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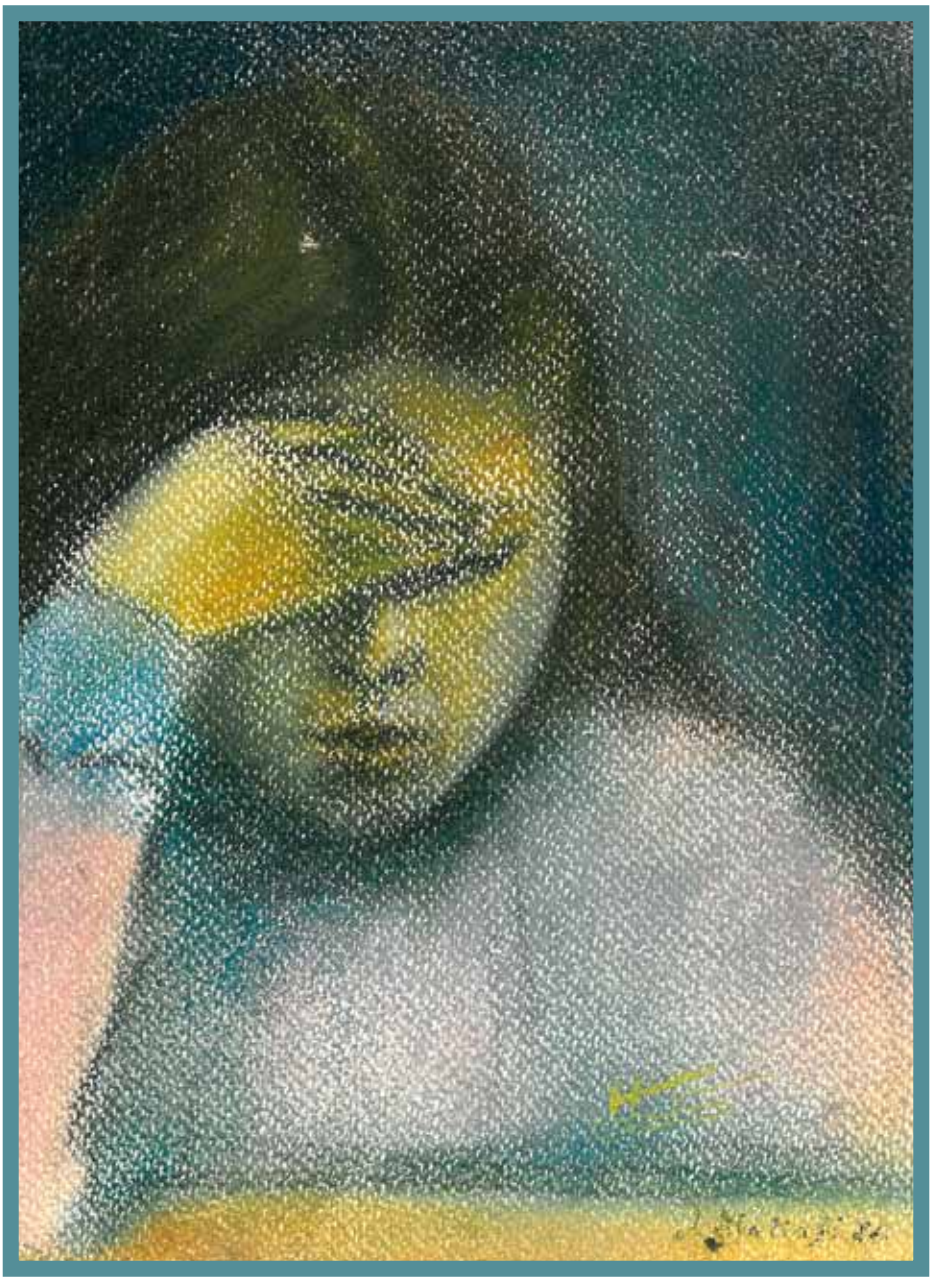

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contents

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ORIGINAL PAPER

Acute Graft Versus Host Disease in Hematopoietic Stem Cell Alotransplant Recipients

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Department of Pharmacology; Medical faculty University "St Ciril and Methodius Skopje, Republic of Macedonia2

Introduction: The transplantation of hematopoietic stem cells (HSCT) is a therapeutic intervention where the hematopoietic stem cells and the cells originating from them are being removed and replaced by the normal stem cells of donor or the patient him/her-self. HSCT today representstandardized biological manipulation for treating malignant, genetic and autoimmune diseases.The application of allogeneic hematopoietic stem cell transplantation (HSCT) is limited by life-threatening complications such as severe or acute graft-versus-host disease (GVHD). Despite intensive prophylaxis with immunosuppressive agents, the incidence of GVHD occurs in 9-50% of patients undergoing transplant with an identical HLA sibling matched donor and 75% of patients undergoing unrelated HLA donors. Aim of study: To evaluate our experiences in GVHD prophylaxis and treatment after alloHSCT, GVHD incidence and prognostic factors and administration of new immunosuppressive regiments. Can we recognize clinical parameters which are associated with occurrence and severity of graft-versus-host disease? Patients and methods: Starting from September 2000 till September 2010, 63 patients (36 males and 27 females) at the age of 16-56 (median range 33 years) with hematological malignancies were treated with alloHSCT on Department of Hematology, Clinical Centre, and Skopje. In 10 patients bone marrow was used as source of stem cells and in 53 patients stem cells were obtained from peripheral blood. From the group of 63 patients, 26 patients have active disease at the time of transplantation. GVHD prophylaxis was accomplished with combination of cyclosporine and metothrexate (Seattle regimen) or more intensive immunosupression regiments. Results: GVHD was noticed in 30 patients (47,6%) and at 33 patients (52,4%) was not noticed a manifestation of GVHD. Acute GVHD was noticed in 24 patients (38%) and chronic GVHD in 20 patients (31,7%) The remaining 32 patients (45%) achieved complete clinical and hematological remission. Lethal outcome was confirmed in 31(49%) patients (9 from chrGVHD,6 from acute GVHD, 16 from disease relapse). Conclusion: The incidence of acute GVHD in our study was 38% and 31% of chronic GVHD. The most common GVHD reaction was registered in female donors and male recipients, with higher GVHD incidence in elderly patients. In all patients stem cells were obtained from peripheral blood. Active disease, sex, source of hematopoietic cells, age and conditional regiments are the most significant predictive factors with the high influence of incidence of GVHD. Key words: acute graft versus host disease in hematopoietic stem cell alotransplant recipients

correspodence

1. INTRODUCTION

HSCT today represent standardized biological manipulation for treating malignant hematological disease, genetic and autoimmune diseases.Graft versus host disease(GVHD) is the most common complication after alloHSCT. With the conditioning the recipient is immunosupressed, the transplant contains the immune-competent cells and although there is HLA compatibility between the donor and the recipient, there is still tissue difference in the so-called cell antigen of the tissue tolerance (minor antigens). (6) There is information that there are other factors such as bacterial, virus infections, etc. which may cause GVHD to appear.The process of GVHD starts with the first phase when the donor T-cells are destroyed by the disease hidden in the genetic card of organism, the infections and partially the conditioning protocols and all results in activation of the recipient's cells making them secrete pro-inflammatory cytokines (tumor necrotic factor alpha-TNFa) and interleukin 1. (11) As a result of the MHC Ag expression (expressed in the form of proteins along the whole cell surface) and molecules adhesion is increased which leads to recognition of the recipient allo-antigens as alien. The interaction between the donor's T-cells and recipient's antigen presenting cells (APCs) increases. This leads to proliferation, differentiation and secretion of cytokines, (II2, INF-γ, NO). It is established that in the presence of perfect HLA ma GVHD match of a related donor, the chances of incompatibility of unknown sites are in the frameworks

of 40-50%. (21) (24) NK cells have the ability to cause GVHD reaction without the mediation of T-cells, chemotaksia of mononuclear phagocytes and damage of target organs, through recipient's target cell apoptosis. MNC or non-MNC minor Ag can be found in all cells and tissues and in the process of transplantation they are transferred between the donor and the recipient. In normal circumstances these antigens shall be recognized by the recipient's immune system and any alien tissue and cells shall be rejected. But if the recipient is has a defined immune system then the immune competent cells contained in the graft shall recognize the recipient's antigens as alien and shall indicate GVHD.(8, 3)The proactive aloreactivity occurring in HLA mismatch transplantation results in decreasing the patients' GVHD and increasing the GVL effect. This paradoxical effect "perfect mismatch" is observed by NK inhibitory receptors of donor's cells and KIR ligands (polymorphic cell surface molecules presented in "natural killer" cells with antigen marks CD56, CD16, CD3) of recipient's hemopoietic cells. In future the genotype of the patients and the panel of cytokines, chemokines and pharmacogens shall be sufficient without any classification of histological compatibility and may be predicted the risk of transplantation and the toxicity associated with it. (12) The main question of the future is if the GVL effect can be separated from the GVHD manipulating the transplanted immune system. The potential target of GVL effect is the normal recipient allogens or recognizing the tumor associated antigens. (13)

The acute GVHD is defined as a syndrome that appears in the first 100 days after the HSCT in related and unrelated transplantations. The transplantation practice shows that the acute GVHD may occur 100 days after HSCT, too. The time of acute GVHD occurrence may help us predict the disease outcome, that is the liver acute GVHD has bad prediction and high percentage of unrelapsed mortality. (22) (20) (11) The acute GVHD directly depens on the histological barrier, number of T lymphocytes, donor's and recipient's characteristics, prophylactic protocols, conditioning protocols (chemo/radiotherapy), patient's age, AB0 incompatibility, donor/recipient's sex mismatch, donor's/recipient's infective status, etc. (19)..The acute of form of GVHD clinic manifestations are presented by changes in skin, GIT and liver.The genetic predisposition and the other HLA antigen differences (genetic polymorphism of cytokines, pharmacogen polymorphism that infiltrates the metabolism of drugs used in conditioning protocols) can be associated with the GVHD occurrence. Clinic manifestations and grades of AGVHD standardized by Glücksberg in 1974 and by the IBMTR Consensus Conference. The acute GVHD is manifested clinically by maculo-papular rash which is not specific and looks like a drug allergic dermatitis. It appears on the soles, palms and after that on the skin of the face and/or generalized dermatitis. The dominant symptom of AGVHD in getting GIT is nausea and watery green diarrhoea. The liver taken from an acute form of GVHD is manifested like cholestatic hepatopathy. GVHD also involves the immune system delaying the immunologic recovery, which results in prolonged immunodeficiency. This is manifested by infections and the risk of further deterioration of immunosuppressive GVHD therapy. The capacity of the epithelial tissue to become a GVHD target organ depends on the degree of differentiation. This is the reason why the acute GVHD gets primarily the epithelial cells with low differentiation. Histological biopsy staging is not used for grading the acute GVHD. Today the grading score system including clinic skin manifestations, GIT, liver and performance status, has been accepted. (2) The surface molecules as (CD4 and CD8) of T-lymphocytes are very important for the evolution of acute GVHD. The genetic characteristics of host and donor define which line of T- lymphocytes shall proliferation.(13)(7) To discover the role of THFα is a scientific and experimental challenge. For this reason the use of antibodies *anti THFα* shall be subject to experimental and clinical experiences. (1) Using bone marrow from an allo-sensible female donor in male recipient shall increase twice or trice the risk of acute GVHD occurrence (1). Using donor's viable lymphocytes for reinduction of remission in patients who had relapse of leukemia after hematopoietic stem cell transplantation is controversial because DLI leads to a higher risk of acute GVHD.(12)(15)(26). Treating the reaction of transplant against recipient;The corticosteroids have a proven role in the treatment of AGVHD with their ability to lysis the lymphocites and their proven anti-inflammatory effect. When treating AGVHD metilprendizolon is applied in doses of 10mg/kg per day, five days, then ten days in doses of 2 mg/kg per day and after that then check the condition of the patient. . It no improvement is made the therapy shall continue applying higher doses of corticosteroids (methylprednisolone 20 mg/kg per day) or different salvage protocols are used such as: ATG, different monoclonal antibodies (OKT3, anti IL-2, CD25, anti TNF-α). (10) (9) The response of AGVHD treatment depends of many factors, such as:degree of AGVHD,beginning time and response to the initial treatment..

2. MATERIAL AND METHODS

Starting from September 2000 till September 2010, 63 patients (36 males and 27 females) at the age of 16-56 (median range 33 years) with hematological malignancies were treated with alloHSCT on Clinic of Hematology. In 10 patients bone marrow was used as source of stem cells and in 53 patients stem cells were obtained from peripheral blood. From the group of 63 patients, 26 patients have active disease at the time of transplantation.

The first 3 weeks after the allogeneic HSCT CsA shall be applied in doses of 3 mkg/kg i.v.-+ MTX and then orally depending on the cyclosporinemia in two day doses.The other preventive protocols for aGVHD shall be performed with application of mycophenolate mophetil 1,5-3 gr/kg per day +30 in combination with CsA in the standard doses and/or in combination of CsA with cor ticosteroids(methylprednisolone) 1mg/kg/day.The individualization in maintaining the cyclosporinemia in the referential laboratory values (200-400 ng/ml) shall be defined twice a week at the Department for Pre-clinic and Clinic Pharmacology with the methodology

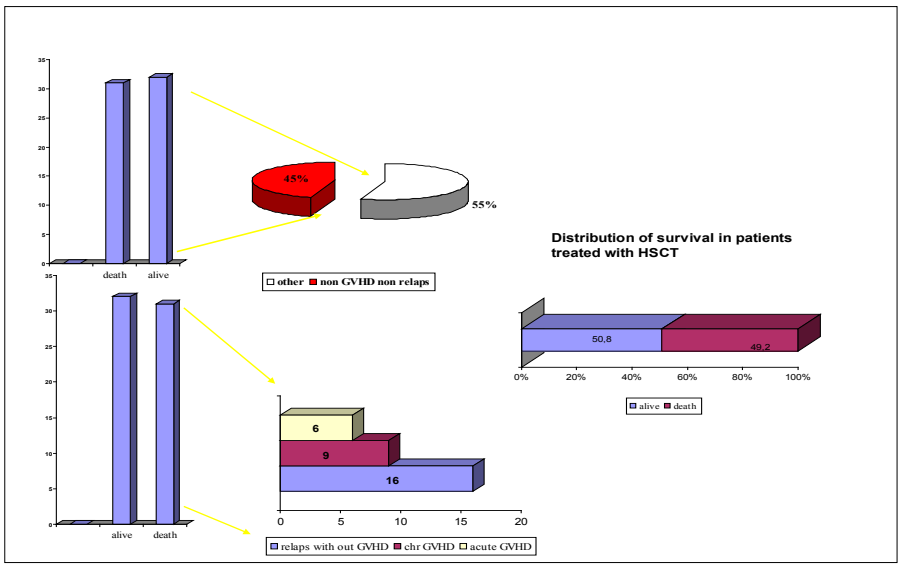


FIGURE 1.

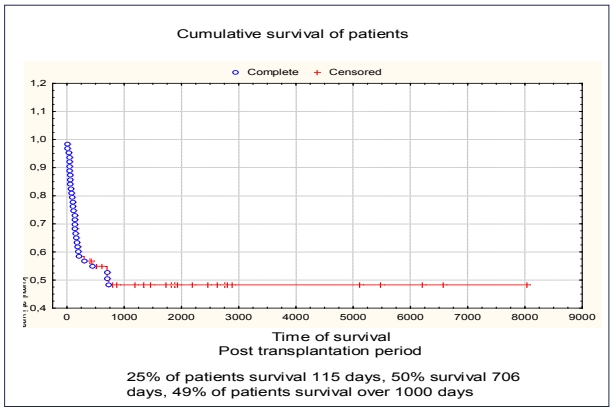
of fluorescent immunized immunoassay.The initial treatment with metilprednizolon 2 mg/kg/day in combination with SuA for three weeks and then reducing the doses of corticosteroids if there are any satisfying therapeutic response.The second treatment for patients who has not achieved regression of the symptomatology shall be applied intensifying the corticosteroids doses from 5 to 20 mg/kg .i.v. (maintaining the level of the doses from 20 to 20 ng/ml. The application of anti-thymocyte globulin and monoclonal antibody be a therapeutic option for both therapeutic lines of immune suppression. The failure in the therapy shall be defined with:progression in the clinic findings 3 days after starting the treatment,no changes in the clinic findings 7 days after starting the treatment,partial response 14 days after starting the treatment.

3. RESULTS

Results are given on figures and pictures.

4. DISCUSSION

A greater step has been made in the prevention and treatment of GVHD but still this problems remains on the list. Despite the progress in the GVHD prevention protocols there is still incidence of 10-80% in the world literature (23) depending on the many risk factors. (5) (14) (17) (18). Our study of patients presents 47,6% of GVHD occurrence (30 patients of the researched group developed GVHD) and confirms the statistic significance of the world experience. Knowing the mechanism of the reaction, the benefit of the GVL effect is desirable as a reaction and its occurrence is associated with lower incidence of relapse in the hematological diseases (13) (7). In the group we have researched, of all 63 patients 16 patients (or 25,3%) have developed relapse without GVHD occurrence. But still the mortality is 23,8% or 31 patients of the total number. 75% of the patients survive for 500 days – those who were only on corticosteroids, and 25% of the patients survive for the same period even not responding to the straight-line therapies and other immunosuppressors.These risk factors are considered to be important because the patients who have increased risk of developing GVHD, should have been treated with a more aggressive prophylactic therapy (4) (16). All achieved parameters have been included into the multi-variant analysis the in order to define or stratify with what size of risk the patient shall be treated in order to be cured, and to see if we can make a systematization of the these risk factors individually for each patient. This shall be a foundation for optimization of the therapeutic approach on one hand and on the other to show if all these risk factors shall confirm their specificity and sensitivity using comparison of more standard prognostic risk factors. The optimization of the therapeutic approach is of great significance for the patients with multiple positive risk factors, who need more aggressive GVHD prophylactics. The first risk factor of our group that correlates with the world risk factors result in developing GVHD is the age of a patient over 40. According to the crossed relation it is a statistically significant risk that increases the chance of GVHD registration almost twice. Also the age of the donor over 40 according to the crossed relation is a statistically significant risk that increases the chance of GVHD registration in the recipients for one and half times. The positive alo-immunization status of the do-



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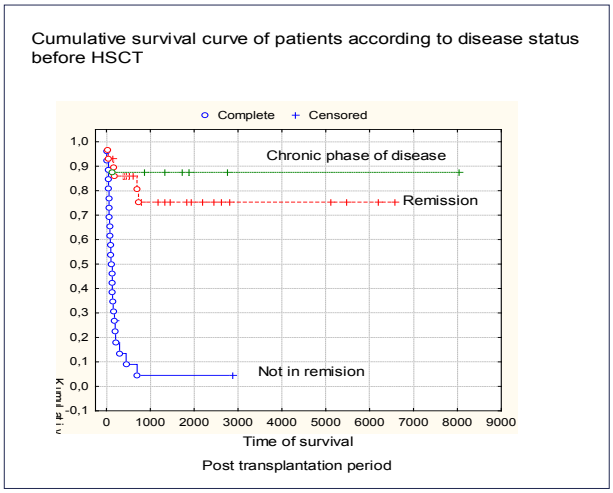
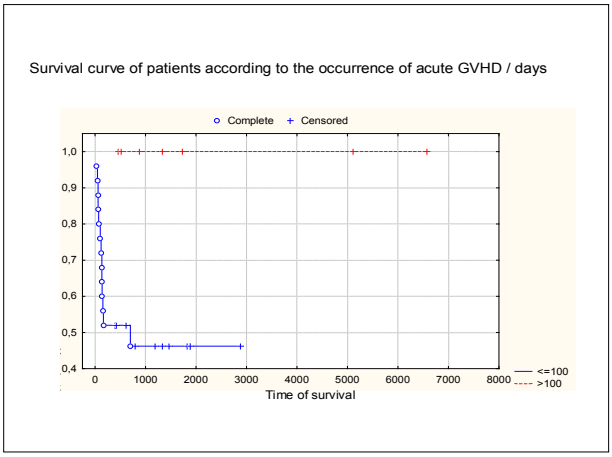


FIGURE 3.

nor showed that GVHD has been registered in 72,2% of the patients and negative alo-immunization status of the donor has been registered in 37,8%. The chance of GVHD occurrence in patients who received alogen graft of nodors with positive alo-immunization status is increased twice. Our experience according to the source of stem cells and GVHd occurrence is statistically insignificant because the group of patients who have received fresh bone marrow, is very small. According to the conditioning protocols depending on the application of myeloablative or non- myeloablative protocols our experience is also insignificant because this group is also very small to indicate statistical significance in GVHD occurrence. According to the GVHD type of prophylactics, the group of patients who have received preventive therapy by Seattle and other immunosuppressors , is too small, and for this reason there is only insignificant statistic dependence. The incidence of acute GVHD in the big random studies in the world indicates to the fact that the acute GVHD occurs in 20-80%.The data presented in our study indicate that the acute GVHD occurs in 38,,1% of the total group of patients treated with alogen transplantation. Our researched group the acute GVHD in grade I and II stage occurred in 11 patients or 45,8% and grade III and IV stage occurred in 13 patients or 54,2%. All our patients with grade III and IV had extensive form of the disease in all three target organs and ended lethal. Our group of patients who had developed grade I and II are young under 40 with one or two positive risk factors, they are alive and do not relapsed the basic disease. 60% of the group of our patients who had developed III and IV grade developed chronic form of GVHD and existed of the same reason.

5. CONCLUSION

The incidence of acute GVHD in our study was 38% and 31% of chronic GVHD. The cumulative survival of the patients with a GVHD: the difference in the survival compared to the presence or the absence of GVHD is being registered during a period between 900 to 1800 days (49% of the patients don't have a GVHD, 45% have a GVHD) in the period which follows the survival gets equal, whereas 25% of the examined survive for 115 days, 50% survive for 706 days, and 49% survive for more than 1000 days. The univariate analysis has shown that the statistical significance as a prognosis markers for GVHD are: the stadium of disease, the days of the occurance of aGVHD and hGVHD since the days of the transplantation, the form of manifestation with GVHD (gradus I, II, vs. transplantation, the form of the manifestation of aGVHD, as well as the respondents who responded to the firstline therapy of GVHD, as well as those patients who developed hGVHD "denovo" type, and whether they've responded to the firstline therapy of hGVHD. Those are important for identification of the patients, through which a basis for an individual assessment of each patient would be made during the each therapy approach. The curve of survival has shown that those patients which showed relapse of



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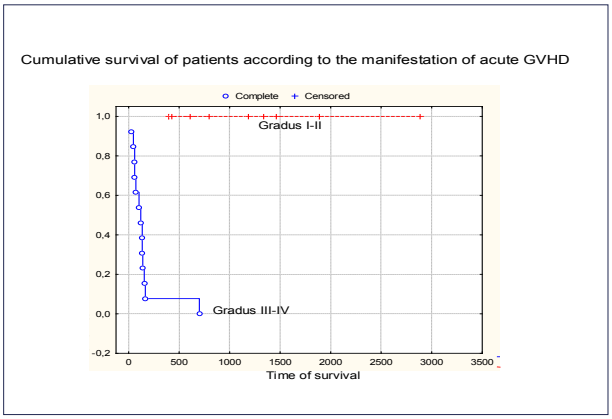

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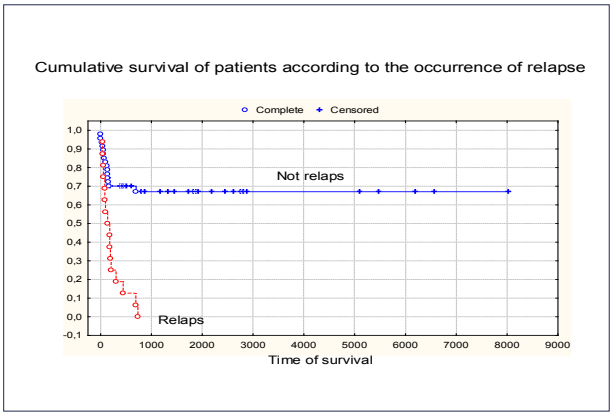

FIGURE 6.

FIGURE 7.

the basic disease and who are primarily resistant to the firstline immunosuppressive therapy and to the acute form of GVHD are candidates for a more aggressive immunomodulation and a usage of new types of cell and molecular therapy. However most of patients with GVHD who have active disease at the time of transplantation, and the question arises whether these patients can recognize and immunosuppressive and immunomodulation before and to develop clinical GVHD with uncontrolled fatal end. From our study this is a clinical benefit.

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ORIGINAL PAPER

Chronic Airflow Obstruction Syndrome Due to Pulmonary Tuberculosis Treated with Directly Observed Therapy–a Serious Changes in Lung Function

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The origin of CAO syndrome in active TB, despite significant similarities with chronic obstructive pulmonary disease (COPD), still remains unknown. The aim of the study was to examine the potential causes and risks for the development of CAO syndrome in new cases of pulmonary TB. Design: Prospective, nest case-control study. Patients: 40 patients with newly detected cavitary pulmonary TB and initial normal respiratory function, diagnosed and treated according to DOTS strategy. Measurements and results: The average values of Snider's radiological score during TB treatment were significantly reduced (p<0.001), as well as average values of non-specific systemic serum markers of inflammation. The average values of FEV_1(%), both before, during and at the end of completion of TB treatment were significantly decreased (p<0.05;). Linear regression analysis confirmed a statistically sigificant association between changes in the values of FEV_1(%), resulting in TB treatment completion, and the value of Snider's radiological score and the sputum culture conversion rate. From the initial findings of normal pulmonary ventilation tests, upon the completiton of TB treatment 35.0% of observed patients developed the CAO syndrome. Logistic regression analysis confirmed a positive familiar burden for COPD, Snider's radiological score at the beginning of TB treatment and sputum conversion rate on culture, as statistically significant predictors, while multivariate logistic regression analysis confirmed Snider's radiological score at the beginig of TB treatment and sputum conversion rate on culture as most significant risk factors for CAO syndrome occurrence and development. Conclusion: The CAO syndrome is often a consequence and significant functional impairment of the respiratory system, during the reparative processes in active TB, even in the absence of risk factors for COPD. Only microbiological cure of TB patients with underlying risks for disorders of lung function, is not sufficient and effective approach for prevention of their further potential health deterioration. Key words : tuberculosis, bronchial obstruction, risk factors, COPD.

