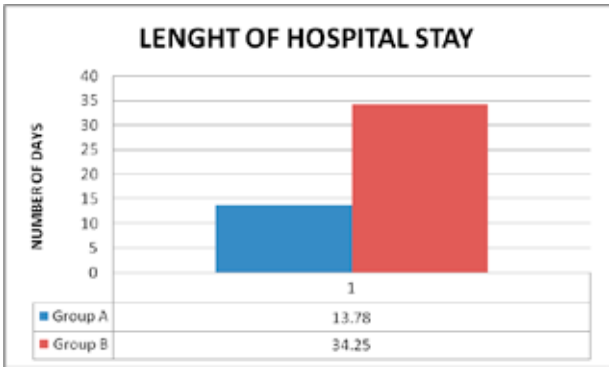

Figure 1. Lenght of hopsital stay in days

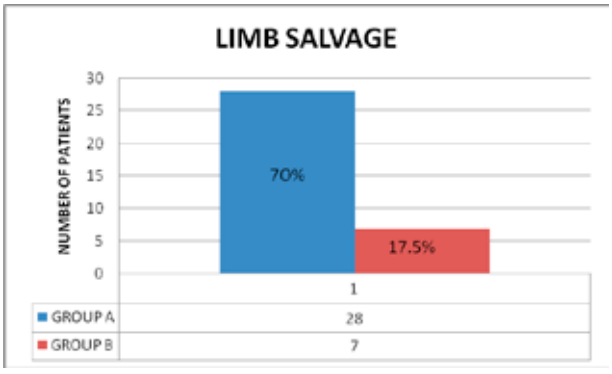

Figure 2. Percentage of limb salvage in analyzed groups

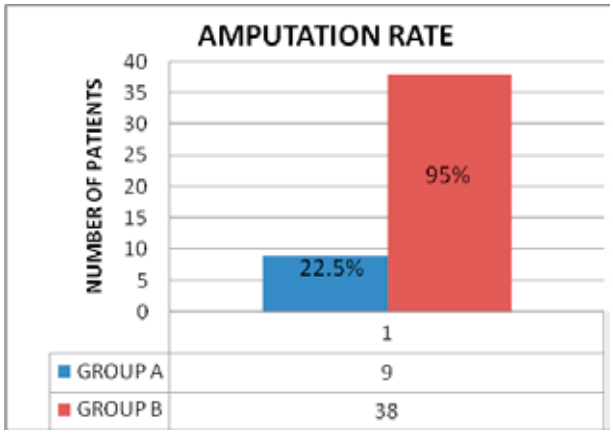

Figure 3. Amputation rate in analyzed groups

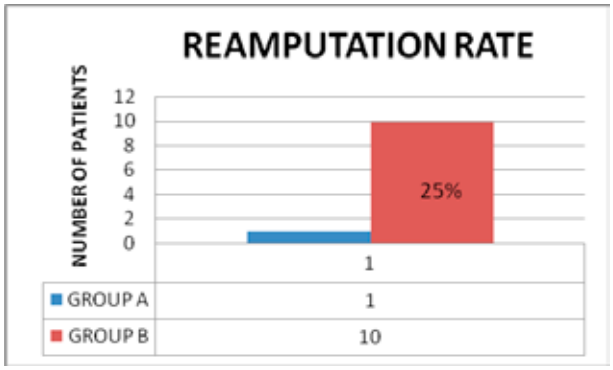

Figure 4. Reamputation rate in analyzed groups

arterial wall therefore thrombectomy procedure was abandoned. After urgent Seldinger angiography was performed, thrombectomy *per se* proved to be sufficient revascularization procedure in case of 20 patients since no haemodynamically significant stenosis was found in affected artery. All these cases coincided with intraopeartive finding of soft plaque and thrombus extraction from the artery with remaining denuded arterial wall that was devoid of presence of significant stenosis. Lifelong acetyl salicylic acid therapy -150 mg/day was administered to all those patients. 3 out of remaining 9 patients after thrombectomy procedure was performed ended up with amputation due to progression of irreversible leg ischemia while other 6 patients were subjected to additional revascularization procedure in the form of bypass with resulting successful limb salvage. Eleven patients that that did not receive successful thrombectomy due to hardness of intra-arterial obstructive lesion were nevertheless subjected to Seldinger angiography and they had the following outcome: 4 amputations (nonexistence of adequate recipient vessel on angiography), 4 bypass reconstructions (2 successful outcomes in 30 days follow up period while remaining 2 patients ended up with amputations due to progression of irreversible ischemia-insufficient outflow to the periphery) and 3 death cases.

Amputation rate in group B was 95% while amputation rate in group A was 22,5%. Difference is statistically significant; p<0,001. Increased need for amputation treatment should be also viewed in the light of possible belated referral of patients with critical ischemia to vascular surgery center as well as inadequate control of atherosclerotic risk factors. This problem is also noticed and reported in developed countries e.g. Great Britain[10]. In other words, timely referral of these patients to appropriate vascular centers will contribute to the decrease of number of amputation treatments[11]. In National Report of Great Britain and Ireland amputation percentage for the treatment of critical limb ischemia was 21,5%[1]. According to this study amputation treatment was directly related to longer intrahospital stay, higher mortality rate and more complex institutional support.

We report need for one reamputation (2,5%) in group A. On the other hand, in the group B due to wound dehiscence of amputation stump and ascending infection, 10 reamputations (25%) were performed. Difference in number of reamputation procedures between analyzed groups is significant; p<0,003.

There were no statistically significant difference in mortality rate between analyzed groups (p<0,077), the first patient died due to postprocedural myocardial infarction, second patient succumbed to massive pulmonary thromboembolism while third patient was lost because of aggravation of general status following stroke for which he was addmitted to the stroke unit prior to occurrence and treatment of acute atherothrombotic limb ischemia. Aune and Trippestad reported 14% operative mortality after 30 days[12]. Wolf and Wyatt reported 26% high mortality rate after one year of follow up period[13]. In National Survey of Great Britain and Ireland total mortality rate for the treatment of critical limb ischemia was 13,5%. Overall score of surgical treatment after 30 days of follow up period was: 28 successful limb salvages (70%), 3 dead cases (7,5%) and 9 patients with major amputations (22,5%). Results of limb salvage rate in our study did not significantly differ from limb salvage rate (75%) reported in National survey of Great Britain and Ireland regarding treatment of critical limb ischemia[1]. According to Baily and Saha after analyzing 130 patients in their one year prospective study, limb salvage rate was 61%[14]. Primary patency of revascularization treatment in the group A, after 30 days, was 70%. 50% (n=20) of revascularizations were in the form of thrombectomy while 20% (n=8) of them were bypass reconstructions. In British and Irish National survey for the treatment of critical limb ischemia, primary patency of performed revascularization procedures at the time of patient discharge from the hospital was 75%[1].

5. CONCLUSION

Surgical thrombectomy as introduction to definitive treatment of critical limb ischemia caused by atherothrombosis gives far superior results in comparison to conservative treatment in terms of higher limb salvage rate as well as lower rate of amputations and reamputations. Furthermore, patient hospital stay is significantly shorter in the group that received surgical treatment. Primary patency rate of revascularization procedures performed in this study was 70% and it positively correlates with published results of other European vascular centers.

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ORIGINAL PAPER

Mediastinal Lymph Node Metastasis Pattern in Clinically N0 Non-small-cell Lung Cancer Patients Who Underwent Surgical Resection

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The aim of this study was to evaluate the incidence, clinical data and patterns of mediastinal lymph node metastasis (pN2) in non-small-cell lung cancer patients who underwent systematic mediastinal lymph node dissection (SMLND). We retrospectively studied 140 consecutive patients [125 male and 15 female, mean ages 54.61±9.23 years (range, 21-75)], underwent SMLND and major lung resections due to non-small lung cancer (NSCLC), from January 2005 till December 2009. Preoperative clinical staging for mediastinal lymph node metastasis was negative (cN0) in all patients. SMLND was defined as a complete removal of mediastinal lymph nodes. Clinicalpathological data were compared according to the pN stage. Lymph node metastasis to the mediastinum was confirmed in 13(9.28%) patients. In squamous cell cancer pN2 were in 8(5.71%) cases out of 82 cases with cN0. On the other side in the adenocarcinomas pN2 were in 5(3.57%) cases out of 48 with cN0. Unvaried analysis revealed central tumor site as predictive factor for mediastinal lymph node involvement. The upper mediastinal compartment was infiltrated in 12(8.57%) cases, middle in 8(5.71%) and lower in 3(2.14%) cases. Pneumonectomy was the most performed surgical procedure in pN2 patients. We concluded that SMLND improves pTNM staging in lung cancer patients who underwent major lung resections with central location of the tumour. Key words: Mediastinal lymph node metastasis, clinically N0 non-small-cell lung cancer, undrewent surgical resection

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1. INTRODUCTION

Lung cancer is common cause of cancer mortality in the developed world. Despite advances in variety of therapies, surgery for NSCLC is still the most effective method of controlling the primary tumor provided it is resectable for cure. The treatment of NSCLC depends of the TNM stage and mediastinal N2 lymph nodes remain a critical part of staging lung cancer patients. For this reason many authors insist on the importance of SMLND for accurate staging (1). In this study we aimed to assess overall rate of pN2 for patients who underwent SMLNS based on our experience. We evaluated all consecutive SMLND and lung cancer resections performed on our department during 5 year period.