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1. INTRODUCTION

The association of tuberculosis (TB) and airflow obstruction significantly more difficult and prolong the course of the specific process in the lungs, while extensive (cavitary) forms of pulmonary TB, with its long-term evolution in cases of chronic bronhogenic forms of the disease, contribute to severe destruction of lung parenchyma. On the other hand, inadequate treatment of bronchial obstruction in patients with active TB can, ultimately, lead to the chronic airway obstruction (CAO) syndrome, with clinical manifestation very similar to that in chronic obstructive pulmonary disease (COPD), but in spite of certain analogies in the etiopathogenesis, clinical, and functional manifestations of these two entities, they should not be equated, but should be differentiated on time (1,2,3).

Causes and development of airflow obstruction in patients with active TB, in addition to the factors of infection, involving other contributing factors to the host–the patient (genetic factors, systemic inflammation and initial volume of specific lesions in lungs), as well as from the environment (cigarette smoking, air pollution and socio-economic living conditions), while clinically manifested bronchial obstruction occurs as their mutual interplay (4,5,6). Recent studies, more clearly indicate the significant association in immunopathogenetic mechanisms in the remodelling of pulmonary extra cellular matrix via matrix-metalloproteinase system (MMPs), in the common pathogenesis of chronic airflow obstruction in the airways, as well in extensive pulmonary TB as in COPD (7,8). Identification of these risk factors is the key for better understanding the develop-

ment of bronchial obstruction in active pulmonary TB, as an important step in further implementation of existing strategies of TB control and treatment (1,5). In this way, the existing specificity and analogy in pathogenesis of CAO, with other bronchial obstruction clinical syndromes and diseases, especially COPD, will be more accurate and with a clear distinction to the initially, very often unrecognized, coexisting bronchial obstruction co morbidity in patients with active pulmonary TB (2,9).

Bearing in mind the global significance of TB and COPD burden, previous studies and theoretical considerations of the origin of airflow obstruction in active TB in individuals with or without coexisting COPD, despite significant similarities found in the etiopathogenesis mechanisms, clinical and functional manifestations, did not show the reliable solutions in adequate detection and differentiation the nature of this pulmonary ventilation disorder (1,2,10).

2. AIM OF THE STUDY

The aim of the study was to examine the potential causes and risks for the development of chronic airflow obstruction (CAO) syndrome in new cases of extensive (cavitary) pulmonary TB with initial normal respiratory function, treated with directly observed therapy in the standard six-months regimen, according to the hereditary burden of COPD, air pollution in living and working environment, cigarette smoking habits and level of nicotine dependence, radiological extent of specific lesions in lungs, sputum conversion rate and non-specific systemic pro-inflammatory indices.

3. MATERIAL AND METHODS

3.1. Patients

The research was performed as a prospective, nest case-control study, in the Clinic for lung diseases, Clinical Centre of Nis, on the planned 40 patients with newly detected cavitary pulmonary TB and initial normal respiratory function, diagnosed and treated according to DOTS strategy and National TB Programme of the Republic of Serbia, in the period from January 2005. until the June 2010.y. Inclusion criteria for the selection of patients in the research were : 1) typical symptoms of pulmonary TB (cough, sputum production, fever, night sweats and weight loss); 2) negative personal history of TB and/or TB treatment; 3) typical fibrocavitary pulmonary infiltrates on standard chest radiographs; 4) at least one smear positive sputum, with the subsequent positive culture on M.tuberculosis; and 5) all research subjects, at the time of the inclusion in the study, could already been on the antituberculosis treatment, but not more than two weeks. The exclusion criteria for the patients from the study were : 1) detection of mono-, or multi-resistant TB bacilli in the first positive sputum culture; 2) coexisting lung disease, defined as posttuberculosis residual fibrosis, and/or clinical, laboratory, radiology and/or hystopathological confirmation of lung pathology other than TB; 3) patients with chronic heart and kidney failure and/or those with chronic metabolic disorders, including liver cirrhosis and diabetes. Risk factors for COPD data, in terms of: familial burden, potential exposure to air pollution in living and working environment for more than 15 years and smoking habits were determined by taking medical history data, and smoking habits are indexed as pack/year, while the nicotine dependence was determined by initially filling the specific questtionairre of Fagerstörm's test for nicotine dependence (11).

3.2. Determining the degree of radiological extent of pulmonary TB lesions

All tested patients was made standard chest radiographs in posterior-anterior projection at the beginning of TB treatment and at the end of the same, after the six months. Interpretation of radiological changes was performed without access to the values of parameters of lung function, and degree of radiological extent of disease were scored according to Snider score system, where each lung was divided into thirds and each of them scored on four level scale from 0 to 3 points, with maximal radiographic score of 18 (12).

3.3. Bacteriological sputum analysis

All sputum samples were taken periodically, in a series of three consecutive morning samples and analyzed by direct smear microscopy (Ziehl-Neelsen stained) and plating the same samples to Lowenstain-Jensen culture (reading of the results after the 60 days of cultivation), as well as the culture resistance test on standard first-line antituberculotics (13).

3.4. Non-specific systemic pro-inflammatory indices measurments

There were determined : erythrocyte sedimentation rate (SE) in the first hour (mm/1h), peripheral blood smear, which was obtained white blood cell count (WBC) expressed in 10^9 / l, serum levels of C reactive protein (CRP) (mg/l) and fibrinogen (g/l). The above parameters of hematological and biochemical analysis were determined at the hospitalization of patients and after the 6 months, upon the completion of TB treatment.

3.5. Lung function measurment

Lung function testing was carried out in the morning by spirometry test, determined the standard spirometric parameters, as follows: 1) forced vital capacity–FVC; 2) forced expiratory volume in first second–FEV_1 and their percentage ratio–FEV_1/FVCx100%. For a final value of each of the examined lung function parameters, there were taken the best score of the respondents from three consecutive measurements. All of the patients, before entering the study were performed a pharmacodynamic bronchodilation test of reversibility, by inhalation of 400 μg salbutamol metered dose inhalation spray. Re-measurement of FEV_1 was performed 30 minutes after the inhalation and positive test was consider as a increasing the FEV_1 for 200 ml or 12% and more from the baseline level. Criteria for bronchial obstruction were: FEV_1/FVCx100%≤70% and level of post-bronhodilation FEV_1≤80% of the reference values (14,15). Pulmonary function test were performed on three occasions: 1) at the begining of the initial phase of TB treatment, 2) at the end of the initial phase of the same (after the 2 months) and 3) at the end of the continuation phase of TB treatment (after the 6 months).

3.6. Statistical analysis

Statistical analysis was performed on the PC. For entering, ranking, clus-

tering, tabular and graphical display of data was used Excel program from Microsoft Office 2003 software package. All calculations were performed using SPSS program (16).

Comparison of mean values of numerical characteristics between the three measurments of lung function, was done by Single Factor analysis of variance (One way ANOVA), forwarded with Tukey post hoc test. The values of characteristics at the beginning and end of treatment of observed patinets were compared by Wilcoxon's Signed Rank test (17). Analysis of the relationship between changes in FEV_1(%) values during the treatment of TB was performed by univariate linear regression analysis (calculated the linear regression coefficient (ß) and its 95% confidence interval). The statistical significance of the regression coefficient is checked by t-test (18). To assess the impact of factors of interest in the development of CAO syndrome there were applied the logistic regression analysis. Approximate values were calculated relative risk (odds ratio-OR) and their 95% confidence interval. Assessing the value of statistical significance was performed by calculating the OR Wald values. Factors for which the univariate logistic regression showed that significantly influence the occurrence of CAO syndrome, were included in multivariate regression models. By applying the method step by step backwards (Backward: Wald), from the multivariate model are excluded those factors whose impact was not statistically significant (17,18). As the threshold of statistical significance level was used to estimate errors of less than 5% ($p < 0.05$).

4. RESULTS

The average age of observed patients was 47.1±15.50 y, of which 62.5% were men and 37.5% women. In the social structure, there were dominated employees (35.0%) and students (15.0%), while the minimum were registered among displaced persons and farmers (5.0%). From the city population belonged 60.0% of patients and the ratio of urban and rural population did not show statistically significant differences. According to medical history, patients were initially cited, as most frequently respiratory symptoms: cough (97.5%), expectoration (87.5%) and dyspnea (67.5%), and from general symptoms fever (27.5%) and night sweats (67.5%). The average duration of symptoms, till the the first appearance of a doctor were 66.40 ± 63.88 days.

Familiar burden for COPD or asthma was registered in 22.5% of patients and continuous exposure to air pollution of more than 15 years, was registered in only 15.0% of patients in their surrounding outdoor living environment, whith regard to 20.0% of them in an indoor living space, while in 22.5% patients were registered occupational exposure to different allergens and respiratory irritants in the workplace. Initially, positive physical examination on bronchial obstruction was registered in 35.0% of patients, while the initial bacterial infection of upper respiratory tract were in 22.5%. The majority of patients were current smokers (52.5%), with average pack/year index of 1.24 ± 0.43/25.64 ± 9.25, while 2.5% of them belonged to a group of ex-smokers, with an average time of quitting of 0.91 ± 3.01 years. Only 45.0% of obsereved patients were non-smokers. There were registered a high level of nicotine dependence in average of 6.73 ± 1.93 Fargestörm score points, while 86.4% of the patients had high and very high level of Fargestörm nicotine dependence. Generally, 37.5% patients had no any risk factor for COPD.

Average Snider's radiological score during TB treatment were significantly reduced from 8.02±3.06 score points at the begining, to 3.13±1.38 at the end of the same, which is significantly lower value ($Z=5.53$, $p<0.001$;), with average score reduction of 4.90 ± 2.12 score points (Figure 1).

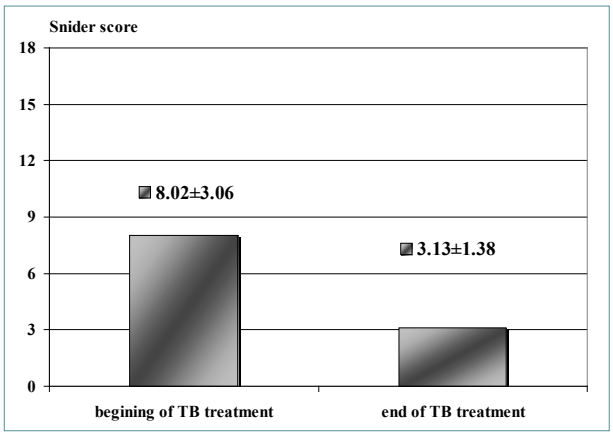

FIGURE 1. Comparing the values of Snider's radiological score and the difference between them. (Note: *–Wilcoxon Signed Ranks test;) Radovic M. Chronic airflow obstruction syndrome due to pulmonary tuberculosis treated with directly observed therapy–a serious changes in lung function.

The average sputum conversion smear rate (microscopy) was 2.72±2.12 weeks, while on culture it was 3.6±1.97 weeks. Average values of non-specific systemic serum markers of inflammation were statistically significantly reduced during the TB treatment (Table 1).

Serum markers of inflammation	Begining of TB treatment	End of TB treatment	Comparison of values at the begining and end of the TB treatment*	The difference between value at the begining and end of the TB treatment
SE (mm/1h)	58.53±29.60	10.85±9.25	Z=5.39 i p<0.001	47.67±27.88
WBC (109l)	9.14±2.95	6.61±1.07	Z=4.64 i p<0.001	2.52±2.79
CRP (mg/l)	51.90±42.07	4.37±3.72	Z=5.50 i p<0.001	47,52±40,44
Fibrinogen (g/l)	6.80±3.11	2.96±1.02	Z=5.26 i p<0.001	3.84±2.92

TABLE 1. Comparing the values of non-specific systemic markers of inflammation. (Note: *–Wilcoxon Signed Ranks test;) Radovic M. Chronic airflow obstruction syndrome due to pulmonary tuberculosis treated with directly observed therapy–a serious changes in lung function.

Positive bronchodilation test was verified in 15.0% of patients, but the average values of FVC, both before and during, as well as at the end of the TB treatment, were statistically significantly increase (I vs. III measurement : $p<0.001$;), as opposed to the values of FEV_1, which have statistically significantly decreased after the completion of the same (I vs. III measurement : $p<0.05$;) (Table 2).

Linear regression analysis confirmed a statistically sigificant association between changes in the values of FEV_1(%), resulting in TB treatment completion, and the value of Snider's radiological score and the sputum culture

Lung function parameter	I measurement	II measurement	III measurement	Comparison of values between tests *
FVC (%)	97.10±11.12	99.52±10.75	101.12±11.66	I vs II: p<0.01 II vs III: p<0.05 I vs III: p<0.001
FEV_1(%)	92.90±11.00	92.50±13.9	88.53±15.83	II vs III: p<0.05 I vs III: p<0.05
FEV_1/FVCx100%	78.02±6.31	76.04±6.99	73.22±8.68	I vs II: p<0.05 II vs III: p<0.05 I vs III: p<0.01

Table 2. Comparing the values of lung function parameters between the three measurements made. (Note: *–ANOVA i Tukey post hoc test;) Radovic M. Chronic airflow obstruction syndrome due to pulmonary tuberculosis treated with directly observed therapy–a serious changes in lung function.

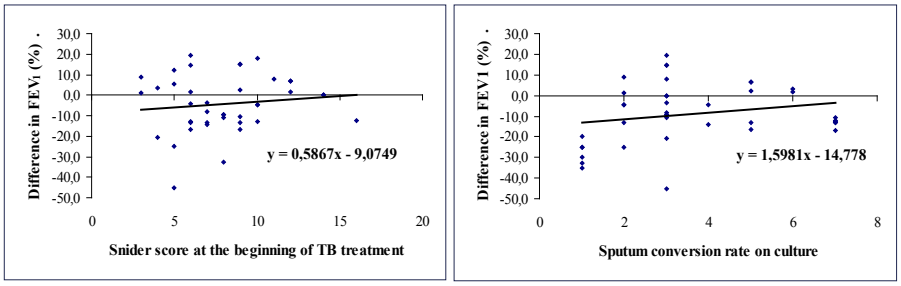

Figure 2. The association between Snider's radiological score at the beginning of TB treatment and sputum conversion rate on culture with changes in the value of FEV1 (%) occurred during TB treatment. Radovic M. Chronic airflow obstruction syndrome due to pulmonary tuberculosis treated with directly observed therapy–a serious changes in lung function.

conversion rate. Any increase in Snider's radiological score at the begining of TB treatment and a slower sputum culture conversion rate during the same, for just one measurement unit, is associated with statistically significantly higher decrease in the FEV_1(%) after the treatment completion, as follows: Snider's radiological score of 0.587% (0.138-1.036%, p <0.01;), a sputum conversion rate on culture for 1.598% (0.204-2.992%, p <0.05;) (Figure 2).

From the initial findings of normal pulmonary ventilation tests, upon the completiton of TB treatment 35.0% of observed patients developed the CAO syndrome. Logistic regression analysis was observed in the group of potential risk factors for COPD, factors of TB activity and factors of systemic inflammation, as well as statistically significant predictors for the occurrence and development of CAO syndrome in observed patients, after the completion of TB treatment, confirmed a positive familiar burden for COPD, Snider's radiological score at the beginning of TB treatment and sputum conversion rate on culture. In patients who have had a positive familiar burden for COPD, the risk for the onset and development of CAO syndrome after finishing the treatment of TB was significantly higher 5.75 times (1.16 times to 28.55, p <0.05;), while any increase in value of Snider's radiological score at the beginning of TB treatment to 7% (2-21%, p <0.04;) and the sputum culture conversion rate of 21% (6-69%, p <0.05;), was also statistically significantly increased the risk for developing the CAO syndrome in these patients (Figure 3).

Multivariate logistic regression analysis, as statistically the most significant predictors for the development of CAO syndrome in the observed patients allocated Snider's radiological score at the beginig of TB treatment and sputum conversion rate on culture, so that each of these factors increase the value for the one measrement unit, therefore is significantly increased risk for developing CAO syndrome : Snider's radiological score at the beginning of the TB treatment for 6% (1-16%, p <0.05;), and sputum conversion rate on culture for 18% (30-50%, p <0.05 ;) (Figure 4.).

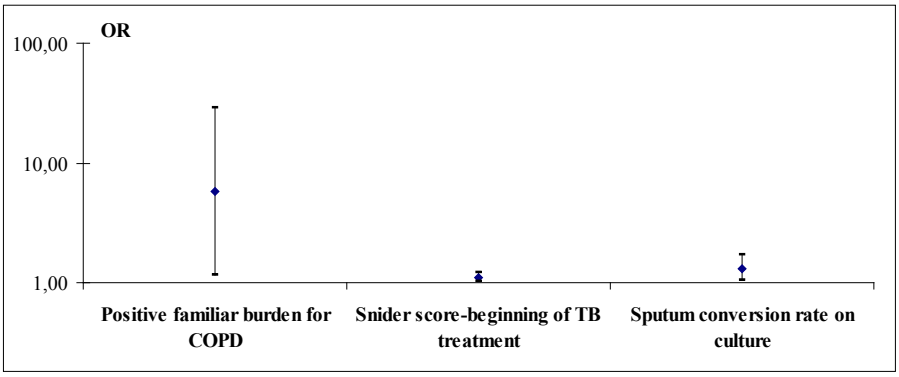

Figure 3. Predictors for the occurrence and development of CAO syndrome. Radovic M. Chronic airflow obstruction syndrome due to pulmonary tuberculosis treated with directly observed therapy–a serious changes in lung function.

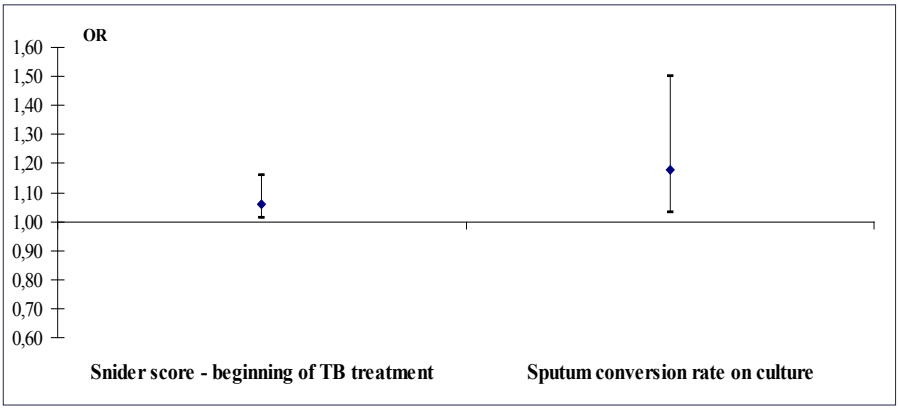

Figure 4. OR values and their 95% CI to assess the impact of Snider's radiological score at the beginning of TB treatment and sputum conversion rate on culture as a major risk factors for the development of CAO syndrome. Radovic M. Chronic airflow obstruction syndrome due to pulmonary tuberculosis treated with directly observed therapy–a serious changes in lung function.

5. DISCUSSION

A number of studies have shown that treatment of pulmonary TB only with antituberculosis drugs may at a certain number of patients (12% -60%) lead to the emergence or worsening of existing bronchial obstruction (3,19). Some prospective studies with longer follow-up period, demonstrated in high percentage, a significant number of cases affected and/or treated for pulmonary TB, which had the same result in permanent airway obstruction or restrictive respiratory syndrome (20,21). In patients with active forms of TB, bronchial obstruction occurs in 52.7% infiltrative, 56.6% fibrous and cavitary, and even 88.2% miliary forms. The severity of bronchial obstruction increases with numbers of smoked cigarettes, initial radiological extent of pulmonary TB lesions, as well as clinical course and duration of active non-recognized and non-treated disease (1,3). Although the extensive destruction of lung parenchyma in TB, with consequent restriction of airflow through the bronchial tree is clinically relatively common, the severity of bronchial obstruction and bronchodilator response, have not been evaluated objectively till these days (12,19). These patients in everyday clinical practice, most all of their symptoms and limitations, including bronchial obstruction, consider as a consequence of active or cured pulmonary TB and in most cases ignored the emergence of severe clinical manifestations and complications. In order to reduce the incidence of irreversible lung function disorders, today along with antituberclosis drugs, there were used bronchodilator medications in order to compensate the genesis and development of acute or chronic airflow obstruction syndrome in patients with pulmonary TB, with no existing systematic and doctrinal approaches yet, such as in other respiratory diseases (asthma, COPD and bronchiectasis) (2,15,22).

Cigarette smoking is the only external agent which is cause-related with the development of chronic airflow obstruction in the airways in COPD. Symptoms of chronic cough and bronchial hypersecretion, were more common in smokers than nonsmokers, as well as severe forms of lung function disorders, especially in patients over 40 years (19,23). Reviewing the smoking habits of patients in our study, current smokers accounted for more than one half (52.5%), while former smokers were 2.5% and the number of non-smokers has moved to more than one third of patients (45.0%), which is corresponding to the data in studies of Kollapan and Gopi (23). The average pack/years index in current smokers was 1.24/25.64, with a high level of nicotine dependance,of 6.73 Fagerstörm's score points, which corresponds to the results in large population smokers study of Janson et al. across the European Union among the population in areas with high TB incidence (24). On the other hand, several surveys conducted in the UK, have shown a higher prevalence of cough and sputum production in populations of people living in areas with significant air pollution. Den Boon in his population study, confirmed the increasing of COPD morbidity and mortality, as well as, a variety of respiratory tract infections, including TB (25). In our investigation, continuous exposure to air pollution in period for more than 15 years, was registered in only 15.0% of patients in their surrounding outdoor living environment, whith regard to 20.0% of them in an indoor living space, while in 22.5% patients were registered occupational exposure to different allergens and respiratory irritants in the workplace. In general, without the examined risk factors for COPD, there were registered just 37.5% patients, which is similar to results of many authors (3,20,26,27).

Although all the mechanisms of systemic inflammation in the pathogenesis of bronchial obstruction in TB patients remained still unclear, it is certain that it acts in active TB as an exclusively linked. In our research, in the studied patients there were registered initially pathologically elevated the mean values of serum markers of acute systemic inflammation, which by the end of treatment significantly decreased to normal ones, or subclinical values, which can explain by the high intensity of infection in active extensive TB, as well as their decline by the end of TB treatment, due to antituberculotics (28,29).

Positive bronchodilation test was verified in only 15.0% of observed patients, which doesn't correlates with the available data in the literature, considering the fact that in patients with active pulmonary TB, this test is positive in overall 44% -88%, depending on the initial registered disorder pulmonary ventilation (19,21). Anyway, the average values of FVC, both before and during, as well as at the end of the TB treatment, were statistically significantly increase, as opposed to the values of FEV_1, which have significantly decreased after the completition of the same, which confirms the possible of reparative procesess during the TB healing as a significant factor for the developing CAO syndrome lately (30,31).

In our study, by the linear regression analysis we confirmed a statistically sigificant association between changes in the values of FEV_1(%), resulting in TB treatment completion, and the value of Snider's radiological score and the sputum culture conversion rate. Any increase in Snider's radiological score at the begining of TB treatment and a slower sputum culture conversion rate during the same, for just one measurement unit, is associated with statistically significantly higher decrease in the FEV_1(%) after the treatment completion. On the other side, logistic regression analysis confirmed a positive family history of COPD, Snider's radiological score at the beginning of TB treatment and sputum conversion rate on culture, as statistically significant predictors for the occurrence and development of CAO syndrome in observed patients, after the completion of TB treatment. Multivariate logistic regression analysis, as statistically the most significant predictors for the development of CAO syndrome in the observed patients allocated in our investigation Snider's radiological score at the beginig of TB treatment and sputum conversion rate on culture, as most significant factors of risk for developing CAO syndrome.

According to the results in our investigation, the influence of positive familiar history on COPD, initial radiological extent of specific pulmonary TB lesions, as well as sputum conversion rate on Lowenstain-Jensen culture, in patients with active pulmonary TB for the CAO syndrome onset, are significant as a predictive factors for resid-

ual bronchial obstruction upon completition of TB treatment (30,32,33). Strong correlation between the initial extent of radiological pulmonary specific lesions and sputum conversion rate on culture, with the emergence of CAO syndrome, in our study, as well as with other authors, but also a statistically significant correlation with registered impaired lung function, expressed through the lung function parameters of interest, clearly show that the residual bronchial obstruction in active pulmonary TB, is an important clinical entity, which can be significant reason for the further health deterioration of cured TB patients (19,33,34). Potential use of actual systematic bronchodilator therapy (GOLD startegy), together with antituberculosis drugs in patients with newly detected cavitary TB forms complicated with CAO syndrome, could be an effective approach for the prevention in the development of serious disorders of lung function and consequent COPD, according to their microbiological cure, improving and maintaining their optimal working and health condition (30,35,36).

6. CONCLUSION

The clinical syndrome of chronic airflow obstruction is often a common initial manifestation of unrecognized chronic obstructive pulmonary disease (COPD), which appaears in the results of our investigation as a consequence and significant functional impairment of the respiratory system, in the field of extensive destruction of lung parenchyma and intense systemic inflammatory response, during the reparative processes in active tuberculosis, even in the absence of risk factors for COPD. Given the small number of studies of this problem in the literature, results of our investigation point to the fact that only microbiological cure of TB patients with underlying risks for disorders of lung function, is not sufficient and effective approach for prevention of their further potential health deterioration.