2. MATERIAL AND METHODS

We retrospectively studied clinical records of 140 consecutive patients with mean ages 54.61 ± 9.23 (range 21-75)] who underwent complete anatomical resection for histological proven NSCLC in five years, from January 2005 till December 2009. Among this group, 125 male patients with mean age 54.45±10.91 years and 15 female patients with mean age 53.16±11.34 years were enlisted. All patients had stage T1-3N0, assessed by preoperative computer tomography (CT) imaging of the chest, brain, abdomen, bone scan and abdominal and supraclavicular ultrasound scanning. Patients with proven N2 or N3 lymph node involvement were excluded from study. None of the patients in the study received preoperative chemotherapy or radiotherapy. Patients with previous or coexistent malignant disease were excluded from the study. Pulmonary and circulatory functions were required to be eligible for radical resections. Complete resection was defined as removal of primary tumor and all accessible hilar and mediastinal lymph nodes with

no residual tumor left behind. SMLND is defined as a radical and block mediastinal lymph node dissection. The major lung resections procedures were lobectomy and pneumonectomy with standard posterolateral thoracotomy. The three compartments included upper or superior mediastinal node (station 1-4), the middle or subcarinal and paraesophageal node (station 7-8) and lower compartment or pulmonary ligament node (station 9). Metastasis to these compartments including either to one or multiple node regarded as positive. All tissue samples were sent to department of pathology. Three major types of carcinoma, squamous cell carcinoma, adenocarcinoma and large cell carcinoma were diagnosed and selected to analyze lymph node pattern.

2.1. Statistical analysis

Statistical analysis was performed using χ^2 test (or the Fisher's exact test as required). Values were expressed as mean ± S.D. (ranges). Univariate analysis was performed to identify factors linked to the status of nodal involvement. P-value ≤ 0.05 was regarded as significant.

Stage	SCC[1]	AC[2]	Others[3]	Total (%)
I	26	18	2	46 (32.9)
II	41	24	6	71 (50.7)
IIIA	15	6	2	23 (16.4)
Total,%	82 (58.6)	48 (34.3)	10 (7.1)	140 (100)
1.Small-cell carcinoma, 2. Adenocarcinoma, 3. Large-cell carcinoma				

Table 1. Postoperative TNM and histological status

	N0	N1	N2*	Total (%)	
Patients	55	72	13	140(100)	
Male	51	63	11	125(89.3)	p>0.05
Female	4	9	2	15(10.7)	
Squamous cc	27	47	8	82(58.6)	p>0.05
Adeno cc	28	15	5	48(34.3)	
Central TS	11	31	10	59(42.1)	p=0.040
Peripheral TS	44	41	3	81(57.8)	
Pneumonectomy	7	32	12	51(36.4)	p=0.021
Lobectomy	48	40	1	89(63.6)	
*group of patients who underwent univariate analysis					

Table 2. Clinicopathological characteristics of patients according to the N status

	UC (n, %)	UMC*(n, %)	MC (n, %)	MLC*(n, %)	LC (n,%)
Total (n,%)	12(92.3)	6(46.1)	8(61.5)	2(15.4)	3(23.1)
Squamous cc[1]	6	3	4	1	2
Adeno cc	4	2	3	1	1
Large cc	2	1	1	0	0
1Cell-cancer; UC, single upper compartment metastasis; UMC*, Upper-middle multiple compartment metastasis; MC, single middle compartment metastasis; MLC* multiple middle-lower compartment metastasis, LC, single lower compartment metastasis;					

Table 3. Compartments pattern of N2 metastasis involvement based on tumor pathology

3. RESULTS

All patients were treated by lobectomy or pneumonectomy with standard posterolateral thoracotomy. There were 3 postoperative deaths or 2.1%. Atrial fibrillation was observed in 12 (8.5%) patients. Wound infections, athelectasis, prolonged air leak and thoracic empyema were observed in 10 (7.1%), 8 (5.7%) 3 (2.1%), and 5 (3.6%) patients. The extent of resection was lobectomy in 89 (63.6%) patients and pneumonectomy in 51 (36.4%). The pathologist revealed 82 (58.5%) squamous cell carcinoma, 48 (34.3%) adenocarcinoma and 10 (7.1%) large cell carcinoma. Postoperative TNM and histological status is shown in Table 1.

Patient's clinicopathological characteristics according to the N status are listed in Table 2. The pattern of lymph node status was N0 55 (39.3%), N1 72 (51.4%) and N2 13 (9.3%). Men were more likely to have lung cancer surgery than women (125/15). Lymph node metastasis to the mediastinum was confirmed in 13 (9.3%) patients. In squamous cell cancer pN2 were in 8 (5.7%) cases out of 82 cases with cN0. On the other side in the adenocarcinomas pN2 were in 5 (3.6%) cases out of 48 with cN0. Univariate analysis revealed central tumor site as predictive factors for mediastinal lymph node involvement. Pneumonectomy was performed in 12 (8.5%) pN2 patients and lobectomy in 1(0.7%). The feature of lymph node metastasis to the mediastinal compartment based on individual pattern is shown in Table 3.

Single or multiple compartments metastasis pattern of N2 involvement based on histology of the tumors are shown in Table 3. We had no significant statistical differences among all groups.

4. DISCUSSION

This study did not reveal an increased morbidity after SMLND in patients with NSCLC compared to the findings of other reports in this respect (2). Our results in general agree with the study reported by Izbicky and associates (3), which described 2001 patients and demonstrated no increase in the rate of broncho-pleural fistula due to interruption of blood supply to the bronchial stump, phrenic and recurrent laryngeal nerve injury, chylothorax and hemothorax. We reported only relatively high incidence of arterial fibrillation (8.5%) and athelectasis (5.7%) probably due to excess denervation after hilar dissection and inadequate controlling postoperative pain. Operative mortality in lung resections reported by Allen et al. (2) was 2.0% compared with 2.1% in current study. Therefore, the fear of increased complications by performing a SMLND is unfounded.

The results of our study confirmed lymph node metastasis to the mediastinum in 13 (9.3%) patients out of 140 patients with negative preoperative mediastinal lymph node staging (cN0). There was strong similarity in the percentage of patients (11.5%) reported by Sugi et al. (4). Sioris et al. (5) also demonstrated that SMLND is necessary for accurate pN2 staging. They found 17% pN2 patients who were preoperatively diagnosed as cN0. This highly accurate staging after SMLND might allow a more precise

selection of the patient chemotherapy protocols with possible benefit in overall survival (6). It also may allow to eradicate otherwise undetected micro metastasis which might result in better local control and improved overall outcome of the patients (7).

This study also analyzed clinicopathological factors that might be significant predictive for lymph nodal involvement in patients who underwent resections of the NSCLC. Univariate analysis revealed central tumor site as predictive factor for mediastinal lymph node involvement with p=0.04. Ketchedijan et al. also showed that central tumors have a higher incidence of lymph node metastasis (8). In their series the incidence for nodal involvement was 50% for central tumor of any size. The major contributors may be intrapulmonary lymphatic route, interlobar lymph node so-called lymph sump and tumor infiltration capability (9).

Considering our results, a lobectomy is acceptable for patients for N0-1 patients with peripheral tumor, and pneumonectomy for N1-2 patients with central tumors. The similar results are revealed by Takizawa et al. (10). In this study pneumonectomy is high correlated with pN2 involvement in patients underwent NSCLC surgery.

The distribution pattern of different N2 compartment metastasis was assessed. The most involved region of mediastinum was upper compartment. We have not recorded different lymphatic spreading pattern of N2 metastasis involvement according to the different histological type of tumor as Wu et al. revealed (11). Our results agree with those previously reported by Kotoulas et al. (12).

5. CONCLUSION

In conclusion, among our group of NSCLC patients who underwent SMLND, 9.3% of patients with preoperative negative mediastinal lymph node metastasis involvement had pN2 disease. Factors as central location of tumor and upper mediastinal metastasis compartment involvement were highly correlated with pN2 disease. SMLND is safe procedure, and improves pTNM staging in NSCLC patients. Results confirmed that SMLND should be performed in all patients who underwent pneumonectomy with central site of the tumor.

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ORIGINAL PAPER

Risk Factors for Development of Hip Disorder Among Newborn Babies in Tesanj Region

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INTRODUCTION Development disorder of the hip is a congenital, dynamic and progressive disease where there is disorder in the development of all elements of hip that is clinically shows as functional disorders. **AIM** To determine clinical and statistical arthrosonographic representation of developmental disorders of the hip at newborn babies in Tesanj region, with or without risk factors. **MATERIAL AND METHODS** The subjects are 300 newborns born in Tesanj region, which are examined in the orthopedic clinics in the period from October 1st 2008 to May 1st 2009. **RESULTS** youngest child in the studied sample had an examination in the first nine and the oldest 42 days, an average of 33 days. In the studied sample representation of the firstborn children was 179, and second born children 97, third born 23. Only one child was born from the fourth pregnancy. Positive family history had 26 children and negative 274. Natural way was born four children, by Caesarean section 51 children. One child was born early but naturally. On time 244 children were born by normal natural way. Of firstborn children, the representation of female children was 80, and the male 99. 6 children were born as twins. Associated anomalies were found in two of the examined children; agenesis of fibula and pes equinovarus. One risk factor had 113 children, two 27 and three risk factors at one child. The remaining 159 children had no risk factor or a developmental disorder of the hip. **DISCUSSION D**evelopmental disorder of the hip is the most common developmental anomaly, which occurs in all races and ethnic groups, ranging from 0.4% to 6%. It is more common in female than male children in the ratio of 1:4 to 1:10. Mutual disorder appears more than one-sided reports. Sided phenomenon affecting more left than right hip. Developmental disorder of the hip is often associated with other developmental abnormalities. Early detection of initial disturbances in newborn is crucial, because of using of early traumatic therapy, which reduces the incidence of operative treatment and secondary complications. **CONCLUSION** Developmental hip disorders in children in Tesanj region, defined by hip sonography Graf, were found in 4.33% cases. If the borderline cases of type I by Graf included in the category of children with possible spontaneous evolution from type I to type II (no prevention measures), the incidence of RCC would be 10.66%. Almost half of children (139) of the investigated sample have a risk factor in the anamnesis. Remarkably high percentage of children born caesarean. The greatest correlation of risk factors, was determined in children with a positive family history, were born with abnormalities of the loco motor apparatus and natural way of born. **KEY WORDS** Developmental disorders of the hip, sonography

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1. INTRODUCTION

Developmental hip dysplasia is a congenital, dynamic and progressive disease in which there is disorder in the development of all elements of the hip joint, resulting in complete dislocation of the joint parts with all the functional disorders. (1) The term "developmental disorder of the hip (DDH) encompasses all levels in the development of these anomalies: dysplastic, subluxated, and luxated hip (2).

The first descriptions of RPK gave Hippocrates. A significant contribution to the knowledge of the diagnosis is given by Ortolan and Palmen, Lorenz, in the treatment of with plaster, Hilgenreiner and Pavlik with their apparatus, and in prevention Roser (3). The significance of surgical treatment of DDH has given in his works Chiari 1955 introducing a pelvic osteotomy, Pemberton in 1959 by etabulum covering and Salter in 1961with innominate bone osteotomy and later with triradiat osteotomy (4). It is known for

certain that the DDH occurs in utero, and happens more frequent in children with positive family history, among the firstborn female children, twins, breech birth or Caesarean section, children who have other congenital anomalies, particularly of the locomotor apparatus (5,6). Identified are also other risk factors such as pelvic disproportion of mother and fetus, the lack of amniotic fluid (oligohydramnios), heavy and extended labor ... (5).

Radiographic hip examination is valid when the child reaches 3 months of life. This is because part of hip cartilage is replaced by bone mass and ossification core of the femoral head forms (7).

Sonography provides an absolutely safe intrauterine visualization of the hip or in the first days of life of a child. In this age most of the hip joints are made of cartilage, which provides a broad "ultrasonic window and display a large portion of the hip joint. In Europe, hip ultrasonography is used according to Graf (3).

For completely correct interpretation of the sonogram has to be shown seven anatomical structures: cartilage-bone border, head of the femur, the transitional groove, joint capsule, labrum acetabula, cartilage acetabula roof, bone acetabulum.

Drawing the base line which is tangential to the iliac bone wing and passing through the intersection and perichondria periosteal or through a place where the periosteal becomes perichondria (11). The second line is a line of the bony roof. It starts from the lower edge of the os ilium, the bottom of the acetabulum and passes tangentially through the bony acetabula roof angle creating alpha. The other line is drawn from the cartilage roof starts with bony bay windows and passes through the center of labrum acetabula making the angle beta. The angle beta indicates the state of the cartilage roof of the hip joint (11,12). According to the values of angles alpha and beta, there are four basic types of hips according to Graf (3,12).

2. GOAL

The goals of research are: to determine the clinical and arthrosonographic finding the hip in newborns in the hospital Tesanj, determine the prevalence and clinical and statistical significance of sonography findings in infants with risk factors and no risk factors, to propose recommendations for early detection of persons with increased risk for DDH.

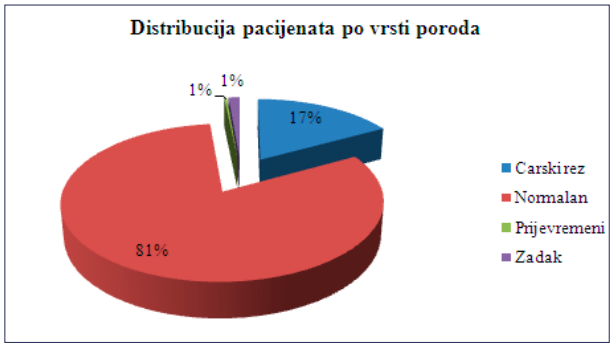

FIGURE 1.

3. MATERIAL AND METHODS

Subjects are 300 newborn infants in Tesanj region, which were examined in an orthopedic clinic in the period from October 1st 2008 to May 1st 2009. The first ultrasound examination was performed in infants who were not older than 45 days.

After taking the anamnesis data from the parent started clinical examination of the newborn. Formed is a questionnaire in which they entered the data used for statistical analysis. In addition to basic data such as general data, sex and age entered the data on the order of pregnancy, type of pregnancy (normal, twins). In the section on birth, entered the data on the type of delivery (normal, premature, by Caesarean section), followed by details on the fetus (head first, breech birth) and birth weight.

Entered are the data on the associated anomalies such as congenital pes equinovarus, pes. valgus and other anomalies and the occurrence of developmental anomalies of the hip in first degree relatives, and information on family history. In a special section were possible remarks.

Separate questionnaire was used for statistical analysis of the data about the DDH risk factors: positive family history, the firstborn female child, breech birth, birth by Caesarean section, twin pregnancy, premature birth, congenital anomalies of the musculoskeletal system, pes equinovarus, pes equinovalgus , various forms of dysplasia, and agenesis. The part of the questionnaire was designed for clinical examination of the hips collected are the data on asymmetry of gluteal, inguinal and femoral groove (Bade sign), the result of abduction test separately for each hip: Ortolani luxation and Palmen reposition sign. Clinical examination was performed by hip sonography. Used is ultrasound machine "Toshiba" with linear probe of 7.5 MHz. Method used is by Reinhardt Graf.

With tests of statistical significance determined is inferential statistics–tests of implicit (additional) and explicit (main) research hypotheses by nonparametric method,–χ^2 test (Chi-square test).

4. RESULTS

The youngest child in the sample had 9 and the oldest 42 days, an average of 33 days. In the baseline there was 179 (59.67%) first born, and the second born in 97 (32.33%), third-born 23 (7.66%)

Probability of true hypothesis about correlation between individual risk factors and research parameters (p) (tested sample)	Gender	Birth order	Pregnancy	Type of delivery	Family anamnesis	Bade sign	Abduction test	Ortolani sign	Palmen sign	Alpha angle (right)	Hip type according to alpha angle (right)	Alpha angle (left)	Hip type according to alpha angle (left)	Hip type according to beta angle (right)	Hip type according to beta angle (left)	Hip type by Graf (right)	Hip type by Graf (left)	Medical treatment
Probability (p)	0.4675	0.1599	NCFT	NCFT	NCFT	0.2228	0.7939	NCFT	NCFT	NCFT	NCFT	NCFT	NCFT	0.4897	0.1888	NCFT	NCFT	0.4064

TABLE 1.

cases. Only one child (0.33%) was born from the fourth pregnancy. Positive family history in the sample had 26 (8.67%) children, while with negative family history was 274 (91.33%). Breech birth was in case of 4 children (1.33%), born by Caesarean section were 51 (17%). (Figure 1) Premature, but naturally born is 1 (0.33%) child. Normal and natural way in the term was born 244 (81.33%) children. From the first-born children, in the sample were 80 (26.67%) female children and 99 (33.00%) male.

As the twins were born 6 (2%) children. Associated anomalies as a risk factor for DDH were found in two children. In one it was an agenesis of the fibula and lateral side of the foot, while in the second the congenital pes equinovarus. With only one risk factor for DDH was 113 (37.67%) children, with two risk factors for DDH 27 (9%) and three risk factors for DDH is born only 1 (0.33%) child. The remaining 159 (53%) children had no risk factor.

Testing of hypotheses about the significance of differences of research parameters (characteristics) in relation to individual risk factors in the sample is presented in Table 1

In the Table (1) NCFT is short: there are no conditions for the testing of hypotheses. NCFT label indicate the fact that at least one cell in the corresponding contingency table have frequencies of 5 or lower.

Based on the tables and rules of reasoning we conclude that for the studied sample:

- There is no correlation between individual risk factor and gender (p = 0.4675);
- There is no correlation between individual risk factors and the order of birth (p = 0.1599);
- There are no conditions for testing hypotheses about the relationship of individual risk factors and pregnancy;
- There are no conditions for testing hypotheses about the relationship of individual risk factors and types of birth;
- There are no conditions for testing hypotheses about the relationship of individual risk factors and family history;
- There is no correlation between individual risk factors and positive Bade sign (p = 0.2228);
- There is no correlation between individual risk factors and positive Abduction test (p = 0.7939);
- There are no conditions for testing hypotheses about the relationship of individual risk factors and positive Ortolani sign;
- There are no conditions for testing hypotheses about the relationship of individual risk factors and positive Palmen sign;
- There are no conditions for testing hypotheses about the relationship of individual risk factors and the angle alpha (right);
- There are no conditions for testing hypotheses about the relationship of individual risk factors and types of hip according to angle alpha (right);
- There are no conditions for testing hypotheses about the relationship of individual risk factors and the angle alpha (left);
- There are no conditions for testing hypotheses about the relationship of individual risk factors and types of hip according to angle alpha (left);
- There is no correlation between individual risk factors and types of hip according to angle beta (right) (p = 0.4897);
- There is no correlation between individual risk factors and types of hip according to angle beta (left) (p = 0.1888);
- There are no conditions for testing hypotheses about the relationship of individual risk factors and types of hip according to Graf (right);
- There are no conditions for testing hypotheses about the relationship of individual risk factors and types of hip according to Graf (left);
- There are no conditions for testing hypotheses about the relationship of individual risk factors and medical treatment.