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PROFESSIONAL PAPER

What Happens with Airway Resistance (Raw) in Asthma and COPD exacerbation

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Background: To show that in exacerbation of asthma and COPD besides decreasing of spirometry value (FVC, FEV1, FEF50, and PEF) also comes increasing of airway resistance (Raw).Patients and methods: This research includes 74 patients, in exacerbation phase of disease. All the patients get spirometry and plethysmography measurements, also includes adequate therapy , and after at least one month on control examination they repeat spirometry and plethysmography and answer a short life questionnaire. Results: The mean value of Raw after therapy in asthma is decreased for -17. 68% and in COPD for -15. 44%. The mean value of Raw in all levels of obstruction is bigger in COPD than in asthma, before and after therapy. After therapy spirometry values (FVC, FEV1, FEF50, and PEF) are much more increased in asthma than in COPD. From questionnaire analyses 78.37 %(58) of patients felt well, 17.57 %(13) felt the same like before therapy and 4.05 %(3) of them felt worst. All the patients who felt worst were in COPD group of patients. All of them had increased Raw, almost all which felt better (96. 43%) had decreased Raw. In asthma nobody felt worst. By most of the patients (76.67%) who felt better Raw is decreased. Conclusion: Adequate therapy in exacerbation of asthma and COPD decreases value of Raw and increases spirometry values. Increasing of spirometry values in asthma is much higher than in COPD. Mean values of resistance in COPD are higher before and after therapy than in asthma. There is a negative connection between subjective experience of illness and the level of resistance. Measuring of Raw can be a good parameter for monitoring COPD and asthma control. Key words: exacerbation of asthma or COPD, spirometry, airway resistance – Raw.

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1. INTRODUCTION

Pulmonary function tests are vastly underused yet they can provide important clinical information. They are designed to identify and quantify defects and abnormalities in the function of respiratory system, and answer questions about how serious obstruction is, does it respond on bronchodilators, and is the treatment helping the patient.[1]

Chronic obstructive pulmonary disease (COPD) is leading cause of morbidity and mortality worldwide. Current definition of COPD is a disease state characterized by airflow limitation and is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles of gasses.[2] COPD is progressive disease characterized by worsening pulmonary function.

Asthma is a serious global health problem .It is a chronic inflammatory disorder of the airways. Chronically inflamed airways are hyper responsive, they become obstructed and airflow is limited (by bronchoconstriction, mucus plugs, and increased inflammation) when airways are exposed to various risk factors.[3]

When COPD and asthma are in question most common test is spirometry (flow-volume-curve).It is a gold standard for asthma and COPD diagnosis. Body plethysmography test is not as common. One of reasons for sure is that plethysmography is not available as spirometry. If we include plethysmography we get much more of data. One of data we can get is airway resistance (Raw).It is used for evaluation of airway responsiveness, provocation testing characterization of various types of obstructive lung disease, localization of the primary site of flow limitation and evaluation of localized obstruction.[4]

The clinical measurement of plethysmographic airflow resistance is also considered to be a gold standard. Measurement of resistance as a function of lung volume provides a useful extension of currently utilized methodology.[5]

When the airways are narrow resistance is increased. Narrowing may be due to bronchoconstriction of inflamed airways in asthma, mucus and thickened bronchi in chronic bronchitis or floppy airways in emphysema.[1]

Airway resistance (Raw) is defined as difference between pressures in alveolus and in examinee mouth necessary for flow of 1 liter of air per second. If increasing is more than 0,3 kPa/l/s, it is sign that resistance is increased and flow rate in the big airway is decreased.[6]

The main point of this research is:

- To show that airway resistance (Raw) is a changing variable in exacerbation of asthma and COPD.
- That therapy at exacerbation of COPD and asthma works not only on improvement of spirometry values as well as decreasing of airway resistance (Raw).
- To show relation between subjective experience of illness (questionnaire) and the level of airway resistance (Raw).

2. PATIENTS AND METHODS

2.1. Design of research

Patients with COPD and asthma which were assigned by their doctor on examination because of exacerbation of sickness were included in this research. History of sickness and finding from functional lab were used in examination. They came with reference for examination and lung function in regular ambulance during the morning. They were also regular patients of practice for asthma and COPD. Patients are included in research if this criteria is satisfied: (1) patients of both gender who have a diagnose of COPD or asthma, (2) patients which had higher parameters of inflammation, and/or decreasing of spirometry values compared to last check up, and/or retrogression of subjective parameters which complicates breath taking, and/or higher need for short term bronhodilatators, enhanced cough and expectoration. Actually asthma patients get included compare to GINA guidelines for uncontrolled or bad controlled asthma.[3] The severity of COPD was classified according to Global initiative for Obstructive Lung Disease (GOLD) stages.[7]

2.2. Patients

This research includes 74 patients, between 23-80 years of age, 40 female (54.05%) and 34 male (45. 95%). From that 36 of patients were with asthma diagnosis and with COPD 38 patients.

Characteristic of patients are presented in table 1.

2.3. Methods

Before intensive therapy all the patients made spirometry and plethysmography and after at least 1 month of recommended therapy they repeated spirometry and plethysmography and answer questionnaire. Questionnaire was really simple, they got only one question to answer, do them subjective feel better, worst or the same. Spirometry and plethysmography were carried out according to ERS/ATS pointers.[8, 9]

All the patients measured: airway resistance (Raw),forced expiratory volume in 1 second (FEV1),forced expiratory vital capacity (FVC),forced expiratory flow after 50% VC (FEV50),peak expiratory flow (PEF) .All the measurements were done on Sensor Medics Vmax device.

	All the patients	Asthma	COPD
Number of patients, N %	74 (100%)	36 (48. 65%)	38 (51. 35%)
Female (%)	40 (54. 05%)	25 (62. 50%)	15 (37. 50%)
Male (%)	34 (45. 95%)	11 (32.35%)	23 (67. 65%)
Age, mean value (year)	56.48	49.45	63.5
Mean value. female (year)	57.55	52.7	62.4
Mean value, male (year)	55.4	46.2	64.6

Table 1. Characteristic of all the patients

	Number of patients with increased values(COPD)	Number of patients with decreased values (COPD)	Number of patients with increased values(ASTHMA)	Number of patients with decreased values (ASTHMA)
FEV 1 (L)	20 (52.63%)	18 (47.37%)	34 (94.44%)	2 (5.56 %)
FVC (L)	22 (57.90%)	16 (42.10%)	30 (83.33%)	6 (16.67%)
FEF 50 (L/s)	26 (68.42%)	12 (31.58%)	33 (91.66%)	3 (8.67%)
PEF (L/s)	28 (73.68%)	10 (26.32%)	30 (83.33%)	6 (16.67%)
Raw (kPa/l/s)	8 (21.05%)	30 (78.95%)	10 (27.78%)	26 (72.22%)

Table 2. Number of patients with increased and decreased spirometry values and airway resistance (Raw) after therapy in asthma and COPD

3. RESULTS

In Figure 1 number of all patients (asthma and COPD) is divided according to level of obstruction (ratio FEV1/FVC- Tiffno index).If level of obstruction is higher (Tiffno index lower) we have bigger number of patients with COPD than with asthma.

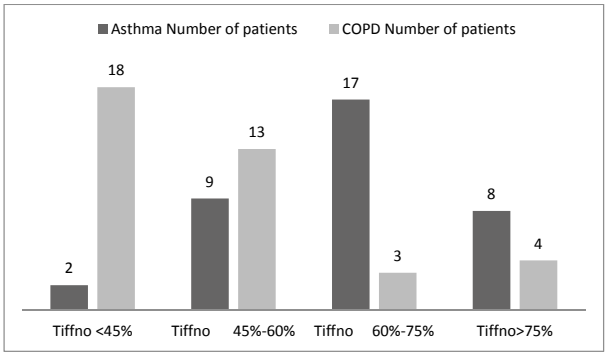

Figure 1 . Connection between number of patients with asthma and COPD with level of obstruction (Tiffno index)

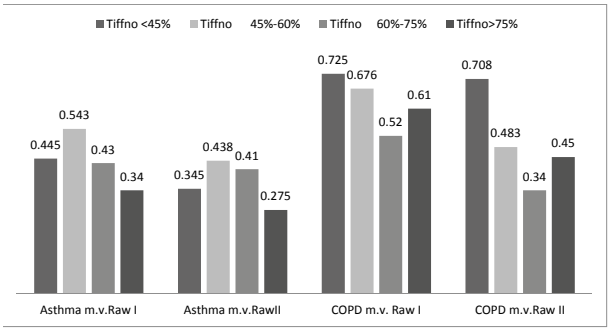

Figure 2 Connection of mean value of Raw from the level of obstruction before(I) and after (I) therapy in asthma and COPD m.v.mean value

At 78. 95% of patients with COPD and 72. 22% of patients with asthma come to decreasing of Raw; number of patients with increased spirometry values is higher at asthma than in COPD (Table 2).

Figure 2 is showing us the mean value of Raw (before therapy-Raw I and after therapy-Raw II) at asthma and COPD according to level of obstruction. Value of Raw in all the levels of obstruction is bigger in COPD than in asthma, before and after therapy.

The mean value of

Raw I in asthma before therapy is 0.40794 kPa/l/s and after therapy Raw II is 0.33581 kPa/l/s. The mean value of Raw I in COPD before therapy is 0.68 kPa/l/s and after therapy Raw II is 0.575 kPa/l/s (Figure 3).

The mean value of Raw in asthma is decreased for -17. 68% and for COPD for -15. 44 %(Figure 4).

Raw according to level of 0. 3 kPa/l/s have a bigger number of patients which value in asthma is lower from 0.3 kPa/l/s than in COPD also before and after therapy. There are 30.56% (11) of patients with asthma before therapy and 50 % (18) of patients after therapy. The number of COPD patients is 5. 26% (2) before therapy and 13. 16 %(5) after therapy (Figure 5).

After therapy spirometry values (FVC, FEV1, FEF50, and PEF) are much more increased in asthma than in COPD. There are slightly increased values in COPD according to increased values in asthma (Figure 6).

From questionnaire analyses 78.37%(58) of patients felt well, 17.57% (13) felt the same like before therapy and 4.05%(3) of them felt worst.

All the patients who felt worst were in COPD group of patients, all of them had increased Raw. 96. 43% of COPD patients who felt better had decreased Raw .In asthma nobody felt worst.76. 67% of them who felt better had decreased Raw (Figure7).

Comparing together Raw I and Raw II from all the patients in asthma and COPD it is obvious existence of decreasing of values of Raw after therapy (Figure8).

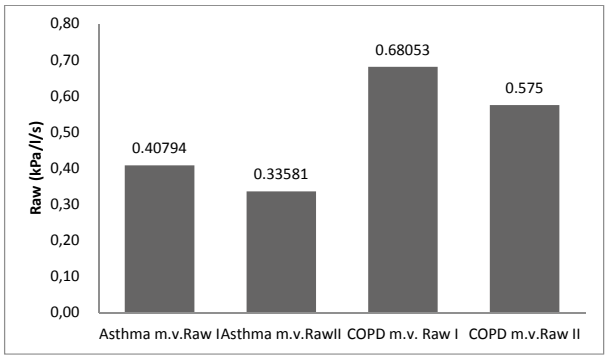

Figure 3. Mean value of Raw before(I) and after(II) therapy in asthma and COPD m.v. mean value

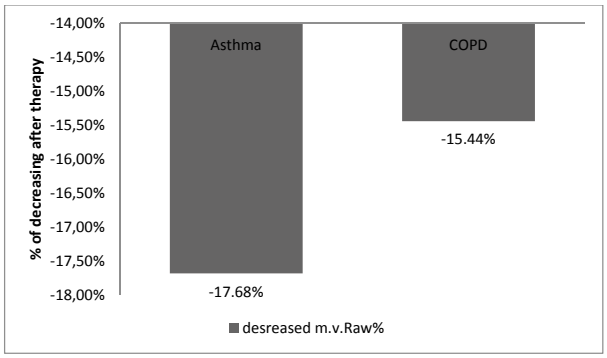

Figure 4. Decreasing of mean value in asthma and COPD after therapy m.v. mean value

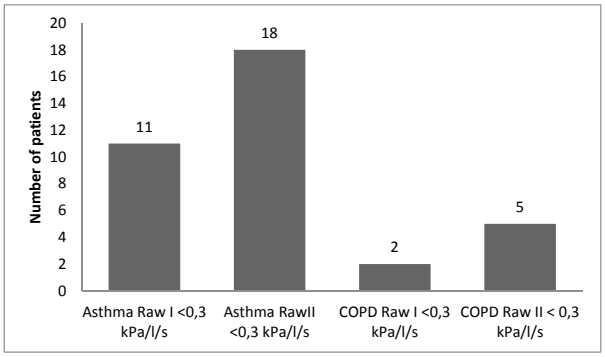

Figure 5. Number of patients with resistance (Raw) under 0, 3 kpa/l/s before(I) and after (II) therapy in asthma and COPD

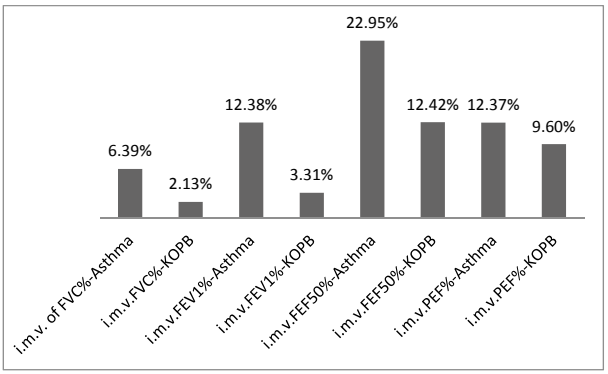

Figure 6. Increasing in mean spirometry values in asthma and COPD after therapy i.m.v. -increase of mean value

4. DISCUSSION

This research involves 74 patients, average age 56. 48 years, who have asthma or COPD. From the level of obstruction they are divided in 4 groups of patients.

They are divided according to Tiffno index(ratio FEV1/FVC).It is better indicator of obstruction than FEV1.[10]Because this parameter involves restriction and shows us the real obstruction..[11]Many lung diseases may result in reduced FEV1,because of that a useful assessment of airflow limitation is the ratio FEV1/FVC (Tiffno index).The ratio is normally bigger than 0.75(75%).[12]

According to level of obstruction there is a bigger number of COPD patients (81.56%) with Tiffno index which is lower than 0.60 apropos number of patients with asthma(69.44%) where Tiffno index is higher than 0.60.COPD patients have bigger level of obstruction and higher mean values of Raw than patients with asthma. In all four groups of patients mean values of Raw in COPD are higher than in asthma. After therapy there is expected improvement of parameters of lung function in asthma patients and slightly improvement of values in COPD patients. Mean values of Raw get decreased both in asthma and COPD, but mean values are still higher in COPD than in asthma.

According to Lall and associates even by kids variability of resistance is noticed. It is answer to bronchodilator therapy. Values of Raw are decreasing, so there is possibility that value of Raw can be used as parameter for monitoring of answer to therapy, but that needs to be investigated.[13]

Morice and associates were monitoring the values of complains (Gaw) which is reciprocal value of Raw, and they came to conclusion that value of Gaw is rising (mathematically that means that Raw is decreasing) after bronhodilatators which is applied by different types of devices for inhalation usage.[14]

Therefore value of

resistance is a variant variable influenced by exacerbation of asthma and COPD. It is obviously existence of decreasing of value of Raw after therapy in asthma and in COPD. Undoubtedly the values of Raw variants depending on level of obstruction. Value of Raw is higher with higher obstruction. After therapy in COPD response is better to Raw than to spirometry value. Raw decreased much more than spirometry values increased. The plethysmography (Raw) should be considered the preferred technique for measuring bronhodilation in COPD clinical trials.[15]In asthma response to spirometry values and Raw are similar.

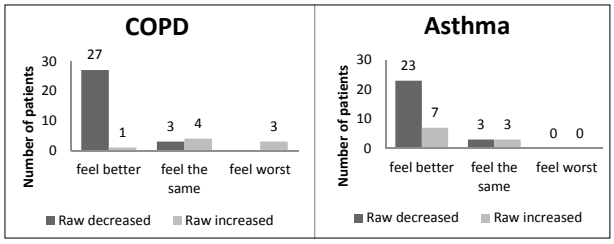

Figure 7. Connection between level of airway resistance (Raw) and subjective experience of illness in COPD and asthma patients

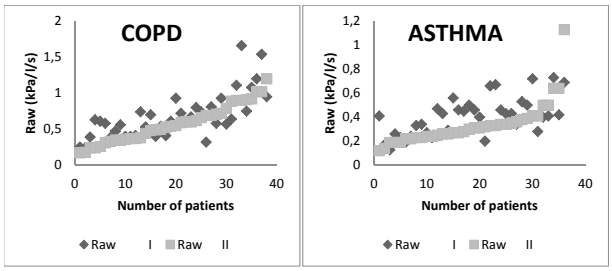

Figure 8. Decreasing of airway resistance (Raw) of all patients (COPD and asthma) after therapy Raw I-before therapy,Raw II-after therapy

There is very good negative connection between subjective experience of illness (questionnaire) and the level of airway resistance (the patients which felt worst had increased Raw and the ones which felt better had decreased Raw).

As we see research answered to the appointed objectives.

5. CONCLUSION

This research shows that adequate therapy in exacerbation of asthma and COPD decreases value of Raw and increases spirometry values. Increasing of spirometry values in asthma is much higher than in COPD. Mean values of resistance in COPD are higher before and after therapy than in asthma. There is a negative connection between subjective experience of illness and the level of resistance. It makes us possible to conclude that measuring of Raw can be a good parameter for monitoring COPD and asthma control. Spirometry and plethysmography are both a gold standard for diagnosing and controlling the asthma and COPD. With bigger obstruction resistance in airways is higher.

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ORIGINAL PAPER

The Evaluation of Impact of Bph Surgical Treatment with the Open Prostatectomy and Transurethral Resection of the Prostate Methods on the Quality of Life

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Introduction/Objective. Benign prostatic hyperplasia is one of the most common diseases in older men. The objective of this study was to evaluate the impact of the surgical treatment of the benign prostatic hyperplasia (BPH) with the methods of open prostatectomy (OP) and transurethral resection of the prostate (TURP) on the quality of life. **Methods.** The research material was based on 80 patients, out of whom 40 patients were treated with the method of open prostatectomy (Group A), and the other 40 patients with the method of transurethral resection of prostate gland (Group B) due to benign prostatic hyperplasia. All patients were under the age of 80 years old (approximate age in Group A 70, 23 with variation interval of 21 years old, and in Group B 69, 37 with variation interval of 22 years old), with the International Prostate Symptom Score (IPSS) value >19 points, postvoid residual urine higher than 150 ml, the weight of benign prostatic gland hyperplasia tissue over 30 grams for method of prostate transurethral resection, and over 80 grams for the method of open prostatectomy. The quantification of the quality of life, as a consequence of urinary symptoms, was done by the Quality of Life Index (QLI) which is question Nº 8 in IPSS. All patients were determined the value of this score before the operation, and then in postoperative period in time intervals of 4, 8 and 12 weeks. **Results**. The QLI arithmetic mean, before the operation, was 5,55 points in Group A, and 5,45 points in Group B. During postoperative checkups in time intervals of 4, 8 and 12 weeks, the arithmetic means in Group A were 0,975, 0,450 and 0,100 points, and in Group B 1,850, 1,700 and 1,575 points. By analyzing the obtained results, there was a highly statistically significant difference between preoperative test results and the results during all the postoperative checkups in both groups, A and B. By testing the difference of the QLI arithmetic mean between the patients in both groups, preoperatively there was no statistically significant difference, but during all postoperative checkups, there was a highly statistically significant difference between the test values. **Conclusion**. The surgical treatment of BPH leads to significant improvement of the quality of life, as a consequence of urinary symptoms. The improvement of the quality of life was more evident in patients whose BPH was treated with the OP method. Key words: Benign prostatic hyperplasia, disease-specific quality of life, open prostatectomy, transurethral resection of prostate

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1. INTRODUCTION

Benign prostatic hyperplasia (BPH) is a frequent disease among men > 50 yr, and its incidence increases with age (1).

BPH is characterized by benign prostatic enlargement (BPE) and can be responsible for lower urinary tract symptoms (LUTS) that include obstructive/voiding symptoms and irritative/or storage symptoms. Voiding symptoms include: weak urinary flow, hesitancy, intermittency, terminal dribbling and incomplete emptying, while storage symptoms include frequency, nocturia, urgency, urge incontinence and dysuria. The prevalence of LUTS in the male population increase with age and has been estimated to be 20-25% for middle-aged men and 40-70% for men aged 70 years (2, 3).

Many urologists use symptoms as a base for establishing diagnosis of subvesical obstruction as well as for the evaluation of treatment successfulness. Many symptom – scores enable objectivization of symptoms i.e. complaints in patients with LUTS and/or BPH. Boyarski (4) was one of the first who discovered such scores, and later was followed by Madsen and coIversen (5), then Fowler, etc.

In 1992, the American Urologists Association (AUA) published Symptom Score Index which was adopted by the World Health Organization in 1993 as the International Prostate Symptom Score (I-PSS) (10). It consists of 7 same questions referring to LUTS as in AUA Symptom Index with additional question Nº 8 referring to disease specific

quality of life (QLI). It became a component in evaluation of patients with LUTS and/or BPH and is reccomended as a precise means i.e. a method in diagnostics and treatment result follow-up in such patients.

Although it is not life-threatening, BPH with its clinical manifestation as LUTS reduces the patients quality of life. Sleeping problems can cause numerous disorders in terms of increased risk of developing cardiovascular diseases, metabolic diseases, depression, as well as increased risk of falling and having consequent bone fractures, etc. (7, 8, 9, 10, 11) In the year 2011, medical therapy is universally the first line intervention for virtually all men presented with LUTS secondary to BPH. Medical therapy alone or in combination does not achieve the degree of effectiveness as surgery.

TURP for many years has been considered as the gold standard for surgical treatment of BPH. Symptoms relief, improvement in maximum flow rate and reduction of postvoid-residual urine have been reported in several experiences. In 1999 TURP represented the 81% surgical treatment for BPH versus 39% of 2005. , and the future will show if this is a marketing driven change or if there is a real advantage in new technologies (12).

In case of prostate of very large size, the gold standard approach is still open prostatectomy, but also in this case the callenge is ongoing, with minimally invasive laser prostatectomy, laparoscopic approach and most recently robotic approach.

Due to BPH prevalence and its impact on quality of life, and its multimode treatment, it is necessary to evaluate the impact of different treatment methods on the quality of life, as a consequence of urinary symptoms.

2. OBJECTIVE

The objective was to evaluate the impact of surgical treatment of BPH with the OP and TURP methods on the quality of life.

3. MATERIAL AND METHODS

The research material was based on 80 patients, out of whom 40 patients were treated with the method of open prostatectomy (group A), and the other 40 patients with method of transurethral resection of te prostate (group B) due to benign prostatic hyperplasia at Clinic of Urology, Clinical Center University of Banjaluka. All patients were under the age of 80 years old (approximate age in the group A 70, 23 with variation interval of 21 years old, and in the group B 69, 37 with variation interval of 22 years old), with the IPSS value >19 points, postvoid residual urine higher than 150 ml, the weight of benign prostatic gland hyperplasia tissue over 30 grams for method of prostate transurethral resection, and over 80 grams for the method of open prostatectomy.

Two fundamental reasons for the OP method were: the weight (size) of the BPH tissue and the association of BPH with the bladder calculosis and diverticulosis, hydrocele, inguinal hernia, the urethra structure.

The IPSS has been used in the research, question N° 8 (Quality of Life Index-QLI) which relates to disease – specific quality of life. The question related to quality of life, as a consequence of urinary symptoms was: "If you had to spend the rest of your life with the voiding situation as it is now, how would you describe it? The answers are numbered in the following way: 0-fascinated, 1-satisfied, 2-mainly satisfied, 3- semi-satisfied (equally satisfied and dissatisfied), 4-mainly dissatisfied, 5-dissatisfied and 6-desperate.

The method of work was as follows:

Preoperative determination of IPSS values (Question N°.8-QLI, twice), by individual examination of all examinees

One group of patients with BPH was treated with the OP method (Group A), and the other with the TURP method (group B) After the operative intervention, in time intervals of 4, 8 and 12 weeks, all patients re-answered question N° 8 (QLI) contained in IPSS.

According to their age, patients have been presented in Table 1 , Figure 1 and 2.

Age	GROUP A number of patients and %		GROUP B number of patients and %	
50.-59.	1	2,50	1	2,50
60.-69.	19	47,50	19	47,50
70.-79.	18	45,00	19	47,50
80.-89.	2	5,00	1	2,50
Total	40	100,00	40	100,00

TABLE 1. Patients according to their age

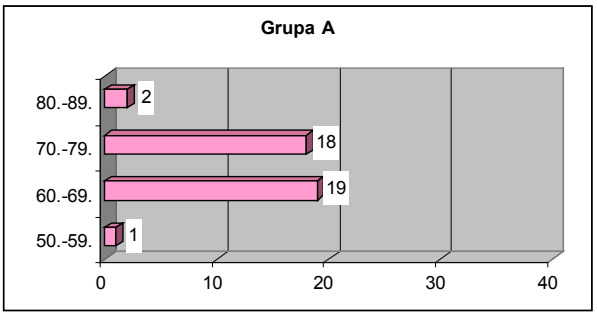

FIGURE 1. Patients according to their age (Group A).