Of 113 children with one risk factor in the sample was mostly female first-born children (19.67%), followed by those born by caesarean section (10.67%), with positive family history (5.33%) (Figure 2). The first clinical examination revealed some of the clinical signs of DDH in 59 (19.67%) children in the sample and without any clinical signs of DDH in 241 (80.33%) child. Asymmetry of skin furrows (Bade sign), was found in 49 (16.33%), abduction test positive in 17 (5.67%), and Ortolani Palmen sign was not verified. Positive two clinical signs (Bade sign and abduction test) were in case of 8 (2.67%) children. There were three children with positive clinical signs of DDH

Sonographic examination revealed DDH in 13 (4.33%) children from which 9 female and 4 male children. In case of 3 children it was a bilateral, and in 10 the unilateral DDH, which makes a total of 16 from which was 8 right and 8 left DDH. In our sample, 287 children had type I by Graf, 12 type II according to Graf, one child type III according to Graf. From a total of 16 altered hips 15 were type II and only one type III according to Graf. We did not found any hip of type IV according to Graf.

Clinical examination of 141 children in whom is determined the presence of risk factors, medical history, clinical signs were found DDH in 33 (23.40%), and of 159 children who have not any anamnestic risk factor was 26 (16.34%) children with clinical signs of DDH.

In 26 children who had a positive family history 21 had no other risk factors for DDH. In the remaining 5 (31.25%) children were found clinical signs of DDH and it was found in 4 cases Bade positive sign, and one child with a positive Ortolani Palmen sign.

Figure 2.

Out of 80 first-born female children 59 had no other risk factors for DDH. From which 21 (30.50%) had clinical signs of DDH: 15 positive Bade sign, 5 abduction positive test and 1 positive for both these characters.

From 4 children who were breech born none had clinical signs of DDH.

From 51 children that were born by caesarean section 32 had no other risk factors for DDH. Clinical signs of DDH at birth by caesarean section had 2 (6.25%) children. In one was found positive Bade sign, and the abduction positive test in other.

For children from twin pregnancies, there were no clinical signs of DDH and with one child who is born prematurely. With congenital anomalies of the locomotor apparatus, there were two children. Neither of them have clinical signs of DDH.

Two risk factors for DDH had 27 children. In 19 there were no clinical signs of DDH and were found in 8. Clinical signs of DDH in 8 children are manifested: a positive Bade sign had a 4, a positive abduction test 2 and a positive sign for both of these 2 children.

Three risk factors had only 1 child in without clinical signs of DDH.

Without risk factors were 159 children. Clinical signs of DDH were found in 26 (16.35%) and a positive Bade sign in 19, abduction positive test in 2 and a positive sign of both in 5 children.

Analysis of 141 children with confirmed anamnestic, clinical risk factors, sonographic DDH was found in 9 (6.38%), and from 159 children without medical history or clinical risk factors for sonographic DDH was found in 4 (2.51%).

In relation to individual risk factors was found sonography of hips following conditions:

From 16 children with positive family history, and without other risk factors, by sonography DDH was found in 2 (12.50%).

Out of 59 first born girl child, and without other risk factors was found by sonography DDH in 4 (6 .77%).

From 32 children born by Caesarean section, and without other risk factors, only 1 (3.12%) had sonographic signs of DDH. One child from a twin pregnancy and one that is born premature, and without other risk factors had sonographic healthy hips (type I by Graf).

With congenital anomalies of the locomotor system in the sample were 2 children, both male. In one it was a congenital bilateral pes equinovarus, while in another the fibula and lateral agenesis of the right foot. In one was found sonographic DDH of the right hip.

From the 27 children with two clinical risk factors for DDH by sonography was diagnosed in 3 children (11.11%). In one child with three clinical risk factors there was no sonographic diagnosis of DDH. Out of 159 children from the tested sample at which it is not established in a single clinical risk factor, at 4 (2.51%) there was sonographic diagnosis of DDH.

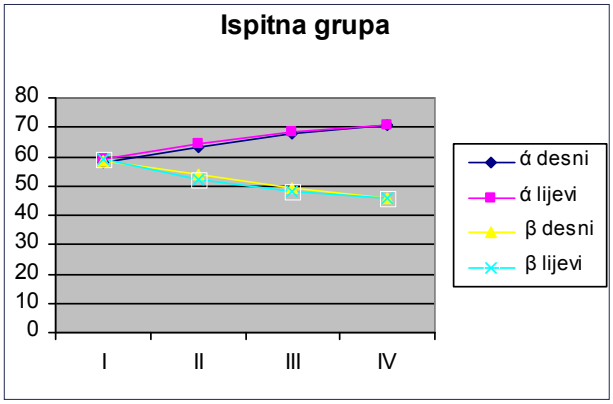

Figure 3.

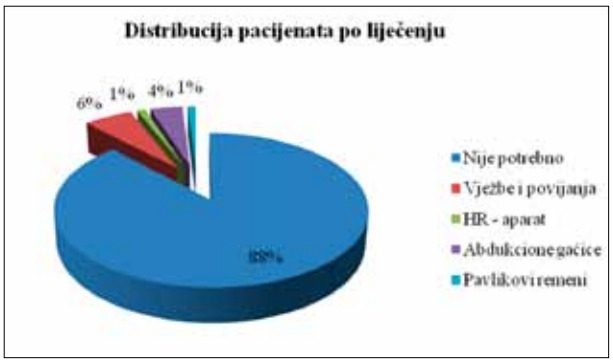

Figure 4.

In relation to individual risk factors by sonography of the hips was found the following conditions:

From 7 children with positive family history, and without other risk factors, DDH was verified by sonography in one case.

Out of 13 firstborn female children, and without other risk factors did not nor by a sonographic diagnosis of DDH,

Of 21 children who were born by caesarean section DDH was diagnosed by sonography in 2 children. Only one child was born from a twin pregnancy with sonography diagnosed DDH.

The maximum value of the angle alpha that was found on the right hip is 78^0, minimum 48^0, and the mean value of 70.44^0. The maximum value of angle alpha on left hip is 78^0, minimum 43^0, and the mean value of 70.40^0 degrees. (Figure 3)

The maximum value of the beta angle on the right hip was 82^0, minimum 39^0, and the mean value of 46.85^0 degrees. The maximum value of the angle beta on the left hip was 83^0, minimum 39^0, and the mean value of 47^0.

Most often value of angle alpha at the first examination of children in the sample was on the right hip 75^0 (41 times), 72^0 and 70^0 (37 times). The left hip angle commonly found value of alpha is 75^0 (43 times) 72^0 (35 times) and 70^0 (35 times).

Most frequent value of the angle beta in the right hip in the sample was 45^0 (30 times), 44^0 (29 times) and 48^0 (25 times). The most common value of left hip angle beta was 44^0 and 45^0 (29 times), and 46^0 (25 times).

Prevention, broadly folded, abduction exercises, treatment with Pavlik stripes and Hilgenrner tracks were involved from the first examination, diagnosis. (Figure 4)

Four weeks after the first clinical and sonographic examinations all children were reviewed for the second time. Clinical examination in neither one child from each sample was reported positive abduction test, and Palmen-Ortolani sign. All had asymmetric inguinal and femoral grooves, Bade positive sign, as at baseline. Any child who at the first examination had sonographic type I by Graf, had sonographic type I also at the second examination. From the 13 children who at baseline

had sonographic type II and type III by Graf, 10 patients (76.92%) were diagnosed with type I. Three children still had type II according to Graf.

At the third examination in the sample, by sonography were established DDH in two children, one male and one female. All children who at baseline had sonographic findings of DDH at the fourth review were healthy.

Measuring the angles alpha and beta in the second, third and fourth review is followed by maturation of acetabulum. The average value of angle alpha at baseline in healthy children in the sample was 71^0, second 73^0, third $73.5^0$and fourth 74^0, while the average value of the angle beta at baseline was 46.5^0, second 44^0, on third 43.2^0 and fourth 42.8^0. (Figure 3)

5. DISCUSSION

Developmental hip dysplasia is the most common developmental anomaly of the locomotor apparatus. It occurs in all races and ethnic groups, ranging from 0.4% to 6% (1,2). It is more common among the Slavic people, Navaho Native Americans... There are so called luxogenic zones such as the Valley of Zeta in Montenegro and Eastern Herzegovina, where the incidence of 9% is found (2). It is much more common in female than in male children and occurs at a ratio of 1:4 to 1:10 in favor of female children (12). More frequent is bilateral than unilateral. In cases of unilateral occurrence affected is more often the left hip than right. It is not rare that DDH is combined with other developmental anomalies (2).

Developmental hip dysplasia (DDH) is the most common disease of the joint. It is manifested as a dislocation in children and in adults as coxartrosis (9). Early detection of initial disorder in newborns and early atraumatic application of the therapy reduces the incidence of surgical treatment and secondary complications (10).

In our prospective study that was conducted in Tesanj from October 1st 2008 to May 1st 2009 we examined 300 children. The sample consisted of only those children who at the time of initial examination were not older than 45 days. The sample includes approximately one-half of children born in this region in time when the research was done. This data indicates that the method of early detection of DDH by sonography is not accepted method by the doctors who deal with this problem on Tesanj region. The incidence of DDH is different and varies in a range from 20-50 or even more per 1000 deliveries (2). For the big difference in the frequency the result is uneven terminology, the size of the study population, ethnic characteristics, and the child age during the examination, the experience of doctors, examination techniques and interpretation of results (5). The lowest incidence is in Hon Kong 0.01%, followed by Northern Ireland 0.14%, Sweden 0.17%, USA by 0.2% to 0.4%, in the UK about 1.5% (2.6,8,12). In Croatia, according to reports from several places DDH screening results show that the incidence is around 2%, although there are regions where it was 0.2% and even higher than 4% (Vrdoljak, Matasovic). The incidence of DDH in Serbia in recent years is around 2%. During 2002 and 2003 at the Department of Gynecology and Obstetrics in Novi Sad and the Institute of Orthopedic-Surgery "Banjica" clinically is examined 4016 newborns by ultrasound and found the incidence of DDH was 1.95% (12). Results of the first screening in Bosnia and Herzegovina, which was carried out in the Tuzla region at the sixties of last century, say that the incidence of DDH us 4.9%, followed by 6.3% (1,6). According to recent findings, the United Kingdom has the highest incidence of DDH in the whole Europe (6).

Data obtained by analysis of the sample indicate that the incidence of DDH in the Tesanj region is high (4.33%) and it is higher than in developed countries of Europe and neighboring countries in the region.

Breech birth was in 4 (1.33%) cases in the sample. The reports from Zagreb, Rijeka, Slavonski Brod in neighboring Croatia is that the breech birth is present in 2-3% of children (3).

Born by caesarean section in the sample are 51 (17%) children. The incidence of caesarean deliveries in the sample is as in developed European countries but lower than in the USA and Canada. According to WHO reports from 2002 and 2004 the incidence of caesarean birth in most developed countries is 10% to 15%, while it is slightly higher in the United States 20% and Canada 22.5%. These data, and data regarding the incidence of breech birth vary from region to region, and considering that a large number of deliveries by Caesarean started as breech birth and the birth by caesarean section has become a kind of trend, these data must be taken with a grain of salt.

The incidence of developmental dysplasia of the hip detected by clinical examination in the literature varies from 1.66% (Barlow), to 40% (Soc, Brecelj). These data do not depend only on the assessors, but also by region and time in which the research was done, and the age of children at the time of the hips examination. During sixties Soc and Brecelj SOC performed DDH research in Donja Zeta and found that the incidence of DDH is more than 40% (1). At the same time the data is completely contrary to Barlow and sets a very low incidence rate of DDH. He surveyed children at birth and then followed up to age 4 months and came to the conclusion that 60% of hips that are unstable at birth, stabilize in the first week and 88% in the next 2 months. The remaining 12% had residual instability. These data indicate that only a clinical examination is insufficient and unreliable method of screening of DDH but that it should be done within the inspection of children's hips.

Most investigators agree that heredity plays a significant role in the development of DDH, and that about 20% of children with DDH have a positive family history (6,8). In our sample 4 (30.76%) children with DDH have a positive family history, which is more than the specified data from the literature.

Of 59 first-born female children from the tested sample, only 2 (3.38%) has a developmental disorder of the hips. The incidence of DDH in first-born female children is even lower than in the whole sample, but higher than in children without risk factors, where the incidence is 2.51%.

Some say that more than 30% of children with DDH are firstborn female children (3). A number of authors have not point out to female first-born children, because they believe all the first-

born child, regardless of sex are at increased risk of DDH due to rigid walls of the uterus, and insufficient space for the development of the fetus. For female children the risk is increased because of greater amounts of estrogen that leads to looseness of the hip joint capsule (4).

In children with breech birth, twins and delivered prematurely within the tested sample has been no outbreak of DDH. In prematurely born children (one in each sample) was established DDH. Many authors believe that the lower risk of DDH is in these children because of better relations between the size of the fetus and the uterus. Data from this study speak in favor of it.

For breech born children in our sample, there was no occurrence of DDH, which is not consistent with data from the literature where it is stated that 20% of children with DDH had breech birth.

6. CONCLUSION

The incidence of DDH in children in the Tesanj region determined by sonography of the hips and using the Graf method was found in 4.33% of cases but is significantly higher than in developed European countries and USA.

If the borderline cases of type I by Graf are included in the category of children with possible spontaneous evolution from type I to type II (without prevention), the incidence of DDH would be 10.66% which is almost 2.5 times more than established.

Incidence of DDH in children with risk factors is 2.5 times more frequent than in children without risk factors.

Prevalence of risk factors in the sample is high. Nearly half of the children (141 or 47%) from baseline have at least one risk factor for DDH in anamnesis. Notably, a higher percentage of children are born by caesarean section.

The highest correlation between risk factors and DDH in the sample was found in children born with anomalies of the locomotor apparatus (50%) with positive family history (12.50%), and children with two risk factors (11.11%).

There was no significant correlation between DDH in first-born female children and birth by caesarean section, although it is slightly higher than in children without risk factors. Twin pregnancy, breech birth and preterm birth have no significance for the occurrence of DDH in our sample.

7th The curve of the value of angles alpha and beta indicates that the potential of acetabula bone maturation is very good in the first 6 weeks. From 6 until the late 12th week ossification potential of acetabulum is good, and after that period begins to weaken.

Clinical examination is not a reliable screening method of DDH. Significant differences in clinical and sonographic findings point to the possibility of diagnostic errors. Healthy children can be declared to be ill or sick to be healthy, which can have serious consequences. Clinical examination must not be omitted, and the first clinical examination should be carried out already at the maternity ward.

Sonography is a reliable method of detecting DDH in newborns. Method by Graf is practical and applicable. The possibility of error in estimating the type of hip by Graf is only in borderline cases. Therefore, the limiting case of type I and type II should be treated as type II, in order to avoid unwanted consequences.

Sonogram hip examination should be introduced as mandatory for all newborns and should be done in the first 6 weeks when ossification potential for maturation of acetabula is biggest, so the results of prevention and treatment of developmental dysplasia of the hip is the best.

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ORIGINAL PAPER

Relationship Between Anger, Alcoholism and Symptoms of Posttraumatic Stress Disorders in War Veterans

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Purpose: Studies among veterans indicate that veterans with posttraumatic stress disorder (PTSD) express anger, hostility and aggression as well as alcohol and substance abuse more then veterans without PTSD. The aim of this study was to analyze the relationship between anger, use of alcohol and symptoms of PTSD in war veterans in Bosnia and Herzegovina (B&H). **Method:** Comparing a group of veterans (n=54) with PTSD who use alcohol and a group of veterans (n=46) who do not use alcohol, the analyzed were dimensions of anger related to PTSD symptoms and alcohol usage. Medical records of patients treated at the Department for Psychiatry in Tuzla, B&H, Harvard Trauma Questionnaire (HTQ) – version for Bosnia and Herzegovina, State-Trait Anger Expression Inventory (STAXI), Structured Clinical Diagnostic Interview (SCID-I) were used in this study. The basic socio-demographic data were also collected**. Results:** A significant correlation is found between alcohol usage, and state and trait of anger (P<0.001), angry temperament (P = 0.001), anger-in expression (P<0.001), anger-out expression (P<0.001), and anger control (P<0.001). PTSD hyperarousal cluster symptoms were significantly correlated to state anger, anger-in expression (P<0.05), and use of alcohol (P = 0.010). **Conclusion:** The results indicate that there is a significant correlation between PTSD arousal symptom with anger dimensions, as well as between anger dimensions and use of alcohol in war veterans with PTSD. Key words: Alcohol Use, PTSD Symptoms, Anger

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1. INTRODUCTION

Posttraumatic stress disorder is frequently co-morbid with other psychiatric disorders (1, 2). Patients with PTSD often use alcohol or other psychoactive substances in order to cope with co-morbid problems such as anxiety or depression (3, 4), or as a way of reducing distress related to particular PTSD symptoms. Some studies point to the existence of high prevalence of aggression, and a connection of anger and aggression with PTSD symptoms (5). Symptoms of PTSD intermediate in the relation between trauma severity and the expression of both verbal and physical aggression (6). A significant number of studies have found a connection between PTSD symptoms in war veterans and aggressive behavior in partners' relationship (7, 8). War veterans' social functioning is considerably affected by relation between PTSD symptoms and the use of alcohol or psychoactive substances (9, 10). The alcohol use in war veterans with PTSD is interconnected with low quality of life (11). Recent study on U.S. soldiers returnees from Iraq in which demographic characteristics of the investigated groups of soldiers were very similar, point to a significantly high level of PTSD, depression and alcohol abuse, as well as to a significant presence of stigma linked to seeking help in mental health services (12,13). The incidence of aggressive and violent behavior in war veterans varies, while studies suggest that it is significantly higher in war veterans with PTSD. The predominant forms of aggressive behavior include auto-aggressive behavior and hetero-aggressive pattern with dominant verbal aggression and impulsive reactions. The level of education, low socio-economic status, childhood abuse, and prior violent behavior showed to be of importance for later occurrence of the aggressive behavior (14). Most studies show a high rate of PTSD symptoms, depression, and use of alcohol in war veterans (1, 3, 10), while difficulties related to anger in war veterans were much less analyzed (15). Chemtob et al. (16) report on a lack of empirical data on the relation between combat-related PTSD and increase in anger. Persons with PTSD symptoms have difficulties in anger control (17). Anger might be a very difficult emotion to deal with, and may

lead to a number of juridical and interpersonal problems (15). In DSM-IV TR (18) the anger is considered to be a possible symptom of PTSD. Angry ruminations and verbal expression contribute to PTSD symptoms maintenance. Several authors have recommended that treatment of PTSD should include anger management in certain groups of PTSD patients (19). The aim of this study is to determine the relationship between the anger and ways of anger expression, as well as the use of alcohol and PTSD symptoms in war veterans from Bosnia and Herzegovina.