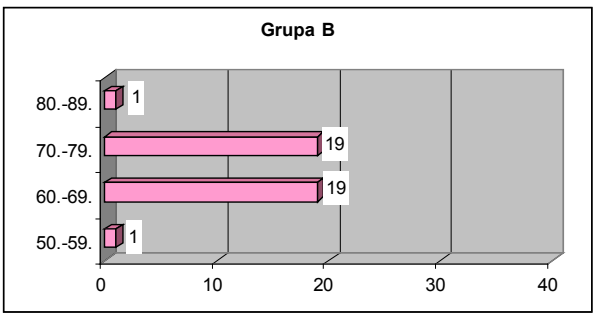

FIGURE 2. Patients according to their age (Group B).

The average age of patients in Group A was 70,23, and in Group B 69,37. According to preoperative values of answers to question N° 8 in IPSS, QLI, the patients have been presented in Tables 2 and 3.

QLI values	GROUP A GROUP B number of patients number of patients
0	0 0
1	0 0
2	0 0
3	0 0
4	0 0
5	18 22
6	22 18

TABLE 2. The QLI values in observed groups

Note: Question related to quality of life, as a consequence of urinary symptoms was: "If you had to spend the rest of your life with the voiding situation as it is now, how would you describe it? The answers are numerated in the following way: 0-fascinated, 1-satisfied, 2-mainly satisfied, 3- semi-satisfied (equally satisfied and dissatisfied), 4-mainly dissatisfied, 5-dissatisfied and 6-desperate.

Groups	AM	SD
A	5,550	0,504
B	5,450	0,504

Table 3. The QLI arithmetic means in observed groups

4. RESULTS

The quantification of quality of life, as a consequence of urinary symptoms, after operative treatments was carried out through IPSS (question N° 8, QLI) in time intervals of 4, 8 and 12 weeks, as shown in Table 4.

Testing the difference of QLI arithmetic means between the test results before the operation, during the first, second and third checkup was performed by t-test **for both groups A and B,** and the following tables show it.

Variables	Test result t p	Conclusion
P-IQL: K1-IQL	52,659 0,000	p< 0,01
P-IQL: K2-IQL	45,499 0,000	p<0,01
P-IQL: K3-IQL	57,737 0,000	p<0,01

Table 5. Comparison of QLI preoperative results and the results of the same test during the first, second and third checkup in Group A.

Note: P-QLI Preoperative Index Quality of Life, K1-IQL first checkup, K2-IQL second checkup, K3-IQL third checkup

Variables	Test result t p	Conclusion
P-IQL: K1-IQL	33,893 0,000	p<0,01
P-IQL: K2-IQL	33,541 0,000	p<0,01
P-IQL: K3-IQL	35,704 0,000	p<0,01

Table 6. Comparison of QLI preoperative results and the results of the same test during the first, second and third check up in Group B.

Note: The symbols of variables used match the ones in the previous table

Tables 5 and 6 show that there is a highly statistically significant difference between preoperative QLI results and the results of the same test during the first, second and third checkups in both groups, A and B.

Time interval of giving an answer about the *qualiy of life*, as a consequence of urinary symptoms	GROUP A AM SD	GROUP B AM SD
4 weeks	0,975 0,158	1,850 0,580
8 weeks	0,450 0,504	1,700 0,464
12 weeks	0,100 0,304	1,575 0,501

Table 4. The QLI artithmetic means during postoperative checkups.

The testing of arithmetic mean difference of preoperative values as well as of values during the first, second and third checkups **between groups A and B** have also been conducted in this study.

Variables	Test results t p	Conclusion
P-IQL	0,888 0,3775	p>0,05
K1-IQL	9,212 0,0000	p<0,01
K2-IQL	11,541 0,0000	p<0,01
K3-IQL	15,930 0,0000	p<0,01

Table 7. Comparison of QLI results between groups A and B, preoperatively and during the first, second and third checkups.

Note: The symbols of variables used match the ones in the previous table

Table 7 shows that there has been no statistically significant difference between total sums of QLI preoperatively between groups A and B, but during all postoperative checkups, there has been a highly statistically significant difference between the test values.

5. DISCUSSION

Until more than three decades ago, the open prostatectomy was the most frequent approach and method for surgical treatment of BPH.

Development of endoscopy and other methodologies has led to significant reduction of use of this methodology in the BPH treatment and has classified TURP (transurethral resection of the prostate) as a gold treatment method, but because of the risk of bleeding and TUR syndrome, patient with large prostates are usually offered open prostatectomy, which provides excellent removal of prostatic tissue. Although some experts think that prostate over 80 g should be treated by open prostatectomy, there is no concensus on this issue yet (13).

It is the fact that there are no opponents to the currently accepted attitude that the improvement of life quality, as a consequence of urinary symptoms, presents the most important goal of BPH treatment from the patient's perspective (14).

IPSS is a simple and valid measure that can be useful for assessing treatment outcomes in men with symptomatic BPH (15).

Although various validated QoL instruments have been used to assess disease-specific QoL in men with LUTS/BPH, the IPSS-QoL is the easiest to administer and the most widely accepted and used (16).

Michael P et all also concluded in their study that IPSS is a convenient tool for assessing disease-specific QoL that can be used when determining treatment strategies and evaluating treatment outcomes in men with LUTS/BPH (17).

Taking into consideration the fact that the objective of this paper was to evaluate and compare the impact of BPH surgical treatment with the OP and TURP method on quality of life, as a consequence of urinary symptoms, the same one has been quantified by question N° 8 in IPSS, Index Quality of Life.

In 100% of our sample, preoperative values of the test have shown that patients were completely dissatisfied or desperate due to the quality of life as a consequence of urinary symptoms i.e. 18 patients in Group A and 22 patients in Group B were dissatisfied and 22 patients in Group A and 18 patients in Group B were desperate. The arithmetic mean of the test, preoperatively, in Group A was 5,55 and in Group B 5,45 points.

Marszalek et al have analized the symptom score after TURP in 25 random and controlled studies between 1996 and 2006 (18). All studies have shown dramatic improvement of the symptom score which was 62% after 12

months and thus the quality of life has significantly been improved.

Bearing in mind all this, our study has shown that the quality of life quantified through IPSS-QoL, as an AM, in Group A was, postoperatively, after 4 weeks 0,975, after 8 weeks 0,450 and after 12 weeks 0,100 points. As a matter of fact, the AM of evaluated QLI among these patients, postoperatively, (12 weeks after operation) was 0,100 points compared to the AM preoperatively which was 5,500 points. Therefore, it shows that the quality of life has improved by 98,2 %. The analysis of obtained results shows that there has been a highly statistically significant difference between preoperative test results and the results during all postoperative checkups.

In the other group of patients treated with TURP method (Group B), the postoperative test AM after 4 weeks was 1,850, after 8 weeks 1,700 and after 12 weeks 1,575 points. As a matter of fact, the AM of evaluated QLI among these patients, postoperatively, (12 weeks after operation) was 1,575 points compared to the AM preoperatively which was 5,450 points. Therefore, it shows that the quality of life has improved by 71,11 %.

The greatest advantages of OP compared to TURP are decreased need to have a re-operation of BPH, better removal of obstructive tissue and avoidance of TURP syndrome (12). The fact that OP does the best removal of obstructive BPH tissue, and therefore reduces even more the voiding symptoms, it can be expected that it is more effective in improving the quality of life, as a consequence of urinary symptoms.

By testing the QLI AM difference between patients treated with OP and TURP, our study has shown that there was no statistically significant difference before operation, but during all postoperative checkups, there has been a highly statistically significant difference between the test values, in terms of greater quality of life improvement after OP.

6. CONCLUSION

The surgical treatment of BPH brings about significant improvement of the quality of life, as a consequence of urinary symptoms.

The improvement of the quality of life is more evident in patients whose BPH was treated with the OP method.

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ORIGINAL PAPER

Selection of Treatment Method for Pelvic Ring Fractures

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Introduction The pelvis is the central part of the body that receives the weight from the vertebral column and transfers it to the lower extremities. It protects the internal organs with its specific structure and shape. **Objective** The study aims to compare the clinical outcomes of emergency non-surgical and surgical treatment of such patients, to analyse the types and severity of complications and final functional outcome. **Material and methods** We present a series of 47 patients treated in the period between 1999 and 2009 at the Traumatology Clinic, CHC Banja Luka. According to Marvin Tile's classification, fractures were distributed as follows: Type A fractures occurred in 19 patients (40.6%), Type B in 18 (38.1%) and Type C in 10 (21.3%). 30 patients (63.8%) were polytraumatised, with craniocerebral injuries in 12 patients (25.5%), chest cavity injuries in 5 (10.6%) and abdominal organ injuries in 13 patients (27.6%). 27 patients (57.4%) had clinical and laboratory signs of haemorrhagic shock on admission, while 26 patients (56.2%) received conservative treatment and 21 patients (43.8%) were treated using surgical methods of stabilisation of the pelvic ring. **Results** The analysis of the outcomes of treating pelvic ring fractures in our series of patients by using radiography (x-rays according to Slatis) showed that out of 47 treated patients, the outcomes were excellent in 28 (60%), good in 7 (15%), fair in 5 (12%) and poor in 7 (14%). The functional outcomes in all patients were evaluated according to the D'Aubigne-Postel scale, on average 18 months after the trauma. The outcomes were excellent in 22 patients (45%), good in 15 (31%), fair in 4 (9%) and poor in 6 (14%). The chi-square test showed that there was no significant statistical difference between the outcomes monitored using x-rays and functional outcomes monitored using the D'Aubigne-Postel scale (p=0.097). The surgical treatment efficiency coefficient was introduced for the purpose of comparative evaluation of treatment outcomes. The surgical treatment efficiency coefficient, compared with conservative treatment, showed that all evaluated parameters were between 1.56 and 16.33 times lower in surgical treatment, which represents the more favourable outcome. **Conclusion** We can conclude that conservative treatment is the treatment of choice for Tile's Type A fractures, external fixator for treating Type B fractures (including all subtypes), and internal fixation, as monotherapy or in combination with external fixator, for treating Type C2 and Type C3 fractures. Surgical treatment, compared with conservative treatment, allows faster mobilisation of the patient and it shortens the recovery period, which in turn lowers the total treatment costs. Key words: fracture, pelvis, fixator, polytrauma, outcome

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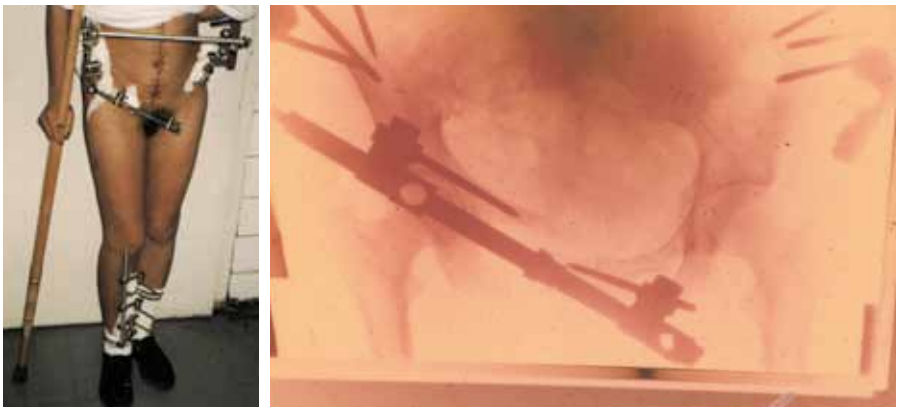
1. INTRODUCTION

The pelvis is the central part of the body that transfers weight from the vertebral column to the lower extremities, with its specific structure and shape it protects the internal organs, while the external side, the upper and lower brims of the pelvic ring serve to connect muscles and sustain body stability (1). The pelvic bones fuse together and do not articulate with each other, thereby forming a semi-ring structure i.e. one half of the pelvis each. The two halves are fused together anteriorly at the pubic symphysis, and are articulated posteriorly with the sacrum. The sacroiliac joints are placed vertically and are exposed to the shear force due to the weight of the upper body part. The sacroiliac complex with the sacroiliac, sacrotuberous and sacrospinous ligaments resists this and this way they maintain the normal position of the sacrum in the pelvic ring. From the centre of the pelvic ring, there is a strong and compact bone arch which spreads along the internal side and is made up of the promontory, linea terminalis on the lateral sides of the sacral bone and lateral iliac bone and the upper brims of the upper pubic bone. This crest is extremely important for the stability and biomechanics of the pelvic ring as it serves to transfer dispersed pressure from the pelvic column to the hip joint. All loads use this route and thus it make sense to try to repair it in case of a pelvic injury – that is why all fractures that disrupt any plane of this crest are unstable pelvic fractures (2). The load forces go along the iliopectinal line up to the acetabulum, and then transfer to the

neck and trochanteric mass of the femur. The basics of pelvic biomechanics entail the understanding that the pelvis is a ring-like structure. Traumatic forces, depending on their direction and strength, cause from most basic to complicated avulsion fractures (single or double fractures), with or without vertical shifts, internal or external rotation of the pelvis, or with or without dislocation of the pelvic ring (2-4). The vital organs of the digestive and urogenital tracts, terminal blood vessels and nerves are located in or pass through the pelvic region. Pelvic injuries are accompanied by considerable bleeding and potential neurological prolapses, and injuries to the urogenital organs. It is for that very reason that everything must be considered on a case-by-case basis, especially unstable pelvic fractures.

Pelvic fractures are painful, accompanied by swelling, haematoma, and prolapse of the function of the pelvis and injured organs. Pelvic fractures occur in approximately 1-3% of all fractures of the osteoarticular system. Pelvic radiography with both hips in the anterior-posterior direction, cranial or caudal x-ray photographs of the pelvis and oblique x-ray photographs, give a good insight into the pelvic injury. Over 90% of all pelvic fractures can be adequately diagnosed by radiography (5, 6). Computerised tomography (CT) provides more precise data on the pelvic injury, while magnetic resonance (MR) is used to assess deep vein thrombosis and provide accurate data on the pelvic organ injury (7, 8). Having diagnosed the injury, and depending on whether it is a polytrauma or just a pelvic fracture and depending on the general condition and age of the patient, the orthopaedist, in consultation with a team of different specialists, from the beginning takes part in making decisions on the schedule and manner of treatment (8). The first priority is to save the patient's life and that depends on complete diagnosis and understanding of potential injuries: haemorrhage, injuries to the visceral organs of the pelvis, etc. (9). Nowadays Marvin Tile's classification is the most frequently used pelvic fracture classification.



Picture 1. Clinical and x-ray illustration of externally fixated pelvis

2. AIM OF THE STUDY

The study aims to compare the clinical outcomes of emergency non-surgical and surgical treatment of such patients, to analyse the types and severity of complications and final functional outcomes. In addition, we show a pin configuration technique which reduces skin irritation and enables greater mobility in the hip and functionality of the patient.

3. MATERIAL AND METHODS

The material in this research is made up of 47 patients treated at the Traumatology Clinic of Banja Luka Clinical Hospital Centre between 1999 and 2009. According to Marvin Tile's classification, 19 patients (40.6%) suffered Type A pelvic fractures, 18 patients (38.1%) Type B and 10 patients (21.3%) Type C (Table 1).

Tile's pelvic injury type	No. of patients	
	f	%
A	19	40.43
B	18	38.30
C	10	21.28
Total	47	100.00

Table 1. Distribution of patients according to Marvin Tile's classification

There were 30 polytraumatised patients (63.8%), who, in addition to pelvic ring fractures, suffered craniocerebral injuries (12 patients or 25.5%), there were 5 patients (10.6%) with craniocerebral injuries, and 13 patients (27.6%) with abdominal organ injuries (Table 2, Diagram 1).

Polytrauma type	No. of patients	
	F	%
Craniocerebral injuries	12	40.00
Chest cavity injuries	5	16.67
Abdominal organ injuries	13	43.33
Total	30	100.00

Table 2: Distribution of polytraumatised patients by degree of injury to organs

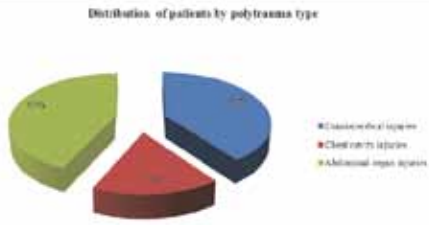


Diagram 1. Distribution of polytraumatised patients by degree of injury to organs

On admission to our institution, 27 patients (57.4%) had clinical and laboratory signs of haemorrhagic shock.

26 patients (56.2%) received conservative treatment (Type A and some patients with Type B1). 2 patients did not accept the proposed indicated surgical treatment.

They were treated conservatively: sling, side-lying and resting. 21 patients (43.8%) with Type B and Type C pelvic fractures were treated surgically (Picture 1). Type C pelvic injuries were treated with internal fixation, AO plates and screws. T

he following approaches were used depending on the location of the pelvic injury: Emile-Letournel's, suprapubic, sacroiliac. There were 6 (12.7%) such patients.

We treated Type B3 injuries with internal fixation and external fixator. 3 patients (6.3%) were treated in this way (Table 3, Diagram 2).

Treatment method	No. of patients	
	f	%
Conservative	26	55.32
Surgical	21	44.68
Total	47	100.00

Table 3: Distribution of patients by treatment method

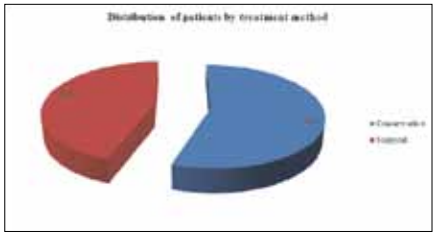
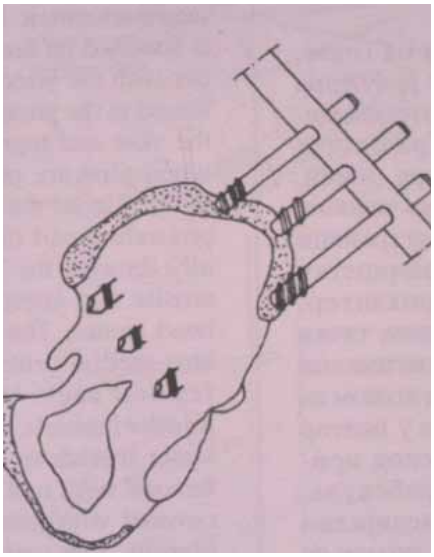


Diagram 2. Distribution of patients by treatment method

We used external fixation in polytraumas, Tile's Type B injuries, i.e. where there was vertical stability with rotational instability. We did not even take iliac bone fractures as a relative counter-indication. We used external fixation mostly in stable "open book" fractures, where both clinical and radiological findings indicated the intact condition of the sacroiliac, iliolumbar, sacrospinous and sacrotuberous ligaments.

We treated 10 patients (21%) with Type B pelvis fractures with Mitkovic's external fixator Type M20, and 2 patients (4.2%) with the Hoffmann external fixator. Pelvic stabilisation with M20 fixator is simple and it can be quickly constructed using 2 frames. 4 pins can be placed on 2 movable clamps, and the assembly of movable clamps and articular tourniquet is made possible by the assembly of the necessary number of stabilisation pins, for every person regardless of the patient's weight and height. The pins are inserted laterally into the iliac bone, attempting to have the pins „penetrate" the cortex (Picture 2). In the lower third of the fossae iliacae there is the relatively voluminous iliac muscle and the chances of a iatrogenous lesion are thus small. This way the pin will not become loose, it has a double leverage action, it is more stable, and it is thus easier and quicker to perform repositioning and maintain stabilisation. The success of treating a pelvic ring fracture is evaluated using radiography, and the functional outcomes are evaluated for all patients using the D'Aubigne-Postel scale.



Picture 2. Schematic illustration of placing M20 external fixator pins

4. RESULTS

The analysis of the outcomes of treating pelvic ring fractures in our series of patients by using radiography (x-rays according to Slatis) showed that out of 47 treated patients, the outcomes were excellent in 28 (60%), good in 7 (15%), fair in 5 (12%) and poor in 7 (14%). (Table 4, Diagram 3).

Treatment outcome according to Slatis	No. of patients	
	f	%
Excellent	28	59.57
Good	7	14.89
Fair	5	10.64
Poor	7	14.89
Total	47	100.00

Table 4. Distribution of patients by treatment outcomes according to Slatis

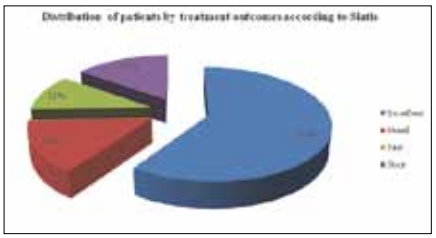


Diagram 3. Distribution of patients by treatment outcomes according to Slatis

The functional outcomes were evaluated using the D'Aubigne-Postel score for evaluating the post-treatment clinical outcomes minimum 18 months after the trauma. The outcomes were excellent in 22 patients (45%), good in 15 (31%), fair in 4 (9%) and poor in 6 (14%) (Table 5, Diagram 4).

Functional treatment outcomes according to D'Aubigne-Postel scale	No. of patients	
	F	%
Excellent	22	46.81
Good	15	31.91
Fair	4	8.51
Poor	6	12.77
Total	47	100.00

Table 5. Distribution of patients by functional treatment outcomes according to D'Aubigne-Postel scale

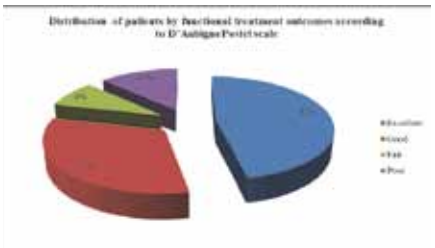


Diagram 4. Distribution of patients by functional treatment outcomes according to D'AubignePostel scale

The chi-square test shows that there is no significant statistical difference between treatment outcomes analysed using x-rays photographs and functional outcomes monitored using the D'Aubigne-Postel scale (p=0.097).

The bad outcomes in 6 patients were manifested in the inability to "close the pelvis", i.e. to close the "open book" with external fixator. The reason for the non-closure of the "open book" was pin tract infection in different degrees in 2 patients, and the loosening of pins due to their inadequate placing in 4 patients.

The surgical treatment efficiency coefficient was introduced in order to comparatively evaluate the treatment outcomes; K_{HL} was the coefficient of surgical treatment, P_{KL} was the observed parameter of conservative treatment, and P_{HL} was the observed parameter of surgical treatment (Table 6).

Table 6 shows that hospital treatment of patients who received conservative treatment amounted to 48 days and of surgically treated patients to 12 days. Independent mobilisation with axillary crutches, weight-bearing, amounted to 60 days in conserva-

Parameter	Conservative treatment	Surgical treatment	Surgical treatment efficiency coefficient in comparison with conservative treatment
No. of patients	26	21	-
Length of hospital stay (days)	48	12	4.00
First verticalisation (days)	49	3	16.33
Independent mobilisation with axillary crutches, weight-bearing within pain threshold (days)	60	10	6.00
Respiratory infections (patient)	11	1	11.00
Pulmonary embolism (patient)	5	3	1.67
Average recovery time (months)	14	9	1.56
Total treatment costs (KM)	KM 306 800	KM 98700	3.11
Average treatment costs per patient (KM)	KM 11800	KM 470 0	2.51

Table 6. Efficiency of surgical treatment compared with conservative treatment

tively treated patients and to 10 days post surgery in surgically treated patients. During hospital treatment, respiratory infections occurred in 11 patients treated conservatively and in 1 treated surgically, and pulmonary embolism occurred in 5 conservatively treated and 3 surgically treated patients. There were no patients with an infaust outcome caused by pulmonary embolism. The average recovery time for patients treated conservatively was 14 months, and for those treated surgically 9 months. As for the treatment costs, according to the Health Insurance Fund price list, the average cost of conservative treatment of pelvic ring fractures amounted to KM 11800 and to KM 4700 for surgical treatment. The efficiency coefficient of surgical treatment in comparison with the efficiency coefficient of conservative treatment shows that all given parameters were between 1.56 and 16.33 times lower for surgical treatment, the fact which speaks volumes itself.

5. DISCUSSION

A head-on collision at 45 km/h or a sideways collision at 25 km/h is enough to cause a pelvic fracture. Two thirds of these injuries are caused by traffic accidents, and mostly affect pedestrians and less often drivers or passengers (8). The mortality rate in closed pelvic fractures ranges between 10 and 20% and in open fractures it exceeds 50% (10, 11). In the studies based on the findings of autopsies of 200 patients hurt in traffic accidents, Moed *et al.* show that 45% of them died of the pelvic fractures they sustained (11,12). Pelvic fractures are the result of the effects of strong forces which transfer to the pelvis, abdomen, extremities, chest cavity, head, etc. Complications, combined injuries and relatively high mortality rate pose an additional problem (13-15). Pelvic fractures can be isolated (9-10 %) or combined in polytrauma (60 – 80%) (16). Solomon L.B. states in his series that out of 1479 pelvic fractures, 1029 were polytraumas, while brain injuries were present in 10% and urological trauma in 7% (17). Injuries to the lumbosacral plexus stand at about 3%, and the L5 nerve root, etc. is most frequently affected. Haematoma and swelling often result in reversible prolapses of the n. femoralis in combined fractures of long bones (7%) (18-20). Approximately 20% of pelvic ring fractures are hemodynamically unstable (20, 21). There were 30 such patients (63.8%) in our series of polytraumatised patients and 12 (25.5%) suffered craniocerebral injuries, 5 (10.6%) suffered chest cavity injuries, 13 (27.6%) suffered abdominal organ injuries. On admission to our institution, 27 patients (57.4%) had clinical and laboratory signs of haemorrhagic shock.