2. SUBJECTS AND METHODS

The subjects enrolled in this study were male war veterans of the Army of Bosnia and Herzegovina, with the average age of 42.84±4.66 years, who did not use alcohol before the war and were hospitalized at the Department for Psychiatry in Tuzla during 2003, when diagnosed with combat-related PTSD according to DSM-IV criteria (18). This research is carried out in the period from September 2004 to February 2005. Data were collected from the admission protocols and medical records. Out of 1166 patients treated in 2003, the 130 (11.2%) were war veterans with PTSD. Their addresses were taken from the protocols and the letter about objectives of this research with a form of voluntary consent was sent via post office. The letter included the info about time schedule ascertained for each veteran as well as the place of investigation and travel costs to be covered. Psychometric tests and clinical assessment is done by clinical psychiatrist and psychologist who did not treat these patients previously. Out of 130 invited veterans, 113 responded among which 6 did not meet the inclusion criteria (4 used alcohol before the war, and 2 were older then 55). During the study procedure, 7 out of 107 war veterans dropped out for various reasons, and the investigated group of veterans with PTSD used some of psychotropic drugs in that period. All veterans used anxyolytics and sedatives, 49 used low dosages of atypical antipsychotics (Risperidon 1 to 2 mg a day), 70 used antidepressants (Paroxetin, Setralin, Fluoxetin). Veterans who use alcohol were taking psychotropic drugs on their own initiative out of recommended protocol, and temporarily taking anxyolytics with alcohol. After discharge 66 veterans were subject to a regular out-patient psychiatric treatment.

3. MEASURES

The State-Train Anger Expression Inventory (STAXI), which provides relatively brief and objectively scored measures of anger experience, expression and anger control, was used for the assessment of anger (20). The STAXI consists of 44 items administered in three parts and distributed across five main scales. In accordance with the above mentioned concept of anger, there exist three main aspects of the STAXI scales: State, Trait, and Anger Expression. Part 1 consists of 10 items to assess the State Anger. Part 2 contains 10 items to measure the Trait Anger. Trait contains two subscales to investigate different dispositions in trait anger–temperament and reaction. Part 3 consists of 24 items to measure Anger Expression. Anger Expression is an experimental composite of the three expression constructs In, Out, and Control. All items are rated on a four-point scale and assigned a score between 1 and 4. Trait-anger items are rated on 4-point scales from „almost never"–1 to „almost always"–4, and the state-anger items are rated on the intensity of feelings from „not at all"–1 to „very much so"–4. The coefficient of reliability for the trait-anger subscale was 0.91, for the state-anger subscale 0.82, and for the anger expression it was 0.79. The index of anger expression is being measured, which enables measuring the total anger expression, levels from 0-1.4 being low, 1.5–2.4 moderate, 2.5–3.4 high and 3.5–4.4 extremely high. Levels of anger expression were determined according to percentile range. Values of anger expression that fall to percentile 5 to 25 are considered to be low; values that fall to percentiles 50 to 75 are moderate; values to percentiles 75 to 90 are considered to be high, and values to percentiles 95 extremely high.

In order to determine alcohol consumption, the Structured clinical interview for DSM-IV, Axis I disorders (SCID-I), and application form for alcohol related disorder (21) were used. The interview format for the SCID includes an initial screen for evidence of any lifetime excessive drinking, followed by items for specific diagnoses of alcohol abuse and addiction. Each item is scored 1 – not present, 2 – mildly present or unclear or 3 – present. Every interview took about one hour. To evaluate traumatic events and the presence of PTSD, as well as the expressiveness of PTSD symptoms, a self-rating Harvard

Characteristics	No of war veterans (N=100)
Nationality	
Bosniaks	98
Serbs	2
Religion affiliation	
Islamic	96
Orthodox	2
Atheist	2
Marital status	
Married	82
Divorced	6
Widowed	4
Single	8
Education	
No education	10
Elementary	30
Secondary School	56
University degree	4
Employment status	
Employed	62
Unemployed	38
Alcoholism in family	
Present	40
Not present	60
Traumatic events	
Wounding	18
Death of the closest	22
Drawing a wounded and killed persons	94
Exposure to a heavy shelling	100
Being captured	10
Persecution	14
Witnessing death of other soldiers	92

Table 1. Socio-demographic characteristic of Bosnian and Herzegovina war veterans (N=100) with Posttraumatic Stress Disorders

Trauma Questionnaire (HTQ), Bosnia and Herzegovina Version (22) was used. For identified traumatic event, the respondents were asked: "How do you feel when you remember that?", rated on a 0-5 scale: 0 – No feeling, 1 – a bit upset, 2 – somewhat upset, 3 – moderately upset, 4 – seriously upset, and 5 – extremely seriously upset. Another part of the questionnaire contained a 16-item scale for measuring PTSD symptoms and the presence of PTSD. Stress level was defined as the frequency of each PTSD symptom in the last month, assessed on the 0 – 5 scale by determining its occurrence: 0 – not at all, 1 – almost never, 2 – sometimes, 3 – moderately, 4 – often and 5 – almost every day. To collect socio-demographic data, a questionnaire designed for this research was used; it contained questions related to general socio-demographic data and questions about family history of alcoholism.

4. DATA ANALYSES

A nonparametric Mann-Whitney test was used for the statistic analysis of differences between the groups in results of answers to questions about socio-demographic data (age, employment, education, marital status, employment of the partner, alcoholism in family). The difference between groups in stress levels, intensity of PTSD symptoms, number of traumatic events, and the score of index' of the subscale anger was analyzed by the factorial ANOVA model. The relation between dimensions of anger, use of alcohol, and PTSD symptoms was analyzed with the Pearson correlations. Collected data were statistically analyzed using the Windows Statistical Package for Social Sciences, version 10.0 (SPSS, Chicago, IL, USA).

5. RESULTS

Most subjects in this study were married, employed, of secondary school educational level, with no family history of alcoholism (Table 1). Average number of reported traumatic events was 4.8±1.75, where witnessing death or wounding of soldier mates prevail (Table 1). In total sample of the veteran group the mean of PTSD symptoms intensity was 3.37±0.41, the mean of stress level was 2.56±0.73, while the mean scores of clusters of intrusive symptoms was 2.78±0.57, avoidance symptoms 2.93±0.47, and arousal symptoms 2.46±0.76. According to SCID-I interview criteria, in the 12-month-period prior to this study, 54 veterans with PTSD used alcohol, and 46 did not use alcohol. There was no statistically significant difference related to age (43.56±4.94 vs. 42.00±42.84, F = 1.394, P = 0.244) between war veterans with PTSD who used alcohol and those who did not use alcohol. Using Mann-Whitney test, no significant difference is found between those two groups related to marital status (Z = -0.422, P = 0.673), level of education (Z = -1.199, P = 0.230), employment rate (Z = -0.729, P = 0.466), and family history on alcoholism (Z = -1.119, P = 0.263). No significant difference is found using Factorial ANOVA analysis in severity of PTSD symptoms (F = 0.268, P = 0.848), the intrusive symptoms (F = 1.404, P = 0.254), the avoidance symptoms (F = 1.625, P = 0.197), hyperarousal symptoms (F = 2.754, P = 0.053), and the number of traumatic events (F = 1.973, P = 0.131). Linear regression showed significant correlation between alcohol usage and the number of traumatic events (r = 0.334, P = 0.009), intrusive symptoms (r = 0.249, P = 0.041), avoidance symptoms (r = 0.309, P = 0.014), and hyperarousal symptoms (r = 0.384, P = 0.003). However, there was no significant relation between the number of traumatic events and intrusive symptoms (r = 0.039, P = 0.393), avoidance symptoms (r = 0.133, P = 0.178), and hyperarousal symptoms (P = 0.059, P = 0.342).

Out of total 100 war veterans with PTSD, a high and an extremely high level of trait anger was found in 18 veterans, a high level of anger-out expression was found in 24, anger-in expression a high in 20, and anger control a high to extremely high level in 46 war veterans (Table 2). Multivariate analy-

Anger Dimensions	No of war veterans related to level of anger expression*			
	Low (0-1.4)	Moderate (1.5-2.4)	High (2.5-3.4)	Extremely (3.5-4.4)
State anger	23	46	28	-
Trait anger	2	80	16	2
Angry temperament	6	66	28	-
Angry reaction	4	56	38	2
Anger expression	-	92	8	-
Anger-in	2	78	20	-
Anger-out	10	66	24	-
Anger controlž	8	42	40	6
* Levels of anger expression were determined according to percentile range; values of anger expression that fall to percentile 5 to 25 are considered to be low; values that fall to percentiles 50 to 75 are moderate; values to percentiles 75 to 90 are considered to be high, and values to percentiles 95 extremely high				

Table 2. Level of anger expression index measured by the State Trait Anger Expression Inventory (STAXI) in Bosnian war veterans with Posttraumatic Stress Disorder (N = 100)