Multidisciplinary approaches to these polytraumas have resulted in the decrease of mortality rate, pain relief, they have made early mobilisation possible, reduced complications, shortened length of hospital stay (21, 22). Haemorrhage has remained the main cause of death in patients with pelvic disruption (23). Arterial haemorrhage may occur in 10-15% of patients with severe pelvic injuries, and only 7-11% require embolisation (24, 25).The second mortality peak occurs within the first hour and the reasons are as follows: epidural and subdural haematomas, chest cavity injuries, pelvic fractures, long-bone fractures, liver and spleen injuries (24). That is why in multiple injuries it is important, having surgically stabilised the patient's vital functions, to find the pelvic fracture in a timely manner and to treat it appropriately.

Screws, plates, and external fixators have in recent years been used in the treatment of unstable pelvic ring injuries, for the stabilisation of bone fragments. Early on, the Hoffmann trapezoid configuration was mostly commonly used for external fixation. Kallan uses external fixation in pelvic fractures for all Types B and with it he achieves and maintains repositioning in 83% of pelvic fractures, and for Tile's Type C1 fractures in 27%. In 1998, Tile presents his experiences with the treatment of 494 pelvic fractures. In this series he states that unstable fractures (Type C) in 92 injured patients (21%) were treated surgically with external fixators in 68 patients (13.76%) and with internal fixation in 24 patients (8.16%). (24) The external fixator is used to restore stability to the anterior pelvic arch, reposition and stability of the subluxated sacroiliac joint. This reposition and stabilisation of the pelvis reduces the mobility of the fracture surface and bleeding is stopped by swabbing, it eliminates pain, makes the treatment of related injuries easier, accelerates mobilisation and verticalisation of the patient. Internal fixation with screws and AO plates is used in Tile's Type C fractures. This stabilisation method results in anatomic repositioning, it prevents pseudoarthrosis and provides a satisfactory pain-free function (24).

In our series of patients, 19 patients (40.6%) suffered Type A pelvic fractures, 18 suffered Type B (38.1%), and 10 patients suffered Type C (21.3%). 26 patients (56.2%) were treated conservatively (Type A and certain patients with Type B1). 2 patients did not accept the proposed surgical treatment and were treated conservatively. 21 Type B patients (43.8%) were treated surgically, and we treated Type C patients with internal fixation, with AO plates and screws placed using an appropriate approach; 3 patients (6.3%)

Miranda mentions that in 218 examined patients who were conservatively treated for pelvic fractures (Types A, B, C), 60% of the patients suffered constant pain and 30% of the patients changed their line of work after the completed treatment (12). Lindahl on the other hand maintains that external fixators yield good results in Type B1 pelvic injuries, while in Tile's Type C injuries they do not maintain the stabilisation of the broken pelvis in approximately 35% of patients (14). 110 patients with unstable ring fixated by the Hoffmann fixator. Pseudoarthrosis complications occurred in 5%, pin tract infections in 24%, pin loosening in 2%, injuries to the femoral cutaneous nerve in 2 %, skin dehiscence in 3% (14). The use of external fixator in Type B and Type C open pelvic fractures enabled controlling this fracture and reduced potential infections (14, 15). Latenser and Gentilello in their series of 37 patients with unstable pelvic fractures treated conservatively and surgically come to a conclusion that the length of hospital stay was reduced by 37.8% in patients who underwent surgery. Physical therapy was not possible in 60% of the unoperated patients even 6 months after the injury, while that percentage amounted to only 15.7% in the operated group. Thus, they come to a conclusion that early surgical stabilisation of the pelvis shortens the length of hospital stay, reduces long-term disability and loss of blood, and results in a better survival rate (16, 17). In our series of patients, the efficiency coefficient for surgical treatment compared with conservative treatment showed that all evaluated parameters (length of hospital stay, first verticalisation, respiratory infections, pulmonary embolism, average recovery time, and treatment costs) were between 1.56 and 16.33 times lower for surgical treatment.

Inadequate pelvic fracture treatment results in late complications manifested by chronic pain, unequal leg length, and difficulty in walking accompanied by compensatory scoliosis, difficulty in sitting, heterotopic ossification and potential neurological prolapses (19, 23).

6. CONCLUSION

By analysing the success rate of pelvic ring injury treatment in our series of patients, we can conclude that conservative treatment is the treatment of choice for Tile's Type A fractures, external fixator for treating Type B fractures (including all subtypes and Type C1), and internal fixation, as monotherapy or in combination with external fixator, for treating Type C2 and Type C3 fractures. Surgical treatment allows faster mobilisation of the patient, it shortens the recovery period, which in turn lowers the total treatment costs as compared to non-surgical treatment.

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ORIGINAL PAPER

Aphasia Disorders Outcome After Stroke

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Introduction: Aphasia is considered to be the most difficult disorders of speech-language communication, and are often companion of all forms of cerebrovascular disease. **Goal:** To determine the outcome of aphasia disorder a year after a stroke and stroke type influence on the outcome of aphasia disorders. **Material and methods:** We analyze one-year outcome of aphasia disorders in patients who had a first stroke. Patients were tested by a speech pathologist with the International test for aphasia, immediately after admission and one year after the stroke. All patients that were hospitalized during treatment had a speech therapy and only a small number of released from hospital. **Results:** Of the 74 patients with aphasia who were discharged from hospital within one year 20 patients died and 2 patients had not responded to control clinical treatment review. Analysis of the remaining 52 respondents determined that from the 10 patients with global aphasia 8 (80%) evolved into another aphasia syndrome, and two (20%) remained unchanged in form. In most cases, global aphasia was transformed in mixed non fluent aphasia (4 of 10 patients or 40%), and in two cases (20%) global aphasia was transformed in Broca aphasia. Broca aphasia (n=20) in other forms evolved in 9 patients (45%), and 11 patients (55%) remained unchanged in form. Anomic aphasia had 11 patients (78.6%) which remained unchanged in form, while 3 (21.4%) evolved into an Alexia agraphia. Full recovery was noted in two patients (3.84%). Type of stroke did not affect the outcome of aphasia disorders. Of the 52 analyzed patients after hospitalization, unfortunately, only 11 (21.2%) had some kind of speech pathology treatment after leaving the hospital. **Conclusion:** After one year in patients with stroke in a significant number of severe cases of aphasia evolve into a lighter. Most often remained anomic aphasia (34.6%), followed by Broca (25%) and Conductive aphasia (7.7%). Type of stroke does not affect the outcome of aphasia disorders. Unfortunately only a small number of patients (21.2%) continued with aphasia speech therapy after leaving the hospital. Key words: aphasia, stroke, aphasia outcome, speech therapy.

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1. INTRODUCTION

Aphasia can be defined differently according to the general neurological and/or neuropsychological definition, aphasia is the loss or damage of linguistic communication that occurs as a consequence of brain dysfunction (1-2).

Treatment of aphasia involves activities of a multidisciplinary nature. The success of treatment depends on the knowledge of the clinical picture, localization of brain damage, etiology (hemorrhage, ischemia) and the remaining speech and cognitive abilities (3).

The rehabilitation process usually begins with the first contact of patients and speech therapists, and ends with the solving of the problem or when is no longer needed additional expert assistance (4). The rehabilitation not only include restoring speech and language function, but the whole personality, and if possible, also the environment in which the patient lives (5).

Speech therapy rehabilitation should begin immediately, or when the general condition of the patient permits it. In the treatment of aphasia speech therapists distinguish three phases. In the first stage or stages are used to stimulating or unblocking methods, in which a relatively intact ability to use for the reactivation of damaged language abilities. When the general condition of the patient is stabilized, aphasia syndrome can be classified, and introduce specific forms of treatment. Modalities in which the focus of treatment is obtained from the tests determine the remaining capacity. Specific period of treatment lasts from six months to a year. As treatment is more frequently applied, the results are better. There is also features in-patient intensive therapy, where patients are treated twice a day. Such intensive therapy can achieve a significant improvement of voice function (6).

Prognosis is made based on: diagnosis of conditions for development in the family and the speech therapist treatment (5). Early accurate prognosis enables: proper selection of patients for treatment, setting realistic rehabilitation goals, plan appropriate treatment, social, health and career planning, timely consultation and informing the family (7). Type of aphasia has a sig-

nificant impact on the course and outcome of partial establishment of voice function (3).

The prognosis is more favorable if the aphasia is posttraumatic or postoperative. If patient is younger, if they have preserved general cognitive ability, as well as the ability to retain information, with left hemisphere lesions, if the rehabilitation is done with the help of a written speech by left hand and if it is possible continuous logopedic work.

The prognosis is less favorable in case of: global aphasia, when the lesions caused a change in behavior and if are present logorrhea and perseveration (7).

In terms of prognosis, optimism is justified in case of conductive and anomic transcortical aphasia. Good prognosis has ipsilateral aphasia, which is attributed to atypical, often both hemispheres organization of speech, and therefore better ability to "hijack" the voice functions of the intact hemisphere. The same category also includes sub cortical aphasia (3).

2. RESEARCH GOALS

Research is made in order to determine the outcome of aphasia disorders one year after the stroke and analyze the impact of stroke type on outcome.

3. MATERIAL AND METHODS

We analyzed one-year outcome of aphasia disorders in patients who had a first stroke and were hospitalized at the Neurology Clinic, University Clinical Center Tuzla. All patients were tested by a speech therapist using the modified International test for aphasia, which is estimated by following modalities: naming the objects on the basis of different stimuli (visual, auditory, tactile), description the use of objects, the naming on the basis of tactile sensations, repeated one-syllable words, display of objects based on the naming by examiners, understanding of the demands, counting from 3-10, answer the questions: "what you eat", "what we write," "what you pay the goods," reading aloud the names of objects, and pointing to objects, writing the names of previously read objects, the transcription of these names and articulation (the naming of 30 phonemes with help). A year or more after the stroke and aphasia disorder patients were invited to review and control by clinical speech therapist have evaluated individually in the presence of a companion of the patient and one speech therapist.

All patients during hospitalization had a speech therapist treatment and only a small number after leaving the hospital.

3.1. Statistical data analysis

After completing the survey obtained data were processed by computer statistical program SPSS 8.0. Data presented are in absolute and relative frequencies. We calculate the basic parameters of descriptive statistics to determine the base characteristics of the subjects, such as the mean and dispersion measures, and to better understand the calculated mean values were used the suitable graphics.

Nominal or categorical variables were analyzed by chi-square test or Fisher exact test. To test the hypothesis about the difference (equality) or the relative proportions of participation, we used the method of testing hypotheses about the difference (equal) proportions of the two sets based on the results from the sample.

4. RESULTS

During the observed one-year period 882 patients with stroke was hospitalized. Based on the neurological and speech pathology findings we selected a total of 192 (21.76%) patients who are diagnosed aphasia. From a total of 74 patients with aphasia who were discharged from hospital within one year, 20 died, and two patients had not responded to control clinical review one year after the stroke.

During the hospital admission of 72 analyzed patients the most frequent was Broca aphasia (33.3%), followed by a global (29.2%) and anomic (20.8%). A year later during the repeated the control examination for a total of 52 patients examined the most frequent was anomic aphasia (34.6%), followed by Broca (25%), conductive, mixed non fluent and alexia with agraphia with the same frequency (7.7%). during the follow up the least was present Wernicke's aphasia (1.9%) and global aphasia (3.8%) and with the same frequency transcortical motor and sensory aphasia (χ^2=55.30, p <0.001) **(Table 1)**.

The analysis of 52 patients who were one year after the stroke tested again,

Aphasia type	During admission		During control	
	No. of patients	(%)	No. of patients	(%)
Global	21	29.2	2	3.8
Broca	24	33.3	13	25.0
Wernicke's	6	8.3	1	1.9
Anomic	15	20.8	18	34.6
Transcortical motor	2	2.8	2	3.8
Transcortical sensory	1	1.4	2	3.8
Transcortical mixed	1	1.4	-	-
Conductive	1	1.4	4	7.7
Thalamic aphasia	1	1.4	-	-
Complete recovery	-	-	2	3.8
Mixed non fluent	-	-	4	7.7
Alexia with agraphia	-	-	4	7.7
Total	72	100.0	52	100.0

Table 1. Types of aphasia immediately after a stroke and a year later

Aphasia type	Unchanged	evolved	Complete recovery	Total no. of patients
Global	2	8	/	10
Broca	11	9	/	20
Wernicke's	1	3	/	4
Anomic	11	3	/	14
Transcortical motor	/	1	1	2
Transcortical Mixed	/	1	/	1
Thalamic	/	/	1	1
Total	25	25	2	52

Table 2. Outcome aphasia disorder one year after stroke in comparison to the type of aphasia

			Aphasia disorders outcome			
Type of stroke	Unchanged		Evolved in other form		Total	
	N	%	N	%	N	%
Ischemia	23	48.9	24	51.1	47	100.0
Hemorrhage	2	40.0	3	60.0	5	100.0
Total	25	48.1	27	51.9	52	100.0

Table 3. Condition of patient during control review, depending on the cause

Type of stroke	Survived		Died		Total	
	N	%	N	%	N	%
Ischemia	47	73.44	17	26.56	64	100.0
Hemorrhage	5	62.50	3	37.50	8	100.0
Total	52	72.22	20	27.78	72	100.0

Table 4. Representation of lethal outcome in relation to the cause of aphasia

it was found that of 10 patients with global aphasia 8 (80%) evolved into another aphasia syndrome, and two (20%) remained unchanged (Table 2). In most cases, global aphasia was evolved in mixed non fluent aphasia (4 of 10 patients or 40%), and in two cases (20%) global aphasia evolved in Broca aphasia. Broca aphasia (n=20) evolved in other forms in case of 9 patients (45%), while in 11 (55%) remained unchanged. Anomic aphasia that was present in 11 patients (78.6%) remained unchanged in form, while in 3 (21.4%) cases evolved into an alexia with agraphia **(Table 2)**.

It is not determined that the type of stroke significantly affect the final outcome of the aphasia disorder in terms of evolution of the primary aphasia disorder during the primary test in some other form of aphasia **(Table 3)**.

From a total of 72 analyzed patients with first stroke and aphasia, 64 had an ischemic stroke, and of this number, 17 (26.56%) patients had a lethal outcome. In patients with hemorrhagic stroke for a total of 8, 3 (37.50%) had lethal outcome. The differences were not statistically significant **(Table 4)**.

5. DISCUSSION

In this study, from the total number of patients with aphasia (n=72) including patients who died after leaving the hospital was the majority of patients with ischemic stroke (88.9%).

Salihovic and colleagues in their study conducted during the 2006 and which included 3864 patients with first stroke indicate that ischemic stroke was diagnosed in 2833 (73.3%) of patients, intracerebral hemorrhage in 612 (15.8%), subarachnoid hemorrhage in 163 (4.2%) and stroke of unknown cause in 256 (6.6%) of patients (8). Sutovic and colleagues in their study analyzed 188 patients with aphasia and found that in 160 (85%) patients the cause of aphasia was an ischemic stroke and in 28 (15%) patients the cause of aphasia was intracerebral hemorrhage (9). Research conducted by Brkic in 2007 found that aphasia was diagnosed in 77.22% of patients with ischemic and 18.82% patients with hemorrhage stroke (10).

In relation to the type of aphasia syndrome in this study one year after the stroke was the most common anomic aphasia (34.6%) which were diagnosed in 18 subjects, followed by Broca aphasia (25.0%) which was present in 13 subjects, conductive (7.7%) in 4 subjects, and with the same frequency the mixed non fluent and alexia with agraphia. At least was presented Wernicke's aphasia (1.9%), which was diagnosed in one patient, followed by global aphasia (3.8%) which was diagnosed in 2 subjects and with the same frequency transcortical motor and transcortical sensory aphasia. A slightly lower incidence of these aphasia syndromes in this study can be interpreted by the fact that a significant number of subjects with global aphasia (52.4%) died after leaving the hospital. A number of respondents with the global (38.1%) and Wernicke's aphasia (50%) were under the influence of spontaneous recovery and/or speech pathology treatment recovered to the level of easier forms of aphasia. Also in this study were recorded the 2 cases (3.8%) of complete recovery from stroke. Death is the most common outcome of global aphasia (52.4%) and Wernicke's aphasia (33.3%) of the patients with the aforementioned type of aphasia. All patients from the sample in this study had speech therapy in the acute phase of illness during the stay at the Neurology Clinic in Tuzla.

Pedersen, Vinter, and Olsen have conducted a study on 270 patients with aphasia caused by stroke patients in three hospitals in Denmark. Assessment of speech and language abilities was performed in the acute stage and repeated the year after a stroke. Results in the acute phase showed that the global aphasia was represented with 32%, Broca with 12%, Wernicke's 16%, anomic with 25%, transcortical sensory with 7%, transcortical motor with 2%, 5% of conductive and isolated with 2 %. The same authors state that the type of aphasia is always changing to a less severe form during the first year. Non fluent aphasia could evolve into fluent aphasia (i.e., the Wernicke's and global Broca in anomic), while fluent aphasia could never develop into non fluent. One year after stroke was found the following frequency: global 7%, 13% Broca, transcortical motor 1%, Wernicke's 5%, 6% and conductive anomic 29% (11).

Godefroj and colleagues conducted a study on 207 patients with aphasia caused by stroke and came up with results that the global and unclassified aphasia amounted to 50% of aphasia syndrome in the acute phase, while Wernicke's, Broca, transcortical and sub cortical aphasia were less frequent (12).

Brust and colleagues conducted a study on 850 patients in the acute phase of which 177 (21%) patients had aphasia. The results showed that 9 patients had Broca aphasia, 24 patients had Wernicke's aphasia, 14 patients had anomic aphasia, 10 patients had conductive aphasia, 7 patients had "isolated" type of aphasia and 107 patients had "mixed type" aphasia (13).

Studies of other authors have found the incidence of aphasia disorders in the acute phase of stroke in 20.34% patients. In terms of frequency of aphasia syndromes the most common type of aphasia was a global (48.51%), followed Broca (23.26%), then followed by anomic (16.33%) and Wernicke's (8.41%), and

that transcortical sensory, transcortical motor and conductive aphasia syndromes are rare in the acute phase of stroke (10).

Upon discharge from the hospital, unfortunately only 11 patients (21.2%) were included in the speech therapy. From a total of 11 patients, 4 (36.4%) has evolved into another form aphasia disorder, and 7 (63.6%) had an unchanged form of aphasia as when leaving the hospital.

These differences were not statistically significant. However, it should be noted that these results do come from a relatively small number of respondents who were involved in speech therapy (21.2%) and some general conclusions should probably include a significantly larger number of subjects, gather information about the course and manner of speech pathology treatment, speed of the recovery, compare the test results for speech and language modalities and the degree of severity of aphasia between the subjects involved in speech therapy and those without, etc.

6. CONCLUSIONS

After a year in patients with stroke there are a significant number of severe cases of aphasia which evolve into a lighter. Most often remains anomic aphasia (34.6%), followed by Broca (25%) and conductive aphasia (7.7%). Type of stroke does not affect the outcome of aphasia disorders. Unfortunately only a small number of patients with aphasia (21.2%) continued speech therapy after leaving the hospital.

The results of the evaluation of speech treatment should remove doubts about the need for speech pathology treatment of aphasia, and indicate the necessity of treating these patients by speech and linguistic rehabilitators, both in the acute phase and after the hospitalization of the patient. In addition to professionals speech therapists should provide specific speech therapy, not only in hospitals but also in health centers and other rehabilitation centers.

Given such a small number of patients covered by the speech therapy is necessary in the teams involved in rehabilitation in the community to include speech therapists in order that patients with aphasia receive appropriate treatment after leaving the hospital.

In this regard, this research which is based on the prognosis is clearly a step forward in the field of aphasia research in general.

Experience gained in this study, as well as its results may serve as an impetus for further in depth research on the prognosis that could eventually lead to significant improvements in the treatment of patients with aphasia.

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ORIGINAL PAPER

The Role of Echocardiography in Diagnosis and Follow Up of Patients with Takotsubo Cardiomyopathy or Acute Ballooning Syndrome

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Background: The transient left ventricular apical ballooning syndrome, also known as takotsubo cardiomyopathy was first described in Japan approximately 20 years ago (Satoh and coworkers, 1991). It was later described elsewhere as well and is being increasingly recognized. Takotsubo Cardiomyopathy characterized by transient apical and midventricular LV dysfunction in the absence of significant coronary artery disease that is triggered by emotional or physical stress. Its name refers to a contraption used for catching octopuses and suggests the aspect assumed by the ventricle during the systole due to the typical regional wall motion abnormalities that occur after onset. Takotsubo cardiomiopathy occurring mainly in post-menopausal women, echocardiography in the Takotsubo cardiomyopathy reveals during its acute phase a ballooning resembling the octopus trap configuration–the apex and lateral ventricular segments are hypokinetic while the base is hyperkinetic - along with reduced ejection fraction. Ventricular function will usually recover within a few days/weeks. Objective and purpose: The objective of this study is to determine the role of echocardiography in detecting and establishing the diagnosis of Takotsubo cardiomiopathy in patients with suspect acute coronary syndrome and during the follow up period. Patients and methods: The study covered 12 adult patients the majority are women (92%) who were subjected to echocardiography evaluation as part of the clinical cardiological examination due to suspect acute coronary syndrome or Takotsubo Stress Cardiomyopathy. The patients were examined on an ultrasound machine Philips iE 33 xMatrix, ATL HDI and GE Vived 7 equipped with all cardiologic probes for adults and multi-plan TEE probes. We evaluated clinical characteristics, LV systolic function, biomarkers, and prognosis in all patients. Results: Among all the patients referred for Echocardiographic evaluation for left ventricle motion abnormalities with suspect acute coronary syndrome, the echo exam revealed 12 patients with acute apical ballooning which involving the left ventricular apex and med-ventricle. The triggering factors were physical stress in 4 patients (33%) and emotional stress in 8 patients (67%). The initial symptom was chest pain (n=8, 67%) rather than dyspnea (n=4, 33%). An initial electrocardiogram (EKG) presented ST-elevation (n=10, 83%) and T-wave inversion (n=2, 17%), other data are shown on Table 2. Among the all patients 8 of them (66%) had normal EF by the 1st follow up (47 ± 51 days), and the rest 4 patients (34%) had normal EF by 68 ± 96 days. Conclusion: Widespread uses of echocardiography has contributed to more frequent recognition of Takotsubo stress cardiomyopathy and highlight the central role of this noninvasive method from an echocardiographers' perspective.

Key words: Takotsubo Stress Cardiomyopathy, Echocardiography, Acute Ballooning Syndrome.

coorespind

1. INTRODUCTION

The transient left ventricular apical ballooning syndrome, also known as takotsubo cardiomyopathy, is a recently described novel acute cardiac syndrome.[1,2,3,4,5,7,8] The syndrome is characterized by peculiar, yet characteristic, transientregional systolic dysfunction involving the left ventricular apex and mid-ventricle with hyperkinesis of the basal left ventricular segments. **Takotsubo cardiomiopathy** was first described in Japan approximately 20 years ago (Satoh and coworkers, 1991). It was later described elsewhere as well and is being increasingly recognized. Takotsubo Cardiomyopathy characterized by transient apical and mid-ventricular LV dysfunction in the absence of significant coronary artery disease that is triggered by emotional or physical stress.

Its name refers to a contraption used for catching octopuses and suggests the aspect assumed by the ventricle during the systole due to the typical regional wall motion abnormalities that occur after onset. Since its first description, this condition has been increasingly recognized: many articles have been reported on this condition and are available on Medline/PubMed. However, certain reports identifying presumed "new" entities (such as apical ballooning syndrome, ampulla cardiomiopathy, broken heart syndrome) characterised by nearly the same clinical features of TC. Precise incidence is unknown, however up to 2.5% of all patients presenting with an initial clinically suspected acute coronary syndrome (ACS). [1 9,10,11,12,13,14,15,16,18,19,20]

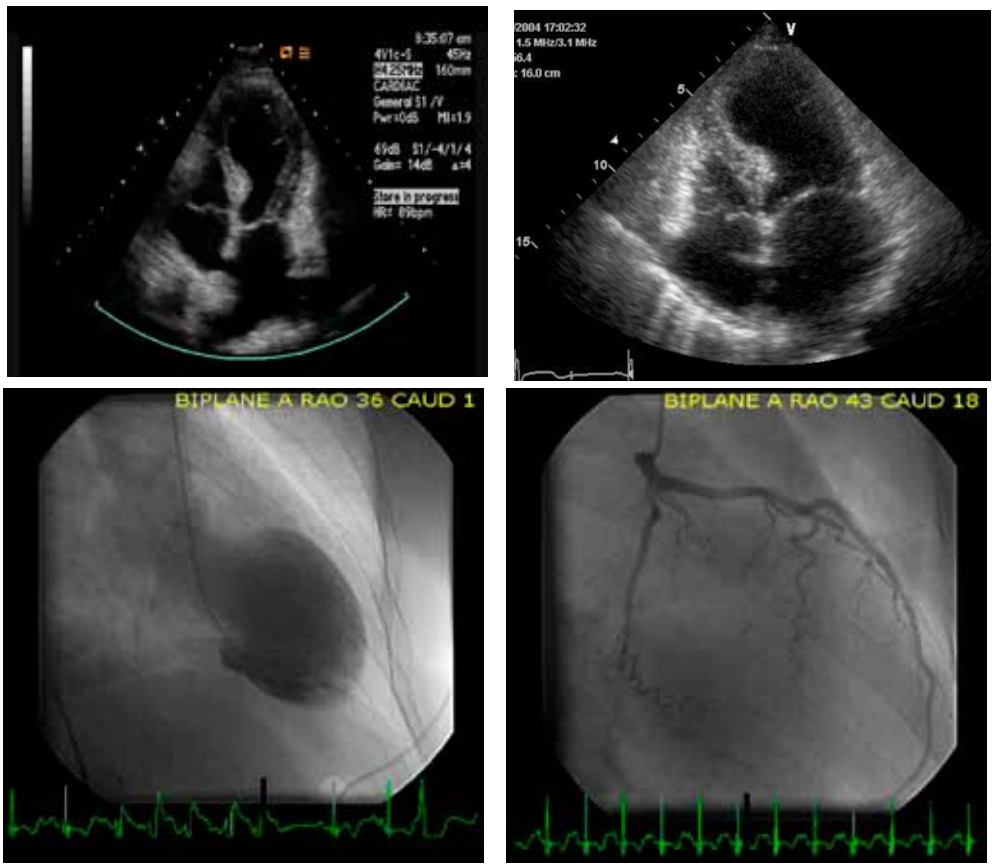

Fig. 1 and Fig. 2. The Echocardiographic finding of transient left ventricular apical ballooning syndrome involving the left ventricular apex and mid-ventricle in the absence of obstructive epicardial coronary disease.

2. RESEARCH OBJECTIVES

The objective of this study is to determine the role of echocardiography TTE and TEE in establishing the diagnosis of Takotsubo Cardiomiopathy or acute ballooning syndrome in patients with suspect acute coronary syndrome, by investigating the wall motion abnormalities of the left ventricle and identifying a transient left ventricular apical ballooning syndrome during the acute phase of symptoms as a part of clinical cardiological investigation. Also to reveal the importance of echocardiography in the follow up period in those patients. The evaluation of wall motion abnormalities of the left ventricle obtained by echocardiography (TTE and TEE) as a noninvasive diagnostic method. Also to determine whether echocardiography can be considered as a reliable diagnostic and follow up modality in detecting and assessing patients with suspect Takotsubo Cardiomiopathy or Acute Ballooning Syndrome. **Figure 1 and Figure 2.**

3. PATIENTS AND METHODS

The study includes 12 adult patients; the majorities are women, who were subjected to echocardiography as part of the clinical cardiological examination. The patients were examined on an ultrasound machine Philips iE 33 xMatrix, ATL HDI and GE Vived 7 equipped with all cardiologic probes for adults and multi-plan TEE probes. The evaluation of wall motion abnormalities of the all left ventricle 17 segments were obtained by echocardiography (TTE and TEE) as a noninvasive diagnostic method in order to establish the diagnosis of Takotsubo cardiomyopathy. In establishing the diagnosis of Takotsubo cardiomyopathy the criteria of Mayo Clinic were used. **Table No. 1**

Proposed Mayo Criteria for the Clinical Diagnosis of the Transient Left Ventricular Apical Ballooning Syndrome:

- Transient akinesis or dyskinesis of the left ventricular apical and mid-ventricular segments with regional wall-motion abnormalities extending beyond a single epicardial vascular distribution.
- Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
- New electrocardiographic abnormalities (either ST-segment elevation or T-wave inversion).
- Absence of Recent significant head trauma, Intracranial bleeding, Pheochromocytoma, Obstructive epicardial coronary artery disease, Myocarditis, Hypertrophic cardiomyopathy.

4. RESULTS

Among all the patients referred for Echocardiographic evaluation for left ventricle motion abnormalities with suspect acute coronary syndrome, the echo exam revealed 12 patients with acute apical ballooning which involving the left ventricular apex and med-ventricle in absence of obstructive epicardial coronary artery disease. According to Mayo clinic criteria those patients has Takotsubo cardiomyopathy–Acute Apical Ballooning Syndrome. The triggering factors were physical stress in 4 patients (33%) and emotional stress in 8 patients (67%). The initial symptom was chest pain (n=8, 67%) rather than dyspnea (n=4, 33%). An initial electrocardiogram (EKG) presented ST-elevation (n=10, 83%) and T-wave inversion (n=2, 17%), other data are shown on

Table 2. Takotsubo cardiomiopathy is difficult to distinguish from acute coronary syndrome on first presentation. The syndrome more often affects postmenopausal women (92%) (mean age 66 years). The blood lab. findings shows relativly milde elevation of cardiac enzyme and biomarkers levels. Among the all patients 8 of them (66%) had normal EF by the 1st follow up (47 ± 51 days), and the rest 4 patients (34%) had normal EF by 68 ± 96 days.

Age, y†	66
Women, %	92
Chest pain, %	67
ST-segment elevation, %	83
ST- segment elevation in precordial leads, %	83
Elevation of cardiac enzyme levels, %	88
Pathological Q wave, %	34
Mean QTc, ms	500
Initial average LVEF†	0.46 ± 0.10
Follow up LVEF†	0.61 ± 0.10
Heart failure or pulmonary edema, %	1
Coronary stenosis > 50%, %	0
Spontaneous multivessel spasm, %	0
Preceding emotional stressor, %	67
Preceding physiological stressor, %	33
In-hospital mortality, %	0
Documented full recovery, n/n %	12/12 (100)
Documented recurrence, n/n %	0

Table 1. Demographic, Clinical characteristics and Echocardiographic data

5. DISCUSSION

Takotsubo cardiomyopathy, also called stress-induced cardiomyopathy, apical ballooning syndrome, or broken heart syndrome, is a transient systolic dysfunction of the ventricles in the absence of significant coronary artery disease. Since its first description in Japan (Satoh and coworkers, 1991), this syndrome has been increasingly recognized and many articles have been reported on this condition and are available on PubMed and EMBASE data bases. The clinical presentation of patients ultimately diagnosed with Takotsubo cardiomyopathy is usually indistinguishable from that of acute coronary syndrome. The etiology of takotsubo cardiomyopathy remains uncertain and it is likely that multiple factors are involved. Although pathophysiology remains unclear, suspicion of catecholamine mediated myocardial stunning is highly favored as myocardial function returns to normal within days to a few weeks. The diagnosis of Takotsubo cardiomyopathy is confirmed by presence of all four Mayo Clinic diagnostic criteria mentioned in Table 1. The most authors of the published studies ***Sharkey et al., Akashi et al., Bybee et al., Kawai et al., Abe et al., Desmet et al., Kurisu et al., Tsuchihashi et al., Inoue et al., Ibanz et al., Ito et al., Igora et al., Matsuoka et al***., are almost sharing the following findings: the prevalence of Takotsubo cardiomyopathy is estimated to range between 0.7 to 2.5%. Female postmenopausal predominance is 90.7%. The mean age of 62 to 76 years. The ECG finding present ST-segment elevation in the precordial leads with chest pain. The lab. Findings shows relativly minor or milde elevation of cardiac enzyme and biomarkers levels. In all patients an episode of of emotinal or physiologic stress frequently perceds presentation with the syndrome The Hospital mortality rates range from 0–8% and are lower than for myocardial infarction as the risk for recurrence episodes, ***Sharkey et al.*** reports 5% of patients had recurrence of Takotsubo Cardiomiopathy within 4.4 years of initial event. Long-term survival is similar to an age-matched and gender-matched population. ***Regnante et al.*** observed a trend in the time of year when Takotsubo cardiomyopathy was most often diagnosed. The pathogenesis of the Takotsubo cardiomyopathy is still unknown. Many explanations have been proposed including multi-vessel coronary vasospasm, abnormalities in coronary microvascular function and catecholamine mediated cardio-toxicity provoked by emotional or physical stress. ***Bybee et al.*** reported on patterns of abnormal coronary flow in the absence of obstructive coronary artery disease in patients with stress-related myocardial dysfunction. ***Wittstein et al.*** noted multi-vessel coronary vasospasm on cardiac catheterization in 70% of Takotsubo cardiomyopathy patients. ***Sharkey et al.*** could not explain diffuse wall motion abnormalities by vasospasm of any single coronary artery. Catecholaminergic or adrenoceptor-hyperactive cardiomyopathy may be the cause of this cardiomyopathy. In all, management of Takotsubo Cardiomiopathy is primarily empirical and needs to be individualized for each patient.

6. CONCLUSION

Takotsubo cardiomyopathy is an important entity to be recognized. Differential diagnosis should be considered among postmenopausal women presenting with characteristic signs and symptoms of an acute coronary syndrome after an emotional or physical stressor. Many explanations have been proposed including multi-vessel coronary vasospasm, abnormalities in coronary microvascular function and catecholamine mediated cardio-toxicity provoked by emotional or physical stress but the cause of the syndrome is not yet known. ST-segment changes and cardiac biomarker elevations may or may not be evident. Despite the absence of obstructive epicardial coronary artery disease, clinical presentation in patients with the syndrome is similar to that of patients with ST-segment elevation myocardial infarction. Coronary angiography typically reveals no significant coronary lesions to account for the marked left ventricular wall motion abnormalities. The left ventricular apical ballooning is transient and the majority of patient myocardial function returns to normal within days to a few weeks. Patients with the syndrome seem to have a favorable inhospital prognosis despite the development of acute leftsided heart failure and hemodynamic instability. A large systematic review found patients with TCM tend to have a lower incidence of traditional cardiac risk factors, such as hypertension, hyperlipidemia, diabetes, smoking, or positive family history for cardiovascular disease. Treatment is aimed at supportive measures including reducing anxiety, alleviating pain, maintaining heart contractility, monitoring fluid balance, and preventing and treating complications. Medical management mainly consists of symptomatic therapy with aspirin, ACE inhibitors, beta-blockers, and diuretics. With supportive care, prognosis is favorable. Cli-

nicians should consider this syndrome in the differential diagnosis of patients presenting with chest pain, especially in post-menopausal women with a recent history of emotional or physical stress. Widespread use of echocardiography has contributed to more frequent recognition of Takotsubo stress cardiomiopathy and highlights the central role of this noninvasive method from an echocardiographers' perspective.

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ORIGINAL PAPER

Quality of Life of Patients Suffering from Parkinson's Disease and Multiple Sclerosis

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Introduction: Multiple sclerosis (MS) and Parkinson's disease (PD) as a chronic disease with unpredictable course, progressive physical disability and cognitive decline broadly affect the patient's life, social interaction, recreational activities and overall life satisfaction. **Goals:** To examine the quality of life of patients with Parkinson's disease and multiple sclerosis, and investigate the existence of differences between the degree of impairment to the quality of life in Parkinson's disease and multiple sclerosis. Methods: A prospective study was made at the Neurology Clinic, University Clinical Center in Tuzla in the period from December 2005 until May 2007. The study included subjects with definite diagnosis of MS and PD. We analyzed 50 patients with PD and 50 patients with MS, with disease duration 1-5 years without cognitive impairment or with low cognitive impairment. Assessment of quality of life was performed by SF-36 scale, which has 36 questions in eight health profiles. **Results:** By consecutive selection of patients with PB is roughly equally represented both sexes, while a group of patients with MS over-represented women. The average age of the PD was 63.18±10.42, and in patients with MS 37.4±8.65 years. In our study the relative influence of PD and MS on quality of life was similar after controlling the duration of the disease, and there were some differences in relation to the degree of clinical disability. Subjects showed the impairment to the quality of life independently of the duration of illness (patients with PD in 88% of cases, and multiple sclerosis in 84% of cases). There are significant differences in the occurrence of poor quality of life in patients with PD in advanced clinical stages of disease for the physical, mental dimension of the SF 36 and the total score. Respondents in stages III-V of the disease were 5.23 times (23%) more likely for poorer quality of life compared to those with less physical disability. In subjects suffering from MS was found that the appearance of poor quality of life does not depend neither on the degree of clinical disability in physical, nor the mental dimension of the SF 36 and the total score. For this result related to MS is influenced in part by a small sample, on the other hand it is possible that patients with MS, although they have greater physical disability seen as a very difficult diagnosis to seal the entire life. **Conclusions:** Patients who are treated due to PD and MS have a high degree (>80%) impairment to the overall quality of life without significant differences in the extent of this impairment between these groups of patients. Poorer quality of life for patients suffering from PD in severe stages of the disease, and the quality of life does not depend on the degree of clinical disability in MS patients. In both groups of patients the appearance of poorer quality of life does not depend on the duration of the disease. Keywords: Quality of life, Parkinson's disease, multiple sclerosis.

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1. INTRODUCTION

Quality of Life (QOL) is the basic paradigm of modern medicine and becomes a relevant measure of clinical practice (1). Assessment of quality of life can be useful to describe the severity of the disease, to monitor treatment and evaluate the effect of new therapeutic procedures. World Health Organization (WHO) gave the following definition of quality of life: "quality of life is the individual's perception of the patient's position in life, in terms of cultural and value system in which they live and in relation to their goals, expectations, standards and the occupations" (2).

Multiple sclerosis (MS) is a chronic inflammatory, non communicable, progressive multifocal demyelinating autoimmune disease of the central nervous system (CNS) (the white mass of the brain and spinal cord), which may manifest by various neurological symptoms. It is the most common disease of the CNS which leads to disability in young people in the developed world, and our country. Predominantly affects young adults in the most productive age, between 20 and 40 years, and rarely under 15 and above 60 years (3).

Parkinsonism is a clinical syndrome that is characterized by tremor, akinesis/bradykinesis, rigidity and disorder of postural reflexes. This syndrome can be caused by various conditions, and Parkinson's disease (PD) is an idiopathic entity of this syndrome (4).

2. GOALS

To examine the quality of life of patients with Parkinson's disease and multiple sclerosis, and investigate the existence of differences between the degree of impairment to the quality of life in Parkinson's disease and multiple sclerosis.

3. PATIENTS AND METHODS

The study was prospective in character and conducted at the Neurology Clinic, University Clinical Center (UCC) Tuzla in the period from December 2005 until May 2007. The study involved subjects with a definitive diagnosis of PD that satisfy current criteria for the diagnosis of PD (clinical criteria for Ransmayr) and MS (revised McDonald criteria) (5,6). We analyzed 50 patients with PD and 50 patients with MS with disease duration from 1-5 years.

Clinical assessment instruments were:

- Hoehn and Yehr scale ratio of Parkinson's disease (7);
- Extended score of disability degree in patients with multiple sclerosis (EDSS) (8);
- Scale of quality of life (SF-36 modern health survey) (9)
- Mini Mental Status (MMSE) (10).

Hoehn and Year ratio of the Parkinson's disease divides disease into five phases. In the first phase, the symptoms are mild, single until phase five when they are severe, double-sided, and when the patient requires constant care of another person. Subjects were divided into two groups: the first group of subjects in phase I and II disease, while another group of respondents were classified in the III, IV and V stages of the disease.

Extended score for assessment of the disability degree quantify disorder of individual functional systems (pyramidal system, cerebellum, brain stem, sensibility, intestine and urinary bladder, visual system, the cerebral functions and other functions). Based on the functional state of the system the degree of disability is made–EDSS (range of scores from the 0.0-normal neurologic findings, a maximum score of 10-death). According to the EDSS the subjects were divided into two groups: one group of subjects with EDSS 0-5.0 and the second group of subjects with EDSS 5.5-10.

SF-36 scale consists of 36 questions which were divided into eight areas (physical function, limitations of physical function, bodily pain, social functioning, general mental health, emotional limitations, vitality and fatigue, general feeling of health). These eight areas are united into two overall dimensions of quality of life and into physical dimensions and the dimensions of mental health and then the total SF-36 scores. The total score is calculated by a computer program (SF-36.EXE) and ranges from 000-100 (up to 25-poor quality; 26-50 medium quality; 51-75 moderately good and over 75-excellent quality of life) (11). During the processing of data was observed physical health, mental health, and total SF-36 scores. According to the SF-36 score the subjects were divided into two groups: subjects with poor and moderately poor score (score of 00-50) and respondents with an average good and excellent single (51-100).

The subjects were free of cognitive impairment or low cognitive impairment as assessed with the MMSE.

In analyzing the data obtained were used standard statistical parameters: mean, standard T-test and chi-square test (X^2-test) to determine the significance of the difference, Fisher's exact test, a computer program SF-36.EXE, odds ratio. The value of $p < 0.05$ was considered as significant.

The study was conducted with the approval of the Commission's Ethics Committee of the UCC Tuzla.

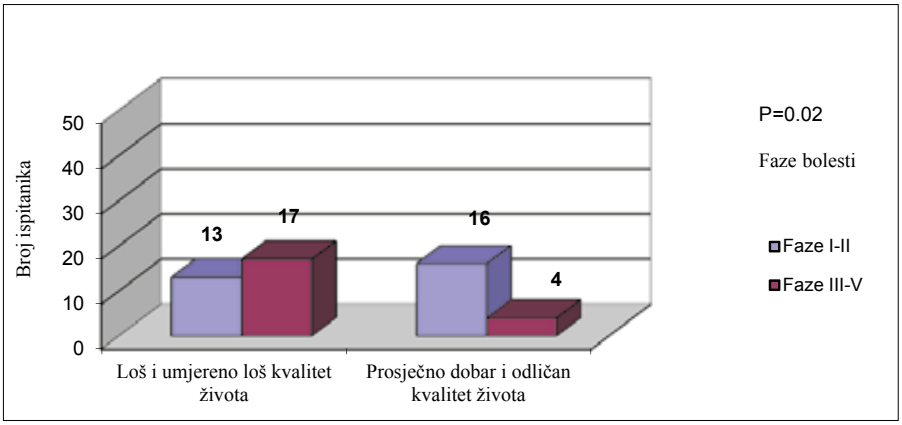

Figure 1. Distribution of patients with Parkinson's disease, according to the overall quality of life and the stages of the disease.

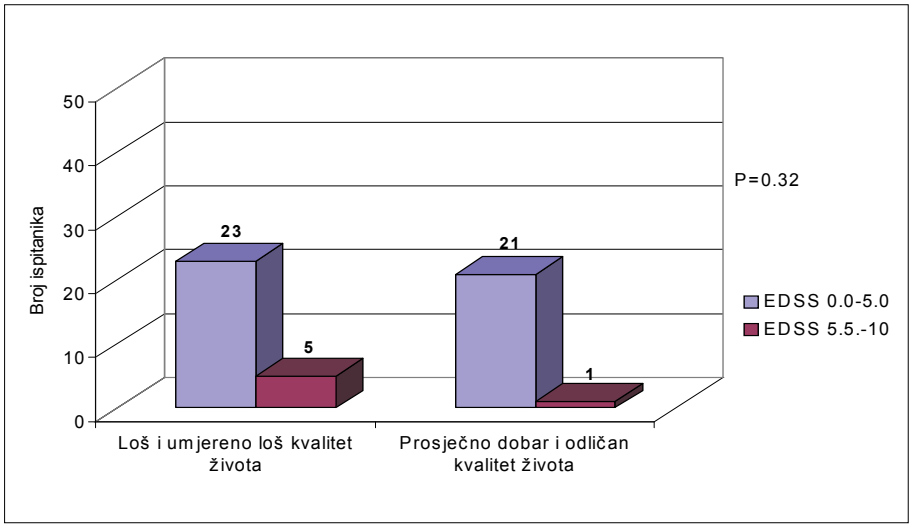

Figure 2. Distribution of patients with multiple sclerosis according to the overall quality of life and the degree of disability.

4. RESULTS

By consecutive selection of patients with PD (50 patients) 54% are women and 46% men. The average life expectancy was 63.18±10:42 years. In the group of MS patients consecutively selected women were 80% and 20% of men. The average age was 37.4±8.65 years. There was a statistically significant difference in average age between patients with MS and PD ($t=13.5$, $p<0.0001$).

In the first group of subjects (disease duration 1-3 years) was 68% patients with

Figure 3. Distribution of quality of life of patients with Parkinson's disease and multiple sclerosis measured by the SF-36 score

PD and 64% of patients with MS, while in the second group (disease duration of 4-5 years) was 32% patients with PD and 36% of patients with MS. It was found that in the first group of subjects with PD (stages I and II disease) was 58%, while the second group (stage III-V disease) 42% of respondents. In the first group of subjects with MS (EDSS score of 0-5.0) was 88%, while the second group (EDSS score 5.5-10) 12% of respondents.

In the group of patients with PD 88% of them had impaired the overall quality of life, while 12% had an excellent quality of life. The most common age group 60-69 years (44%) had the greatest impairment to the overall quality of life. There was no statistically significant difference in the occurrence of poor quality of life in relation to duration of disease (p=1.0). The emergence of the poor quality of life significantly different in the first (phase I-II) and the second group (stages III-V) (p=0.02). The chance for occurrence of poor SF-36 score was 5.2 times higher in subjects in whom the disease is in stage III-V (Figure 1).

Total SF-36 scores, as an indicator of quality of life was reduced in 84% of persons with MS, while 16% of them had an excellent quality of life. The age group of patients with MS from 30-39 years had the highest (62%) impairment to the overall quality of life. There was no statistically significant difference in the occurrence of poor quality of life in relation to the degree of clinical disability (p=0.3) (Figure 2).

Calculating the odds ratio we obtained results that the poor and moderately poor SF-36 scores are 4.5 times more frequent in the group of patients with EDSS 5.5-10. The quality of life by SF-36 score was impaired regardless of the duration of the disease in patients with MS (p=0.1). Low and moderately low SF-36 score was 3.3 times more frequent in the group where the disease lasts longer (4-5 years).

Quality of life of people with MS and PD as measured by SF-36 scale showed impairment in all eight domains: physical function, physical limitations, physical pain, general health, vitality, social function, emotional limitations and mental health. Patients with PD and MS had a similar profile in terms of viability (42 and 40 points), limitations in the emotional category (51 and 49 points) and mental health (48 and 51 points). Patients with multiple sclerosis had a better score for physical function, physical limitations, general health and social function (for each subscale difference of 8 points), and subjects with PD had a better score for physical pain (difference of 7 points) (Figure 3).

There was no statistically significant difference in the degree of the quality of life impairment in relation to physical and mental functioning of the overall SF-36 scores in these two neurodegenerative diseases (p=0.8).

5. DISCUSSION

When comparing the quality of life of people with MS and PD was found that the impairment of the quality of life was approximately the same in both groups of respondents (88% of respondents with PD and 84% of those with MS have impaired quality of life). In the study by Riaz and associates (12) the relative impact of PD and MS on quality of life was similar after controlling the duration of illness and other demographic variables. In this study the relative influence of PD and MS on quality of life was similar after controlling the duration of the disease, and there were some differences in relation to the degree of clinical disability. Respondents suffering from PD showed impairment to the quality of life independently of the duration of the disease while there was no significant difference in the occurrence of poor quality of life in patients with clinical advanced stage of disease for physical, mental dimension and the total SF 36 scores ($p<0.05$). In subjects suffering from MS was found that the appearance of poor quality of life does not depend on the length of the disease, nor on the degree of clinical disability in physical, mental dimension and the total SF 36 scores ($p>0.05$). This result related to MS is influenced in part by a small sample, on the other hand it is possible that patients with MS, although they have greater physical disability seen as a very difficult diagnosis to seal the entire life.

These results were confirmed in a study by D'Alisa and associates (13) which show that in patients with MS quality of life is determined by personal disposition, regardless of neurologic or functional disability.

On the other hand, according to Leger and associates (14) acceptance of illness (disability) plays an important role in psychological distress in people with physical disabilities. This study further found that the two groups had similar disease profile in terms of viability (42 and 40 points) and limitations in the emotional category (51 and 49 points) and mental health (48 and 51 points). Patients with MS had a better score for physical function, physical limitations, general health and social function (for each subscale difference of 8 points for all comparisons) ($p>0.05$), while respondents with PD had better scores for bodily pain (dif-

ference 7 points) (p>0.05).

Study by Riaz and associates (12) shows that two groups had similar disease profile in terms of physical constraints (19:18 points), bodily pain (54 and 56 points), general health (43 and 43 points), vitality (34 and 35 points) and social function (49 and 51 points) (p>0.05 for all comparisons). In this study, patients with MS had lower scores for physical function (difference of 11 points, p<0.05). The biggest difference between the two groups was in terms of limited-emotional category, where the group with multiple sclerosis had significantly better scores than the PD group (difference 18 points, p<0.005). Patients with MS and PD had similar health profiles in six of eight areas, but the score in those with MS was lower in terms of physical function and better score in the field of mental health, which could be explained to the subjects with MS, adjust psychological demands of illness (12).

In our study, subjects suffering from PD have poorer SF-36 scores for all areas except for physical pain which is consistent with the results of the study by Schrage and associates (15). Patients with PD and MS have similar health profiles in all eight areas (no significant differences in the profiles), but slightly lower scores in those with a PD in terms of physical function, physical limitations, general health, social function and mental health, a better in terms of bodily pain and slightly better in terms of vitality and emotional limitations.

Although we did not find statistically significant difference in the degree of the quality of life impairment observed among groups of respondents, however it can be concluded that the poorer quality of life in patients with MS. Onset of disease in MS patients was significantly earlier than the beginning of the PD. Age group 30-39 years was most often in people with MS as the most productive part of society, compared to affected by PD, where most present respondents aged 60-69 years, when because of age, regardless of disease specific dimensions the quality of life is certainly impaired.

Shortcomings of our study are small sample size and the need to monitor the quality of life for an extended period of time when we would probably get more precise data on the impairment to the individual dimensions of quality of life. The contribution of the study is that for the first time in our conditions is given importance to evaluation the quality of life in order to identify and reveal areas where the disease affects that are not apparent by clinical examination.

6. CONCLUSION

Patients who are treated due to the PD and MS have a high degree (>80%) of impairment in the overall quality of life without significant differences in the degree of this impairment between these groups of patients.

Poorer quality of life has patients suffering from PD in severe stages of the disease, and the quality of life does not depend on the degree of clinical disability in MS patients.

In both groups of patients the appearance of poorer quality of life does not depend on the duration of the disease.