Dimensions of anger	War veterans with PTSD (N=100)					
	Who use alcohol (n=54) M4SD	Who do not use alcohol(n=46) M4SD	Type III Sum of Squere	Mean Squere	F	P
State anger	2.1440.61	1.5640.37	5.33	1.77	6.08	0.001
Trait anger	2.3140.45	1.8640.41	3.41	1.13	6.41	0.001
Angry temperament	2.2940.55	1.8040.45	3.54	1.18	4.44	0.008
Angry reaction	2.3640.46	2.1140.57	2.25	0.75	3.03	0.038
Anger expression	2.2240.11	2.1540.14	0.13	4.52E-02	2.81	0.050
Anger-in	2.2940.26	2.0040.26	1.26	0.42	5.97	0.002
Anger-out	2.3240.42	1.7140.30	5.12	1.70	12.53	<0.001
Anger control	2.1040.67	2.7540.55	6.72	2.24	6.06	0.001
PTSD- Posttraumatic Stress Disorder, M-mean, SD–standard deviation, F value for factorial ANOVA						

Table 3. The mean of anger scores and differences in dimensions of anger measured by the State Trait Anger Expression Inventory (STAXI) in Bosnian war veterans with Posttraumatic Stress Disorder who use alcohol (n=54) and do not use alcohol (n=46)

sis used for fixed factors of alcohol usage found a significant difference in the dimensions of anger between war veterans with PTSD who use alcohol and those who not use alcohol (Table 3). In relation to cluster symptoms of PTSD and dimensions of anger, using linear regression it is found a significant correlation between hyperarousal symptoms and the state anger (r = 0.285, P = 0.022), and angry temperament (r = 0.270, P = 0.029), anger expression (r = 0.342, P = 0.008), and anger-out expression (r = 0.279, P = 0.025), while between intrusive symptoms, avoidance symptoms and dimensions of anger there was no significant correlation. A significant correlation is found by linear regression between the number of traumatic events and state anger (r = 0.267, P = 0.031), angry temperament (r = 0.266, P = 0.031), anger-out expression (r = 0.354, P = 0.006), and anger control (r = 0.281, P = 0.024). There was no significant correlation between the intensity of PTSD symptoms and state anger (r = 0.027, P = 0.425), trait anger (r = 0.023, P = 0.437), angry temperament (r = 0.021, P = 0.443), angry reaction (r = 0.009, P = 0.475), anger-in (r = 0.124, P = 0.195), anger-out (r = 0.142, P = 0.163, and anger control (r = 0.105, P = 0.235).

6. DISCUSSION

In this study most veterans with PTSD have had moderate to extremely high level of trait anger, angry reaction, and anger-in expression; moderate to high level of angry temperament, anger-out expression, and state anger. Moderate to high index of anger control was present in the largest number of veterans, which is opposite to expected results and results from other studies (16, 17). A significant correlation between the intensity of PTSD symptoms and score of anger dimensions is not found in this study, while a significant relation between symptoms of hyperarousal and state anger, angry temperament, anger expression and anger-out expression is found, which is similar to the results of Evans et al. (8). Also, a significant correlation is found between the number of traumatic events and state anger, angry temperament, anger-out expression and anger control. Possible explanation for the results obtained is that this study enrolled veterans who were taking one or more psychotropic drugs during the period of investigation, and most of them underwent treatment. It is also possible that veterans are afraid of their aggressive impulses and may lack self-efficacy with regard to anger control, and therefore, they are more likely to "stuff" their anger (23).

With regard to alcohol consumption, 54 veterans from Bosnia and Herzegovina enrolled in this study used alcohol, and a significant relationship is found between PTSD symptoms and use of alcohol, which does not differ from the results obtained in previous studies (4, 10, 12, 24). It is found that war veterans with PTSD who used alcohol have had significantly higher level of the trait anger, the state anger, the angry temperament, and higher expression of anger-in and anger-out, and a weaker control of anger compared to veterans suffering from PTSD who did not use alcohol. Studies indicate that hyperarousal symptoms of PTSD are related to alcohol usage too (25, 26). The studies conducted on war veterans in Croatia (24, 27), Bosnia and Herzegovina (28), Iraq and Afghanistan (19), and Vietnam war veterans (7, 15) showed a high level of aggression in veterans with PTSD who have alcohol-related disorders. Also, Lasko et al. (29) found in Vietnam veterans that those with PTSD had a higher aggression score compared to veterans without PTSD, and that aggression intensity was determined more as a part of PTSD. The association of PTSD symptoms with aggressive behavior and directing aggression outwardly was also found in studies related to violent behavior of war veterans against their partners (8, 15), and interpersonal violence (30). However, a relationship between anger, PTSD symptoms and alcohol consumption in veterans is being analyzed in only several studies (31). No statistically significant difference is found in socio-demographic variables, number of traumatic events, stress level, and severity of PTSD symptoms between veterans with PTSD who use alcohol and those who do not use alcohol. But a significant correlation of hyperarousal symptoms and state anger, angry temperament, anger expression and anger-out expression was found. As a symptom of PTSD, hyperarousal appears as a predictor of anger and alcoholism. It is found by Taft et al. (32) that hyperarousal symptoms were directly associated with aggression and indirectly with alcohol related-problems. Also, Savarese et al. (33) report that there is a complex interaction between hyperarousal and alcohol consumption in predicting violence. Some explanations for the connection of hyperarousal symptoms and aggressions may relate to changes in the activity of areas of the brain such as nucleus accumbens in the dominant hemisphere (34).

Based on the results obtained in this study, it can be concluded that there is a significant relationship between anger, alcohol consumption and PTSD symptoms where the cluster of hyperarousal symptoms is significantly correlated with anger dimensions and use of alcohol. It can also be concluded that exposure to a larger number of combat-related traumatic events is directly connected with alcohol usage and anger dimensions.

There were several methodological limitations in this study. Firstly, the factor related to duration and methods of treatment was not included. The study is carried out in the group of veterans who underwent in-patients treatment only with psychotropic drugs, while investigation took place one to two years after the hospitalization. Secondly, this study did not include other psychological factors such as depression and anxiety where the emotion of anger is present; and the occurrence of aggressive behavior in war veterans with PTSD who have a high index of anger and who use alcohol is not analyzed. This study indicates the need for exploring the anger related to the above mentioned factors. Also, the results of this study show that in the treatment of war veterans with PTSD it is necessary to explore the emotions of anger as important factor to managing therapeutic interventions.

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PROFESSIONAL PAPER

Concurrent Chemoradiation for Cervical Cancer: Results of Five Randomized Trials

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Background: Cervical cancer is the second most common cancer among women's in Bosnia and Herzegovina. Most of these women's in the time of diagnosis are with advanced disease. In the 1999 NCI issued a clinical alert, recommending that chemo radiation should be implemented as new treatment for these patients. Aim: To determine a survival, loco regional control and toxicity in patients with cervical carcinoma treated in Institute o Oncology from 2000-2006. Patients and methods: This is retrospective study. Data of five hundred and fourteen patients diagnosed as cervical cancer FIGO stage Ib, -IVb and presented in our institute, were analyzed. We treated 345 with combined chemo radiotherapy, 162 with radiotherapy alone and 7 patients with symptomatic therapy. In the follow up 134 patients were lost, so 373 patients were analyzed for survival, loco regional control and toxicity. Subgroup of 148 patients with advanced disease and grade of tumor unknown and 136 patients with known grade of tumor were compared for time to local progression, time to distant metastasis and time to death. Results: Median age in this group of patients was 52 (27-85). Of 514 patients 492 were treated with curative intentions and 15 got palliative treatment. All treated patients finished their planed therapy. Follow up was from 6-78 months, median 28 months. From 373 patients who were analyzed 65 died, progressions were observed in 77 patients. Acute toxicity G3/G4 experienced 109 patients, and late toxicity G3/G4 8 patients. Patients with advanced disease and unknown grade of tumor cells had significantly shorter time to local progression, distant metastasis and death. Conclusion: The combined therapy for cervical cancer is the safe and good tolerated treatment. In the group of patients with advanced disease we observed 81% overall survival, 55.9% disease free survival for median follow up of 28 months. . In the group of patients with early disease we observed 90% overall survival, and 78.8% disease free survival for median follow up of 28 months. There were no deaths caused by treatment. Key words: cervical cancer, chemotherapy, radiotherapy

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1. INTRODUCTION

In the United States alone, 11150 women this year will be diagnosed with invasive cervical cancer. That is roughly 30 females a day, every day, for a year, in America alone. About 3,870 women will die from cervical cancer in the United States during 2008. In the UK, over 2,700 women are diagnosed with cervical cancer, and cause around 950 deaths each year in the UK. In the whole Europe around 50000 women will be diagnosed with cervical cancer, 25000 will die, and more important 175000 living with cervical cancer in some stage of disease. [1]

Cervical cancer was once one of the most common causes of cancer death for American women. The cervical cancer death rate declined by 74% between 1955 and 1992. The main reason for this change is the increased use of the Pap test. This screening procedure can find changes in the cervix before cancer develops. It can also find early cervical cancer in its most curable stage. The death rate from cervical cancer continues to decline by nearly 4% a year.

The burden of cervical cancer is particularly high across the whole of Eastern Europe. The systematic screening for cervical cancer is not jet established in the most of Eastern Europe countries. The dramatic contrast between West and East European states merits particular attention from the health authorities of the countries concerned and the EU as a whole. [2]

The prognosis for patients with cervical cancer is markedly affected by the extent of disease at the time of diagnosis. The current death rate is far higher than it should be and reflects that, even today, Pap smears are not done on approximately 33% of eligible women. Among the major factors that influence prognosis are stage, volume and grade of tumor, histological type, lymphatic spread, and vascular invasion. The 5-year relative survival rate for the earliest stage of invasive cervical cancer is 92%. The overall (all stages com-

bined) 5-year survival rate for cervical cancer is about 72%. [3]

Cervical cancer is still very high in incidence among women's in Bosnia and Herzegovina. Around 65% of patients in the time of diagnosis are with advanced disease. All of them who reach doctor are treated in Institute of Oncology in Sarajevo as the only institution with radiotherapy department in the whole country. [4]

Improvement of survival in patients with advanced cervical cancer was evident from year 2000. New standard therapy including concomitant chemotherapy and radiotherapy proposed by NCI in 1999 was main factor for this development. [5]

2. PATIENTS AND METHODS

This is retrospective study. We analyzed records of all patients treated in Institute of oncology in Sarajevo from the year 2000 to 2006, diagnosed as invasive cervical cancer. There were 514 patients with histological diagnosis of cervical cancer.