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ORIGINAL PAPER

Etiological and Clinical Characteristics of Lymphadenopathy at Child Age in Tuzla Canton

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Lymphadenopathy is defined as an abnormality in the size or character of lymph nodes, is caused by the invasion or propagation of either inflammatory cells or neoplastic cells into the node. Numerous factors, such as age, localization, size and consistency, present and previous pathological conditions are very important in order to define the future diagnostic and therapeutic course. **Objective:** The aim of this study was to determine the etiological and clinical characteristics of lymphadenopathy in children in the area of the Tuzla Canton. **Patients and Methods:** This retrospective–prospective study analyzed the medical records of the Department of Pediatrics in Tuzla of 334 patients in age from 0 to14 years, in which the clinical signs of palpable lymph nodes of one or more regions was diagnosed in the period from January 1st 1998 to June 30th 2003. The anamnesis data, clinical findings, diagnostic procedures results, therapeutic approach and disease outcome etiology defined lymphadenopathy were analyzed. **Results:** Out of 334 children, localized lymphadenopathy have been verified in 230, and generalized in 104. Male/female ratio was 1:1.8. Final results of our study have shown the etiologies as following: Infectious etiologies, 79.34%, neoplastic 11.34%, and non-neoplastic 9.28%. In neoplastic etiologies, lymphoblastic leukemia has been the most often verified neoplastic disease (68.4%), not related to the age or sex of patient, and equally presented as localized and generalized lymphadenopathy. In this study lymphomas were presented by generalized lymphadenopathy. **Conclusion:** The regional and generalized lymphadenopathy in children depends on their etiology and has significant prognostic value for the disease. KEY WORDS: LYMPHADENOPATHY, ETIOLOGY, CHILDHOOD

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1. INTRODUCTION

Lymphadenopathy is a common diagnostic and therapeutic problem in pediatrics (1). Almost all children develop lymphadenopathy at least once during childhood, usually in response to various infections (2). Localized lymphadenopathy is most commonly caused by an infectious agent, and generalized forms are often part of the diagnostic-therapeutic and prognostic unfavorable conditions (3). Distribution of the enlarged lymph nodes compared with characteristics depending on the anatomical localization and age-related reference values, it can often give basic guidelines for the establishment of differential diagnosis and determining the etiological causes (4). The etiology of increased lymph nodes may have clinical and diagnostic significance. Because of the wide spectrum of causes of lymphadenopathy is easier and more acceptable to discuss them within the categorization of lymphadenopathy, or discuss the causes of generalized and regional lymphadenopathy. Generalized lymphadenopathy is defined as an increase of more than 2 groups of interrelated groups of lymph nodes (5). In the literature there is very little data on the incidence of lymphadenopathy in children and is generally considered part of certain pathological conditions or within individual etiologic factors.

The clinical picture of lymphadenopathy is neither unique nor simple. Depends, above all, the etiological factors and age of the patient. According to the agent and the appearance of involved lymph nodes symptoms and clinical findings could be divided into several categories according to the local and general symptoms and signs. Due to the width of etiological agents, symptomatology in children is almost individual.

The study was undertaken in order to determine the etiology of diagnosed lymphadenopathy in relation to age and sex, and distribution of regional and generalized lymphadenopathy in relation to the etiology and the time period examined.

2. PATIENTS AND METHODS

The retrospect–prospective study included children of both sexes, aged 0-14 years, in which there were clinical signs of palpable lymph nodes of one or more regions, which were hospitalized

in the Clinic for child diseases in Tuzla in the period from January 1st 1998 to June 30th 2003. Total number of respondents was the 334.

From the medical records were analyzed anamnesis data (personal and family history), clinical findings, laboratory tests (ESR, complete blood count, transaminases, copper, and beta2mikroglobulin), microbiological tests (swabs of throat and nose), serological analysis of the Ebstein Barr virus (EBV) and cytomegalovirus (CMV), radiological examination of the thorax, ultrasound of the neck and abdomen, and cytological and histopathological tests results.

3. STATISTICAL ANALYSIS

In the statistical analysis of data obtained were used the standard descriptive measures, and measures of central tendency (mean), absolute measures of dispersion (variance and standard deviation). To test the statistical hypothesis, we used one-way tests. When testing a hypothesis based on one sample, we used z-test for testing hypotheses about the proportion of the basic set. When testing a hypothesis based on two samples, we used z-test for testing hypotheses about the different proportions of two sets.

4. RESULTS

From a total of 334 children, 116 (34.73%) were girls and 218 (65.27%) boys. The ratio of girls and boys was 1:1.8. In relation to the total number of treated children, we found that lymphadenopathy was significantly more often diagnosed in boys than girls. The average age of the children studied was 6.72 years (δ±4.02) and 7.03 (δ± 3.93) year for girls and 6.56 (δ± 4:05) G. for boys.

Regardless of gender, in relation to age, lymphadenopathy in children have only partly similar curve trends and impressions, which shows that the age of 2 to 4 years in both sexes is an important risk period with nearly identical intensity and dynamic of reporting. After that age, age 80-10 year and 11 to 14 years in girls represents another significant spike in verified lymphadenopathy. Whatever the cause, boys have slightly larger fluctuations and a substantial rise in verified lymphadenopathy occurrence only in the prepubescent age (Figure 1).

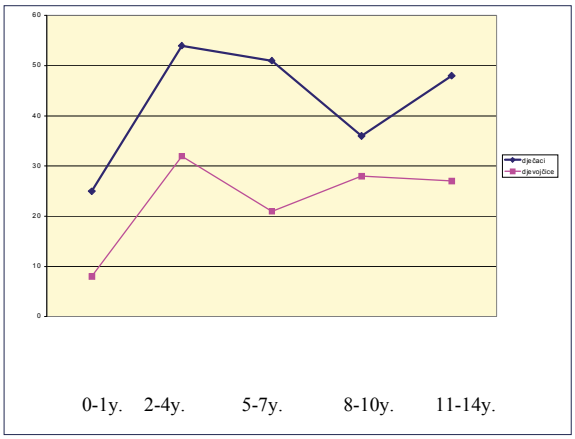

Figure 1. Distribution of lymphadenopathy in relation to age

In 230 (68.86%) cases there was regional, and in 104 (31.14%) generalized lymphadenopathy and statistics showed that lymphadenopathy in our study was significantly more likely to manifest as a regionally in relation to the generalized ($Z = 6.91 > Z\alpha = 0.05 = 1.64$).

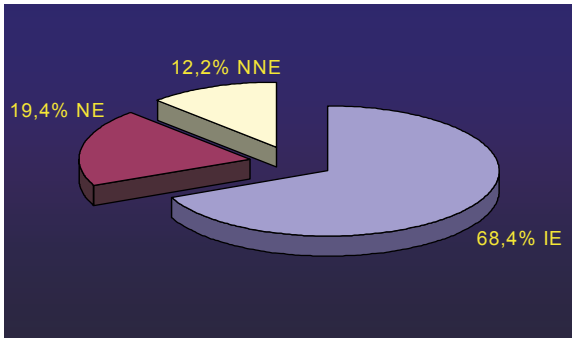

Figure 2. The etiology of generalized lymphadenopathy

Infectious etiology (IE) is the dominant cause of lymphadenopathy in children in our study. Infectious diseases as a cause of lymph nodes enlargement in children with continuing significant presence in all the years of analyzed period, show a marked spike in 2000 which was followed by a linear decline in frequency. The overall representation of infectious agents are highly significant factor ($Z = 10.693 > Z\alpha = 0.01 = 2.33$) in the occurrence of lymphadenopathy in children. Neoplastic diseases of children ages have a uniform appearance of the dynamics, while factors non neoplastic etiology with two spikes in 2001 and the first six months of 2003 account for more than 67% of verified cases.

Within regional lymphadenopathy, as well as the overall representation, an infectious etiology with the 198 (84.08%), makes a significant factor in the development of lymphadenopathy, followed by less frequent, neoplastic etiology with 19 (8%) and non neoplastic etiology with 19 (8%) cases. In the infectious etiology of regional lymphadenopathy bacteria are significantly more common cause in relation to viruses and parasites, with very high significance level ($Z = 4.986 > Z\alpha = 0.01 = 2.33$). Significantly, there is still high share of Mycobacterium tuberculosis (29.85%) in the etiology of infection and parasites, Toxoplasma gondii is the sole cause of verified regional lymphadenopathy.

Region	1998	1999	2000	2001	2002	2003
Cervical	9	18	16	9	8	5
Mediastinum	5	14	10	5	5	-
Supra clavicular	-	-	1	-	-	-
Axillary	5	1	3	4	2	2
Inguinal	5	4	8	2	2	4

Table 1. Representation of certain regions of generalized lymphadenopathy of infectious etiology in the examined period

The regional lymphadenopathy infectious etiology cervical lymph nodes are a series of mostly the affected region, followed by mediastinal, axillary and inguinal regions.

By analyzing the neoplastic etiology of regional lymphadenopathy, we found that most verified malignant disease of children ages regardless of gender and age is lymphoblast acute leukemia, while other malignancies have relatively uniform incidence of neoplastic processes that manifest by regional lymphadenopathy in children at our Canton over 90% of cases lead to the increase of cervical lymph nodes.

Non neoplastic etiology presented a mixed picture of different conditions that directly–or indirectly by spreading disease–a reactive response, leading to

enlargement of lymph nodes. Largely verified, etiologic non neoplastic state, the result of reactive changes in lymph nodes, such as sinus histiocitosis, cysts, non-specific granulation, situations after the vaccine...

In generalized lymphadenopathy infectious etiology was significantly more often represented with 68.4% (Figure 2). As in the regional and generalized lymphadenopathy in the etiology of infection is usually represented by a bacterial etiology with 67.16%, followed by the virus as the cause of 31.34%. Mycobacterium tuberculosis as the most frequently identified bacteria in 64.4% cases, cause a significant ($Z = 01.93 > Z\alpha = 0.05 = 1.64$) generalized lymphadenopathy, while 38.1% with EBV usually verified by a virus.

Within the generalized lymphadenopathy of infectious etiology cervical and mediastinal lymph nodes is mostly affected region, which followed, axillary and inguinal regions (Table 1).

Acute lymphoblast leukemia was evenly represented in all the years of analyzed period, both manifests as regional and generalized lymphadenopathy, while lymphomas in children aged manifest only by generalized lymphadenopathy.

Generalized lymphadenopathy due to expansion of neoplastic process, primarily involves enlargement of cervical lymph nodes and mediastinal region. Representation of others and the relationship of other regions depend on the type of malignant processes. Supra clavicular and abdominal enlargement of lymph nodes is characteristic of epithelial tumors of the stomach and bowel cancer (1 case), and abdominal inguinal combination was found in Wilms tumor. Involvement of more than two regions is generally characterized by a primary neoplasm of lymphoid tissue.

5. DISCUSSION

Due to the large number of different diseases that can lead to enlargement of lymph nodes to determine the true cause in children can be difficult. Therefore, in the diagnostic evaluation of lymphadenopathy in children should pay attention to the increased localization of lymph nodes, abnormal values in a complete blood count (CBC), abnormalities in the x-ray image (radiograph) of individual regions, and abnormal ultrasound findings. In the above, one of the most important is the size of lymph nodes in relation to the child's age. In healthy children lymphoid tissue is slightly enlarged after birth until the age of 8 to 12 years, after which it gradually decreases during puberty, and continues to decline throughout life. Bilateral palpable lymph nodes in the neck region up to 2 cm can be found in children with previously verified upper respiratory tract infections. Almost 50% of children aged less than 2 years have palpable lymph nodes of the neck. Although, more than 25% of malignant tumors in children are found exactly in this region, less than 2% of palpable nodes are malignant. However, in children, each lymph node in the neck, larger than 1 cm should be considered as lymphadenopathy. Axillary nodes to 1 cm and inguinal up to 1.5 cm in diameter in older school-age children are usually common finding in children aged 7 years requires monitoring, and for infants from 2 months are the indications for diagnostic testing. The presence of even a particle supra clavicular nodes (<0.5 cm) regardless of age, are always a reason for further detailed diagnostic evaluation and are often associated with malignancy (6). In patients with lymphadenopathy in primary care, prevalence of malignant etiology is only 1.1. Key factors that speak in favor of malignant etiology include older age, regardless of age, they are hard, fixed lymph nodes that persist for longer than two weeks, and have supra clavicular localization. Lymphadenopathy may be the only clinical sign, or one of the few non-specific symptoms of the disease. Knowing and recognizing these factors is crucial in the treatment of vague lymphadenopathy whose follow-up can last up to a month, after which a biopsy is the method of choice to diagnose its etiology. A wide range of causes, which lead to enlargement of lymph nodes are easily categorized and remembered using the mnemonic acronym "MIAMI" meaning: Malignancies; Infection, Autoimmune disorders, Miscellaneous and unusual conditions (7). The exact incidence of lymphadenopathy, regardless of age, is not known, and is usually considered within individual etiologic factors. One of the few studies of population which gives valid results is the Danish study which reported an annual incidence of 0.6% lymphadenopathy in the general population. According Reddy in 25% of biopted lymph nodes was verified the secondary malignancy, and 20% of cases it is a primary malignant tumor of lymphoid tissue (8). In the United States malignant etiology and autoimmune diseases in children are much less common cause of lymphadenopathy in relation to infectious etiology (6).

In relation to the total number of children (334) with verified lymphadenopathy in our study, 79.34% had infectious etiology, 11.34% had neoplastic etiology, and 9.28% non neoplastic etiology. Very similar results were presented by the Granada and co-authors who found infectious etiology in 81% of verified cases of lymphadenopathy in children, and neoplastic in 16% (9). The percentage of malignant etiology is basically very low in children but increases with age. The largest part of detected lymphadenopathy in children is infectious or benign in etiology, with a history of short duration and mainly regional.

In our study, in 230 cases it was a regional, and 104 generalized lymphadenopathy. In the literature there is little data dealing with the problem of comparative representation and manifestation of diseases of regional or generalized lymphadenopathy. Therefore, very detailed, and above all well directed history is essential to further determine the etiology of lymphadenopathy. Particular attention should be paid to immunization status of the child and the accompanying reactions. The distribution of lymphadenopathy is usually drained in the evaluation of certain diseases. Within regional lymphadenopathy, usually infectious etiology was present with 198 (86.08%) cases, followed by considerably less common, neoplastic etiology and non neoplastic etiology with the 19 (8%).

Physical characteristics of the enlarged lymph nodes are very important in defining the possible etiology. With infection, the affected lymph nodes are asymmetrically enlarged, tense, dis-

cretely interconnected, and erythematosus skin over. Nodes affected by metastatic cancer usually are hard and fixed. Nodes enlarged neoplastic lymphoid proliferations are usually solid, nonpresstresed and interconnected (10). Careful palpation of the submandibular, front and rear of the cervical, supra clavicular, axillary and inguinal regions in a simple, fast and non-aggressive way of a preliminary differentiation between regional and generalized lymphadenopathy. According to literature data, the most affected region in the infectious etiology is cervical, followed by inguinal and axillary regions (7,10). These data are entirely consistent with our results, which show a slightly more often affected mediastinal region. Although a significant number of cases are relatively quickly diagnosed and successfully treated, some entities, such as atypical mycobacterium, cat-scratch disease, toxoplasmosis, tuberculosis, leading to persistent lymphadenopathy over several months, which can be replaced by malignant processes (7). Our results show that bacterial infections in children treated at the Clinic of Pediatric Diseases, University Clinical Centre Tuzla, and the most common cause of lymphadenopathy of one or more regions. In addition to streptococcal and staphylococcal bacteria, Mycobacterium tuberculosis is 29.85% of regional lymphadenopathy primary cause of disease, while in generalized lymphadenopathy her presence even more significant ($p>0.05$). A retrospective study of Moore and colleagues, involving biopted lymph nodes from 1332 children aged less than 15 years, with the manifest lymphadenopathy, showed the presence of granulomatous inflammation in 36.3% of cases, while tuberculosis lymphadenitis was confirmed in 54.5%. A higher proportion of tuberculosis detected in this study compared to our study may be explained by the long period of time in which the study was conducted (1976-1999), but it certainly confirms the high prevalence of tuberculosis in the last decade (11). In support of this view speak the Tygerberg study with 23.6% of verified tuberculosis of cervical lymph nodes, and a study conducted in Nigeria with 32.7% of TB in children (12,13). Recent studies indicate that in developing countries, the expected annual risk of tuberculosis infection in children is 2.5%, with a marked increase in the number of tuberculous lymphadenitis in the last two decades (14). Data from the same studies indicate that children mortality tubercular etiology is responsible in 8-20% of cases, depending on the health and social standards of the country. According to the World Health Organization, only in the United States (U.S.), as a developed country, the incidence of tuberculosis has declined by 13% in all age groups during the period from 1985 to 1994, but the percentage of disease among children under 15 years is increased by 33% (15). In the verified bacterial etiology of lymphadenopathy dominated by streptococcal and staphylococcal infections, particularly in children older than 3 years. Group A streptococcal infection, with consequent adenopathy are actually associated ailments of school children, especially in spring and autumn (16). Staphylococcus aureus (37%) and group A streptococci (16%) from the study by Trobs and colleagues almost entirely reflects the bacterial flora verified in our material in the presence of some other much less represented in mixed infections (17).

It is interesting that in the infective etiology, and regional, particularly generalized lymphadenopathy (31.34%) in the examined period, are the viruses which caused increased lymph nodes in children are significantly represented. Within a viral etiology in particular has a significant role EBV and is usually verified in generalized viral lymphadenopathy (38.1%). This is somewhat higher than in the study by Benesch and associates (23%), conducted at the Child and the pediatric clinic of the University of Graz (2). Such a difference in the prevalence of EBV among our respondents in relation to the Austrian study may explain the still present a number of migrations to the region, as well as poor socioeconomic conditions, especially in the returnee and refugee settlements.

The etiology of malignant disease of childhood that we verify, acute lymphoblast leukemia is usually verified disease (68.4%), regardless of gender and age of the child, which equally manifest as regional and generalized lymphadenopathy. Generalized lymphadenopathy at the time of diagnosis was present in 70% of children with ALL and in 31% of children with AML, as in the case of ALL, which almost completely agrees with our results. Among sick children in our study lymphomas manifest only by generalized lymphadenopathy, while literature data are mainly from developed countries, give opinion that the lymphomas in children are more often manifested by regional lymphadenopathy (6). In children older than 6 years, dominated by non-Hodgkin and Hodgkin lymphomas, which are in 80-90% of cases of Hodgkin's associated with cervical lymphadenopathy, as opposed to 40% of non-Hodgkin associated lymphadenopathy. Until 7 age of the disease occurs more frequently in boys (10:1), and after the 12 years of age of incidence is approximately equal in both sexes (1,1:1) (18).

In the study by Moore and associates which considered the diagnostic aspects of cervical lymphadenopathy in children 2/3 of 154 patients with neoplastic altered and enlarged lymph nodes had lymphoma, a further 10 had lymphadenopathy associated with leukemia (19). The study also reported more Tygerberg lymphoma (Hodgkin's/non-Hodgkin's lymphoma–33%/23.5%) than leukemia (5%). In our experience, the leukemia is more often verified malignant disease (45.16%) than lymphoma (19.35%). Although it has been verified by a small number of lymphoma in the analyzed period, as in other studies of Hodgkin's lymphoma aged children are more common than non-Hodgkin (9,12). According to data of Bergeron, the occurrence of lymphoma there is a slight male predominance in the age of 15 years, while the incidence of occurrence in this age of about 5.5 cases per million children (20). In our study of 6 verified lymphoma, 2 were diagnosed in boys and at the ages of 11 and 11.5 years, while other were girls at the age of 8, 1 and 13.5 years.

Other diagnosed malignancies are mostly single cases of malignant tumors (neuro blastoma, Wilms tumor) are typical for children's age, or tumors whose incidence has its peak to adult age (melanoma and colon cancer), and whose appearance in children is certainly a

consequence of additional genetic mutations. Sills and colleagues have put forward the fact that these tumors are most common in the first 6 years of age, as confirmed by our results, and to 27% just manifested lymphadenopathy of the head and neck (6). Cervical series of lymph nodes and in our material are usually the affected ones. Neoplastic processes that manifest by regional lymphadenopathy in children in our study in over 90% of cases, leading to enlargement of cervical lymph nodes, and generalized lymphadenopathy primarily involves the cervical lymph nodes enlargement, then mediastinal, inguinal and axillary regions. Representation of other regions depends on the type of malignant processes of the primary tumor. Malignant process in the lymph nodes usually provides a solid, less mobile and connected to the lymph nodes. Very careful palpation is essential to the differentiation of benign reactive lymph nodes due to frequent inflammation may be fibrotic and firm.

Viral illnesses (such as EBV, adenovirus, enerovirus, herpes virus, and CMV) frequently cause lymphadenitis and lymphadenopathy. Together with bacterial infections that affect the drainage of lymph nodes, giving similar symptoms and appearance of the lymph nodes. Usually there is a case of "warm" nodes which are the size of 2-6 cm, erythematosus skin over them, warm, tense and sometimes fluctuating. "Cold" nodes are usually a reflection of sub acute or chronic inflammation, are less tense and not warm. They are not accompanied by suppuration so it is difficult to distinguish them from simple non inflammatory enlargement of lymph nodes. Lymphopmatous lymph nodes are usually nonpresstresed, symmetric, rubbery, mobile, and usually 1.5 to 2 cm in diameter. Metastatic infiltrated lymph nodes are mainly nonpresstresed, extremely hard, large, and immobile and fixed to the substrate.

The diagnostic evaluation must be determined and guided by clinical evaluation, but it certainly needs to include certain laboratory analyze, microbiology, serological, radiological examination and other diagnostic procedures such as cytological and histopathological analysis (5).

6. CONCLUSION

The clinical picture of lymphadenopathy in children is neither simple nor uniform, which is why the diagnosis is very complex and demanding, with a very different etiology and requires almost an individual approach. It is precisely these data which underscore the need for improved of diagnostic methods, development of effective therapies, control of clinical trials, as well as improving supportive care for patients.

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ORIGINAL PAPER

Epidemiological and Microbiological Control of Hospital Infections in Surgical Patients

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Introduction: Intra-hospital infections in surgical wards pose a significant problem, particularly in patients with impaired natural defense potential. They significantly complicate and increase the cost of basic treatment of the patient and sometimes leave permanent damage. Active control of their appearance is of paramount importance in their prevention. **Goal:** By this study we try to determine the frequency of individual agents, their anatomical and gender distribution at the Clinic of Surgery, University Clinical Centre Tuzla in 2005.v **Results:** Our study showed that gram negative bacteria were more common trigger of IHI (76.37%), and especially the urinary and respiratory tract and surgical wounds infections. We also showed that men from older age groups are more likely to have IHI. **Conclusion:** Active surveillance and tracing for agents, especially in high-risk groups of patients is the best method of prevention of IHI occurrence. Keywords: intra-hospital infections, anatomical distribution, age distribution, gender distribution, Clinic of Surgery University Clinical Center Tuzla.

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1. INTRODUCTION

The most common cause of intra-hospital infections (IHI) are bacteria. The types of bacteria that cause IHI changed over time depending on the application of antibiotics, diagnostic and therapeutic procedures. In addition, the properties of individual bacteria are responsible for their epidemiology. Staphylococcus species inhabit the skin and nasal mucosa. In normal circumstances they do not live in the environment and are relatively resistant to drying. The sole source of infection is the man, and most often it is spread over hands.

Gram-negative bacteria poorly tolerate drying and are rarely transmitted through the air, so infections are usually endogenous. Escherichia coli, for example, are mainly transmitted by hands, poorly sterilized and disinfected equipment and contaminated solutions. Pseudomonas aeruginosa, a normal inhabitant of the intestinal tract, is a typical opportunist who can live in solutions, even in a disinfecting agent. Some gram-negative bacteria such as Klebsiella and Komenzali of normal skin flora, better than others tolerate drying and are almost regularly on hands.

Staphylococcus aureus and Pseudomonas aeruginosa, as causes, occupying leading positions in secondary infection of surgical wounds. This probably contributes to the natural phenomenon of carriage. Specifically, in 30 to 50% of healthy outpatient population are in Staphylococcus aureus carrier state, and in 20-25% of the population of Pseudomonas aeruginosa (1).

In recent decades, significantly changed etiological structure of IHI, in which substantially affect the disease occurrence manner. Instead of the classic causes as the causes outbreaks of infections have been reported usually bacteria from the hospital environment: Gram negative bacilli (Escherichia coli, Klebsiella species, Acinetobacter species, Serratia species, Proteus species), followed by bacteria of the genus Pseudomonas, and more Gram-positive bacilli–Staphylococcus aureus, Staphylococcus epidermidis and Enterococcus species (2,3,4).

According to a source of microorganisms that cause them, intra hospital infection can be divided into two basic groups. The first group consists of endogenous or auto infections caused by microorganisms that patients carry in their body, and a second group consists of exogenous infection caused by microorganisms from the environment. The term cross-mark is one exogenous infection that are directly or indirectly transmitted from one person to another and exchanged among patients and staff. Iatrogenic or artificial ones resulting from medical intervention by pathogenic micro-organisms entering the body, most often during the performance of diagnostic and therapeutic interventions (1).

2. RESEARCH GOAL

The main goal of this research is to establish an active epidemiological surveillance of the emergence of bacterial

intra-hospital infections at the Clinic of Surgery-University Clinical Center in Tuzla (UCC) and thereby determine:

- The type of bacteria that cause IHI,
- Distribution of bacterial IHI pathogens according to anatomical localization,
- IHI distribution according to age and gender of patients.

3. METHODS AND PROCEDURES

The research sample included examination of the frequency of appearance of IHI on a sample of 5187 patients at the Clinic for surgery who were treated in 2005, which has 104 hospital beds and provides an annual of 30 000 hospital days. Tests were carried out using a form made on the basis of recommendations of the Federal Advisory Committee (Healthcare Infection Control Practices Advisory Committee–HICPAC) that is formed within the Center for Disease Control and Prevention–CDC in Atlanta USA. Study used multiple tests that are conducted through several surveys, which are characteristic of the research instrument and adapted to this type of testing. This data is tracked and collected during daily, weekly and monthly monitoring criteria and classification of hospital infections with internationally recognized definitions established by the CDC.