Early disease- FIGO stage Ib and IIa had 114 patients and 400 were with advanced stage of disease.

Surgery with adjuvant radiotherapy had 110 patients, 345 were treated with combined chemotherapy and radiotherapy concomitantly, 52 with radiotherapy alone and 7 with symptomatic therapy.

Radiation therapy

Radiation therapy was delivered with high-energy linear accelerator (Philips) from 2000 to 2005 and (Siemens Primus plus) after, using 18 MV photons at 2Gy/d, 5days/wk with no planned breaks. All patients were treated with using two–dimensional treatment planning (render plan). Brachitherapy was delivered with Selctron-Nucletron LDR, and NTP planning or Gama Med plus-Varian HDR and ABACUS planning. We used four field box techniques with AP+PA fields and two lateral fields, no central shielding, to TD 45-50Gy. Brachytherapy was given on Selectron LDR after completing of external radiotherapy with two fractions of 15 Gy one week break, or on Gama Med plus HDR weekly one fraction of 5 Gy to TD of 25 to 30 Gy, during and after external radiotherapy.

Age	20-29	30-39	40-49	50-59	60-69	70-79	80-89
Patients	2	61	170	152	85	40	4
Percent	0.3	11.8	33	29.5	16.5	7.7	0.7

Table 1. Patients due to age.

Stage-FIGO	Ib	IIa	IIb	IIIa	IIIb	IVa	IVb
Patients	109	5	264	1	124	8	3
Percent %	21.2	0.9	51.3	0.1	24.1	1.5	0.5

Table 2. Stage of disease.

PHD	Squamous cell	Adenocarcinoma	Adenosquamous cell	Other
Patients	461	37	9	7
Percent %	89.6	7.2	1.7	1.3

Table 3. Histology of patients

Grade	G1	G2	G3	Gx
Patients	44	144	90	236
Percent %	8.5	28	17.5	45.9

Table 4. Distribution of patients due to grade of tumor

Chemotherapy

Chemotherapy was delivered as monochemotherapy weekly, during radio therapy, for five or six cycles, or polyhchemotherapy platinum based. Every week prior to cycle of chemotherapy we check standard laboratory tests.

Majority of patients got cis-diamminedichloroplatinum 40 mg/m^2, and small group got cis-diamminedichloroplatinum, gemcitabine, or 5 fluorouracil or taxanes.

From the year 2000 to 2006 we accepted 514 patients with diagnosis of cervical cancer. The most of patients were between 40 to 60 years, median 52. The most of patients were with advanced disease. The most of patients had squamous cell carcinoma.

The most of patients had G2 grade of tumor cells, but almost 50% of patients had no G of tumor cells. The most of patients had some kind of combined treatment (88.5%). The most of patients were treated with curative intentions.

The most of patients got standard monochemotherapy concomitantly with radiotherapy.

3. RESULTS

Follow up was from 6 to 78 months, median 28 months. In the first 2 years patients were looked at every 4 months, to fifth year every 6 months and to 10 years once a year. We check standard laboratory analysis, gynecological exam and CT scan every year. We lost 134 patients in follow up mostly due to geographic distance and due to health care autonomy in different regions of Bosnia and Herzegovina. From 514 patients 7 refused specific oncology therapy, so we analyzed 373 patients.

Most of patients had good response to treatment. Subgroup of patients with known G of tumor cells had better time of response in all categories.

Local progression (l.p.) had 19, distant (d.p.) 31 and both (l.p.+d.p.) 27 patients. Death occurred in 63 patients, 61

Treatment	Surgery and radiotherapy	Combined chemo-radiotherapy	Radiotherapy alone	Symptomatic therapy
Patients	110	345	52	7
Percent %	21.4	67.1	10.1	1.3

Table 5. Distribution of patients due to treatment

Radiotherapy	Curative	Palliative
Patients	492	15
Percent %	95.7	4.3

Table 6 Distribution of patients due to radiotherapy course

Response	Complete response	Stabile disease	Progression
Number	234	62	77
Percent %	62.8	16.6	20.6

Table 7 Distribution of patients due to response

Year	I	II	III	IV	V	VI
Number	25	20	7	6	3	2
Percent %	39.6	31.7	11.1	9.5	4.7	3.1

Table 9. Distribution of deaths thru years

Metastasis	Pulmo	Liver	Bones	Other
Number	14	13	21	16

Table 10. Distribution of distant metastasis

Metastases in two organs were found in 4 patients and 1 patient with metastasis in 3 organs.

Metastases were treated with radiotherapy in 26 patients and chemotherapy in 32 patients. In 6 patients we performed just symptomatic therapy due to poor ECOG status.

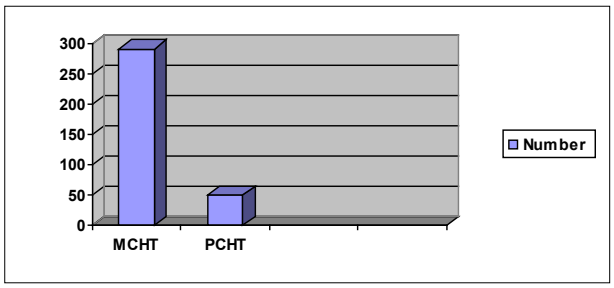
Toxicity

Acute toxicity mostly neutropenia G3/G4 experienced 109 patients, and they had pause in treatment for one to two weeks.

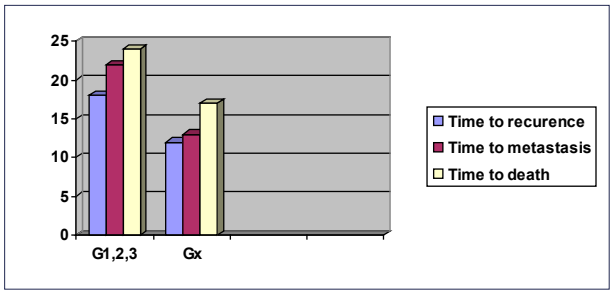
Late toxicity experienced 14 patients (2.6%)

Necrosis of small bowls had 3 patients, recto–vaginal or urethra–vaginal fistulas in 4 patients and palliative surgeries were performed for all of them.

Seven patients had edema in both legs, and symptomatic therapy was performed.



Graficon 1. Distribution of patients due to scheme of chemotherapy



Graficon 2. Comparison of response of patients due to grade of tumor cells (G)

4. DISCUSSION

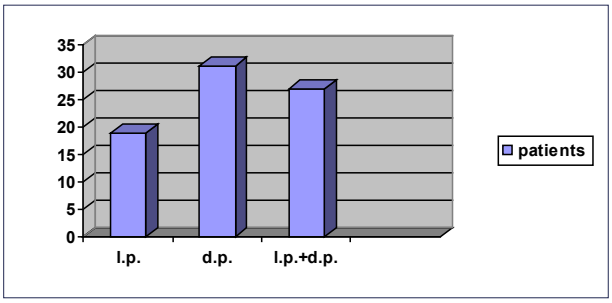
To evaluate results of our Institute and to compare with results of similar studies in literature is very important for us. In this way we can check our standard treatments and its efficacy.

With number of total population nia and Herzegovina (500) shows that we had fewer patients then can be expected. In this study we treated about 20 % of patients annually from the number we can expect.

This can be connected with poor organization of the oncology in the country, poverty of population, no organized screening for cervical cancer and still present shame of disease.

Peak of disease is between 40 to 60 years of age which is consistent with other countries in the world. Distribution of stage and histology of our patients are the same as in the other countries.

Presented data of grade of tumors cells shows us that around 50% of patient's grade was not known in the time of decision of treatment. There are medical centers in the country where pathology is poor and not adequate to fulfill all requirements of modern oncology practice. This is one of important points witch have to be discussed among executives in the planning of health care. Pathological diagnosis is one of the main prognostic factors in gynecological oncology and has to be further improved.



Graficon 3. Distribution of patients due to progression type

The most of our patients were treated with combined concomitant chemo radiation treatments, and with curative intentions, according to standard in the world.

Results of this study are consistent with reported results of other institutions. Survival with no signs of disease was 62.7% for follow up of 28 months. [6, 7, 8]

Acute and late toxicity were as expected, and as reported in the most of literature. [9, 10, 11]

The most of deaths occurred in the first two years after the treatment, and none of it was caused by therapy.

5. CONCLUSIONS

- In our Institute we treated 514 patients with invasive cervical cancer thru years 2000- 2006.
- Median age of patients was 52 years.
- In 45, 9 % patient's histological grade of tumors cells was not known.
- Optimal standard therapy received 88, 5 % patients.
- Median follow up was 28 months.
- Survival with no signs of disease was comparable with other similar studies in literature for this period of time.
- Time to recurrence, time to metastasis and time to death was better in the group of patients with known grade of tumor cells.
- Late toxicity G3/4 was observed in 2.6% of patients, for this follow up time.
- No deaths occurred due to therapy.

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