4. RESULTS

By testing the difference in frequency of appearance of G+ and G- causes of IHI by Mann-Whitney test we obtain a value of 1738,000 for which the $p<0.05$, which means with statistically significant difference in the incidence of a single group of bacteria as the cause of IHI. This difference exists between the individual causes as we have proved by X^2 test where $X^2_{(9)}=96.571$ for which the $p<0.05$. X^2 tests have shown that there is a significant statistical difference between the types of gram-negative bacterial pathogens of IHI ($X^2_{(6)}=83.480$, $p<0.05$), and that there is a significant statistical difference between the types of gram-positive bacterial pathogens of IHI ($X^2_{(2)}=29.647$, $p<0.05$).

At the Clinic of Surgery University Clinical Center Tuzla in 2005 urinary tract infections (UTI) are usually caused by Klebsiella pneumoniae in 34.48% cases, followed by Pseudomonas aeruginosa with 24.14%, Proteus mirabilis with 12.07% and Staphylococcus aureus with 8.62%, while Acinetobacter species caused 10.34% of infections, Escherichia coli 6.90% and Streptococcus species 3.45%.

Infections of surgical wounds (SWI) has been caused by Klebsiella pneumoniae in 23.91%, followed by Staphylococcus aureus and Pseudomonas aeruginosa with 17.39%, Acinetobacter species in 15.22%, Escherichia coli with 13.04%, Streptococcus species 6.52%, Proteus mirabilis 4.35%, and Serratia marcescens with 2.17%.

Respiratory tract infections (RTI) are caused mainly by gram-negative bacteria as Pseudomonas aeruginosa 25%, Klebsiella pneumoniae 21.88% and Acinetobacter species15.63%, then Escherichia coli and Staphylococcus aureus in 12.50%, Proteus mirabilis6.25%, Streptococcus species, and Serratia marcescens with the 3.13% cases were recorded as the cause.

Bacteremia (BACT) have caused the most Staphylococcus aureus in 25.93% cases, followed by Acinetobacter species and Klebsiella pneumoniae in the 14.81% of the cases, then the coagulase-negative staphylococci, Pseudomonas aeruginosa and Proteus mirabilis, each with 11.11%, and Streptococcus species, Serratia marcescens and Escherichia coli as the causative agents of bacteraemia were detected in 3.70% of cases.

Other infections (OI) are caused mainly by gram-positive bacteria as Staphylococcus aureus in 15.79% cases, Streptococcus species in 26.32% and coagulase-negative staphylococci in 5.26%, and from gram-negative bacteria as the causative agents were most commonly Proteus mirabilis with 26.32%, followed by Klebsiella pneumoniae in 10.53%, and Escherichia coli, Acinetobacter species and Citrobacter species as a cause other infections was recorded in the 5.26% cases.

Analyzing data on hospital infection of urinary tract (UTI), we found that there was significant difference in their frequency in relation to age group ($X^2_{(3)}=38.529$, $p<0.05$). Most of them were in patients older than 65 years (53.45%). There is also a significant difference in the number of infected in relation to gender ($X^2_{(1)}=33.138$, $p<0.05$), where men are more often affected.

ISOLATED MICRO ORGANISMS CAUSES OF IHI	N	%
GRAM-POSITIVE BACTERIA	43	23.63
Staphylococcus aureus	27	14.84
Coagulase negative staphylococci	4	2.20
Streptococcus species	12	6.59
GRAM-NEGATIVE BACTERIA	139	76.37
Klebsiella pneumoniae	44	24.18
Acinetobacter species	23	12.64
Pseudomonas aeruginosa	33	18.13
Escherichia coli	16	8.79
Proteus mirabilis	19	10.44
Serratia marcescens	3	1.65
Citrobacter species	1	0.55
TOTAL	182	100.00

Table 1. Isolated and identified bacteria as the cause of IHI at the Clinic of Surgery, University Clinical Center Tuzla in 2005.

		NUMBER (%) IHI									
		UTI		SWI		RTI		BACT		OI	
		N=58		N=46		N=32		N=27		N=19	
AGE	<18	3	(5.17)	4	(8.70)	2	(6.25)	4	(14.81)	3	(15.79)
	19-45	11	(18,97)	7	(15.22)	5	(15.63)	4	(14.81)	4	(21.05)
	46-65	13	(22.41)	18	(39.13)	11	(34.38)	8	(29.63)	5	(26.32)
	>65	31	(53.45)	17	(36.96)	14	(43,75)	11	(40.74)	7	(36.84)
sex	male	45	(77.59)	28	(60.87)	20	(62.50)	12	(44.44)	12	(63.16)
	female	13	(22.41)	18	(39.13)	12	(37.50)	15	(55.56)	7	(36.84)

Table 2. IHI distribution according to age and gender of patients at the Clinic for Surgery, University Clinical Center Tuzla in 2005.

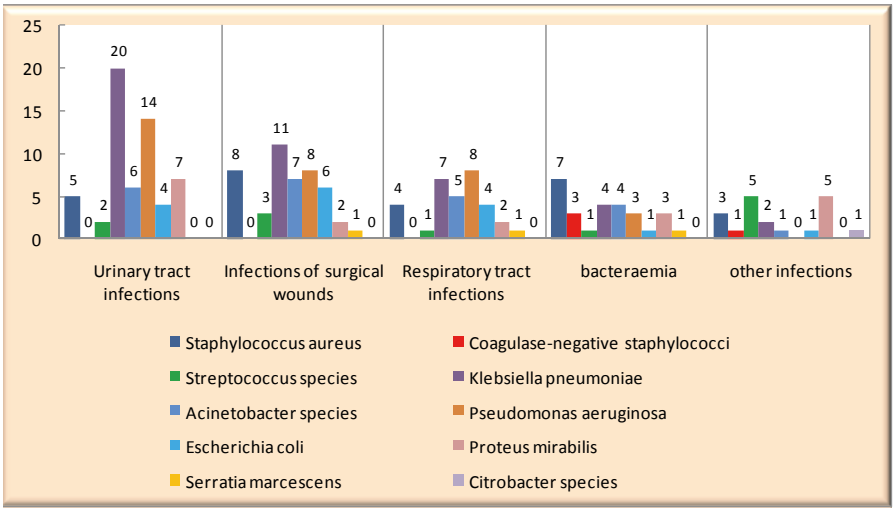

FIGURE 1. Anatomical distribution of bacterial pathogens by type of IHI

Infections of surgical wounds (SWI) were diagnosed mainly among patients in age group from 46-65 years (39.13%), and differences in infection rates between age groups were significant ($X^2_{(3)}$=17.275, p<0.05) . The difference in gender distribution of infected surgical wounds is not significant ($X^2_{(1)}$= 3.522, p>0.05).

Respiratory tract infections (RTI) are diagnosed mainly among patients older than 65 years (43.75%), and there is a statistically significant difference in infection rates between age groups ($X^2_{(3)}$=15.000, p<0.05). The difference in gender distribution of patients was also statistically significant ($X^2_{(1)}$= 7.192, p<0.05). Men are more often affected by IHI of the respiratory tract.

Bacteremia (BACT) are the mostly represented among patients aged over 65 years (40.74%), but this difference was not statistically significant ($X^2_{(3)}$=6.864, p>0.05) nor a statistically significant difference in gender distribution of bacteremia ($X^2_{(1)}$=0.296, p>0.05).

Analyzing data on other infections (OI), we see that the highest rate is recorded in patients older than 65 years (36.84%), but the difference in the frequency of the IHI infection of other localizations according to age groups was not statistically significant ($X^2_{(3)}$=2.456, p>0.05), and also infected or distribution by gender was not statistically significant ($X^2_{(1)}$=1.684, p>0.05).

5. DISCUSSION

Hospital environment, characterized by specific profiles of microbial flora, and the patient, the holder of the physiological flora of microorganisms, are already infected or carrier, with reduced defense mechanisms are a suitable medium for the emergence and spread of intra-hospital infections. Under such conditions, and many opportunist microorganisms more prominent, are causing new infections. Cross-transmission of bacterial strains among patients and staff change occurs among the bacteria, which causes the multiplication of resistant strains. Following the underlying disease, hospital infections can cause a different degree of complication. Most are due to transient complications, which eventually are healed. However, they can sometimes become a bigger problem than the underlying disease and cause permanent damage, such as disability or death. Whatever the outcome, hospital infections requiring prolonged treatment, which significantly increases the costs and burdens on hospital stay and health care funds. It is understood that all of this in addition to economic, causes also implications in the social, psychological and emotional terms (1).

On the basis of continuous epidemiologic surveillance of hospital infection in the Clinic of Surgery UCC Tuzla in 2005 a total of 182 registered IHI with the incidence rate of 3.5%.

In Slovenia in 2001 the one-day trial conducted in 19 Clinics of Surgery to determine the prevalence of IHI, and identify predominant micro-organisms and risk factors. At total of 6695 patients found the IHI prevalence of 4.6% (5).

During the 2005 distribution of IHI at the Clinic for surgery showed that the most common were UTI with a total of 58 infections, followed by SWI with a total of 46 infections, while the RTI were registered in 32 cases. Bacteremia was identified in 27 cases, while the OI (gastroenteritis, skin infections, and conjunctivitis) was recorded in 19 cases.

According to Narong and associates distribution of IHI by anatomic localization was for surgical wound infection 37.9%, 26.3% of urinary tract infections, 24.3% of respiratory infections, 7.1% of bacteremia and other infections 4.4% (6) .

As the results of a multicenter study of hospital infections in Germany in the surgical wards, Hauer and colleagues 1996 report that the incidence rate of IHI was 3.5%. The most common were urinary infection (42%), followed by respiratory infections (20.6%), infections of surgical wounds (15.8%), bacteremia (8.3%) and other infections (13.7%) (7) .

Jankovic and colleagues (1998) made a two-month study of the IHI incidence at the Center for Surgery in Belgrade, according to the CDC methodology. In their investigations of the incidence rate in the intensive care unit was 13.7%, and at a surgical ward 6.0%. Infections of surgical wounds were the most common (31.4%), followed by urinary tract infection (23.1%) and respiratory infections (19.9%) (8).

Similar studies were done by Gikas and colleagues in Greece on surgical wards. Their results show that in 1999 was registered 148 hospital infections from a total of 1037 surgical patients, or 14.3%, and the results from 2000 show that from a total of 868 patients, 88 had intra-hospital infections, or 10.1% (9).

The causes of hospital infections could be almost all microorganisms, but usually they are bacteria. The types of bacteria that cause intra-hospital infection have changed over time depending on the application of antibiotics and the application of new diagnostic and therapeutic procedures. Today, agents are often conditionally pathogenic bacteria, although it may be non pathogenic microorganisms. An important characteristic of bacteria that cause intra-hospital infections is resistance to antibiotics. Laboratory diagnosis of causes

of intra-hospital infections is a key link in the chain of procedures, which are fighting against their spread.

By monitoring the types of pathogens and their representation in individual departments, as well as sensitivity to antibiotics, it is possible already in the microbiological laboratory to register IHI. Typical types of sensitivity to antibiotics may cause to point to a common source or route of transmission of these infections.

The results we obtained in our research on the type of IHI pathogens and their representation in the Clinic of Surgery, University Clinical Center Tuzla showed that gram-negative bacteria were predominant in comparison to gram-positive bacteria, and most of them were Klebsiella pneumoniae. It most commonly caused urinary tract, surgical wounds and respiratory tract infections.

Numerous literature data indicate that gram-negative bacteria are the predominant cause of intra-hospital infections in intensive care and general surgical wards. It is estimated that over 70% of the IHI causes are gram-negative bacteria (10,11,).

Gram negative bacteria mostly caused urinary tract infections, surgical wound infections and respiratory tract infection, which is identical with the research of other authors (12,13,14,15,16).

Our research has shown that IHI is more prevalent in older patients that we can explain by the reduced natural immunity of the elderly, and greater exposure of these people to these strains of bacteria, because they more often visit the hospital wards. Also, male patients significantly are more likely to have an IHI particularly of urinary and respiratory tract, and the reason may also be greater exposure of male patients with these agents (catheterization), or a weaker immune response (smoking) in any case this requires closer examination.

6. CONCLUSION

IHI represent a significant problem of modern surgical departments, so the adequate monitoring and preventive measures are crucial in struggle against them. Type of organism and the frequency of IHI at the Clinic of Surgery, University Clinical Centre Tuzla are not much different from the results found in literature. Therefore, we have developed methods of fighting against IHI. Should pay more attention to vulnerable groups, patients, and for them to perform active search for IHI agents (men with UTI and RTI), and older patients.

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ORIGINAL PAPER

Evaluation of Working Capacity in Case of Mental Disorders

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Incidence of mental disorders in our country and in the world is growing and significantly impact working capacity. The goal of the study: to investigate which group of mental disorders and to what extent impacts the disability comparing two analysed years (1999 and 2009). Material and Methods: 420 subjects were processed (143 in 1999 and 277 in 2009) from the Una-Sana Canton with mental disorders who were referred for evaluation of working capacity at professional authority in the first instance (Disability Commission) in Bihac. Disability Commission gave „ Review, assessment and opinion" for each individual from which the author recorded data into the questionnaire necessary for the study. Results: More men are sent for evaluation, aged 50 and over, who are not employed. Number of assessments has increased by almost double. The most addressed are from the group of affective disorders, who did not have disability during 1999 in majority, but in 2009 they are the leaders in disability, with schizophrenia. Conclusion: there is increased number of assessments, and most of them from the group of affective disorders whose participation in disability increases. Schizophrenia and affective disorders are the leading causes of disability. Key words: mental disorders, working capacity, assessment

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1. INTRODUCTION

Mental disorders can occur at any age, lifestyle and includes emotional, intellectual processes, verbal and nonverbal behavior. Psychiatry and occupational medicine study how the professional work and working conditions affect mental health. There is a growing prevalence of mental disorder in the structure of morbidity, as well as sick leave and disability in our country (1).

Mental and behavioral disorders, with cardiovascular disease are leading causes of disability in our country and the world (2).

In the postwar period were significantly toughened the relations between employees and professional work, with the increasing demands of the employer, which are devastating for employees with mental disorders. All this leads to long absences from work, difficult return to work process and the frequent demission and/ or referral for evaluation of working capacity. On the other hand, poor socioeconomic conditions, poverty are leading to deterioration of underlying disease, which increases the number of assessments by disability commission.

The goal of this study was to examine which group of mental disorders and to what extent affect the disability, to determine whether there is a difference in the number and type of evaluations in a ten-year period (1999-2009), and to further define the parameters: gender, age, years of service, qualifications, employment status, motivation for the job.

2. MATERIAL AND METHODS

The study involved employees from Una-Sana Canton of both sexes, aged from 18 to 65 years, who are referred for evaluation of working capacity by the Disability commission in Bihac, and whose leading problem are mental illness and behavioral disorders. Study period was from January 1st 1999 to December 31st 1999 and from January 1st 2009 to December 31st 2009. Data source was "Assessment, evaluation and opinion" issued by the Disability commission. The author has made a special-form questionnaire in which we recorded all relevant data for the study of „Assessment, evaluation and opinion". Assessments of the Disability commission were as follows: The first category of disability (loss of working capacity), Second category of disability (remaining work capacity), and the disability does not exists, the test is not completed, the treatment is not completed. The first two assessments provide a disability, and the other two exclude it. This pattern is multi-layered, selected. This study was of clinical epidemiology type, descriptive, retrospective and analytical.

3. RESULTS

A total of 420 subjects were assessed: 143 in 1999 year, and 277 in the year 2009. Among respondents there were 273 (65.0%) males and 147 (35.0%) women. There were no significant differences in the type and year of assessment in relation to sex.

In 1999 assessed as with disability was 60 (41.96%) persons, and in the year 2009, 159 (57.40%).

It is evident that from the total number of referred persons in the year

1999 more than half was not assessed as with disability 83 (58.04%), and in 2009 there is significantly lower number of 118 (42.60%).

According to the group of mental disorders–schizophrenia (F20-F29) participate the most in disability in 1999 with 22.38%, although in 2009 there have been no significant changes regarding to total number of referred (18.77%). Persons with affective disorders (F30-F39) are mostly referred to disability commission (43.57%) in the year 1999 were mostly assessed as without disability (24.48%), and in 2009 they mostly participated in disability (25.27%)–Table 1

In Figure 1 can be seen the participation in the disability by groups of mental disorders and years of assessment. In 1999 in disability mostly participated persons with schizophrenia and in 2009 mostly participated those with affective disorders (depression). This can be explained by the large number of persons with depression score–Table 2.

Number of assessments, regardless of whether it was or not with verified disability increases with age. Total working experience does not have significant impact on those who receive disability and those who have been rejected, as well as in the analyzed period. A significant number of persons with low education was referred for the assessment (42.41% in 1999 and 42.65% in the year 2009), while disability is more common among the persons with the medium to high education. Most of the persons referred for the assessments are unemployed and without any motivation to work.

F00-F99	1999 (n=143)		2009 (n=277)		Total
	DISABILITY n %	WITHOUT DISABILITY n %	DISABILITY n %	WITHOUT DISABILITY n %	N %
F10-F19	2 1.40	7 4.89	10 3.61	12 4.33	31 7.38
F20-F29	32 22.38	15 10.49	52 18.77	17 6.14	116 27.62
F30-F39	21 14.68	35 24.48	70 25.27	57 20.58	183 43.57
F40-F49	5 3.50	24 16.79	27 9.75	25 9.03	81 19.28
F00-F09 & F50-F99	---	2 1.39	---	7 2.52	9 2.15
Total	60 41.96	83 58.04	159 57.40	118 42.60	420 100.00

Table 1. Assessment of working ability by groups of mental disorders (F00-F99) ** and years of assessment (N = 420) ** Groups of mental and behavioral disorders. F10-F19 Mental and behavioral disorders caused by use of psychoactive substances. F20-F29 Schizophrenia, delusional and disorders of schizophrenia type. F30-F39 Affective disorders (mood disorders). F40-F49 Neurotic, stress-related and somatoform disorders. F00-F09 Organic and symptomatic mental disorders. F50-F99 Other mental and behavioral disorders

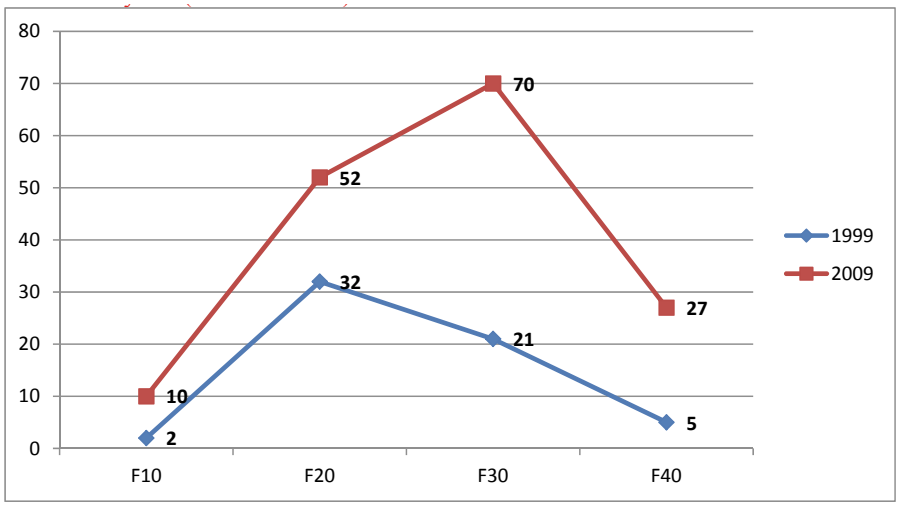

Figure 1. Distribution of disability by groups of mental disorders (F00-F99) and the assessment years (1999 and 2009)

F00-F99	DISABILITY in % (1999) N = 60	DISABILITY in % (2009) n = 159
F10-F19	3.33	6.29
F20-F29	53.33	32.70
F30-F39	35.00	**44.03**
F40-F49	8.33	16.98
Total	100.00	100.00

Table 2. Distribution of disability by groups of mental disorders (F00-F99) and the assessment years (1999 and 2009)

4. DISCUSSION

Taking as an indicator burden of disease and as a result a disability for normal family, social and occupational functioning, among the top 10 most common causes are disorders from the 4 groups of mental disorders: depression, alcohol dependence, schizophrenia and manic-depressive disorder (WHO, 2004).

Leading cause of loss of working capacity in the analyzed period was schizophrenia. Schizophrenia is characterized by a disorder of thought, emotion and behavior and is on top of rankings in other countries when it comes to disability (3,4). This leads to social withdrawal and difficulties in communication, as the biggest obstacles to professional acceptance (1). In addition to the undoubted success of modern psychiatry and good remission phase, in our country poor working conditions lead to new crises, poor vocational rehabilitation and resettlement (5).

In the analyzed period, the largest number of referrals for assessment was persons with the affective disorders. During the year 1999 most of them was not assessed as with disability, while in 2009 it participated with the highest percentage of disability (44.03%). These are the cases of first depressive episodes and repeated depressive disorders. In survey done by Novakovic during period 2005/2006 with affective disorders, assessed as with disability was 47.89% persons (6). Working conditions, poor living standards, "progression" of disease, are the leading cause of long illness duration, loss of working capacity and suicide (7). In developed countries, depression is among the top five chronic diseases, with a tendency of continuous growth (8). Canadian authors point out as the problem of disability major depression, which can hardly be avoided (9).

Many of the symptoms of depressive

disorders are incompatible with working activities, and in particular: loss of interest for the job, fatigue, gloomy moods, feelings of guilt, and thoughts of suicide.

5. CONCLUSION

From the total number of health insured persons referred for the assessment approximately the same number assessed as with and without disability.

Number of evaluations increased during the analyzed period.

The largest number of referrals to the assessment of the health insured persons was with affective disorders (depression).

Schizophrenia and affective disorders are responsible for majority of disabilities.

Depression in any clinical form is inactivating a large number of skills relevant to the profession.

Increased number of mental disorders is a reflection of the cumulative stress that is caused by the economic poverty, wars and the overall deterioration of living conditions in the country in transition period.

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PROFESSIONAL PAPER

Surgical treatment and complications of treating pancreatic tumor

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Pancreatic tumor is one with the worst prognosis of all cancers, and the tenth most frequent cancer in Europe, making the 3% of all cancers affecting both sexes. Most patients seek treatment when the disease is in an advanced stage and the level for possible respectability is low. Late presentation of the disease is responsible for the short survival period of 6 months and a five-year survival of 0.4 to 5% of patients. At the Clinic for Surgery in Tuzla during period from January 1st 1996, to January 1st 2011, a total of 127 resection surgeries were performed due to malignant tumors. The goal of this study is to show that adequate assessment of operability, proper surgical strategy and modern techniques of creating anastomoses reduces morbidity and mortality, results in fewer postoperative complications and contributes to better surgical results. In our sample the most common place of tumor location was the head of pancreas, in 69 (59.7%) patients. Men develop this type of cancer more often than women in the ratio of 2:1, while the median age of patients was 62 years. We faced postoperative complications with 37 (29.1%) patients, pancreatic fistula being the most prevalent complication, occurring in 16 (12.6%) patients. Overall early and late postoperative mortality was observed in 12 (9.8%) patients. Conclusion: Patients with chronic and hereditary pancreatitis are at a higher risk of developing pancreatic cancer and should be screened for the purpose of early diagnosis. The staging of pancreatic cancer has improved, with the accuracy of 85-90%. Postoperative complications, morbidity, and mortality are significantly reduced ($p<0.05$) if the standardized operational procedure is applied and if modern techniques are used to create pancreaticojejunal anastomosis as the anastomosis carrying the highest risk. KEY WORDS: PANCREATIC CANCER, RESECTION SURGERY, COMPLICATIONS.

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1. INTRODUCTION

Pancreatic tumor is one with the worst prognosis of all cancers, and the tenth most frequent cancer in Europe, making the 3% of all cancers affecting both sexes Most patients seek treatment when the disease is in an advanced stage and the level for possible resectability is low. Late presentation of the disease is responsible for the short survival period of 6 months and a five-year survival of 0.4 to 5% of patients. There is only 5-10% patients with a resectable tumor have an average rate of survival of 11-20 months and a five-year survival 7-25% of patients. However, almost all patients die within 7 years after surgery. Early diagnosis and surgical treatment may provide a chance to these patients. Risk factors includes smoking, fat rich diet, carcinogens (azaserine, nitrosamine), genetic predisposition, chronic pancreatitis, hereditary pancreatitis, pancreatic cancer in the family, cystic fibrosis, Peutz-Jeghers syndrome, breast cancer in the family, familial adenomatous polyposis while coffee has not been proven as a risk factor. The progression from normal ductal epithelium to an intraepithelial pancreatic neoplasia of a low grade (PanIN) and to a high grade of malignancy PanIN is connected with specific genetic changes. Early changes include Her-2/neu and K-ras mutations; intermediate changes include p16 mutations; changes connected with carcinoma in situ or early invasive carcinoma include p53, BRCA2 and DPC4 mutations. Symptoms of pancreatic cancer are weight loss in 92% of cases, jaundice 82%, pain 72%, dark urine 63%, light stool 62%, anorexia 64%, and nausea 37%, weakness 35%, vomiting 37%, and itching 24%. *Conditions that are a contraindication for the resection of pancreas* includes liver metastases (of any size), involvement of nymph nodes, peritoneal carcinomatosis, infiltration of transverse mesocolon, involvement of lymph nodes of the liver hilum. *Conditions that are not a contraindication for the resection of pancreas* are the infiltration of duodenum

or gastric antrum, infiltration of peripancreatic lymph nodes, infiltration of lymph nodes along porta hepatis that can be removed by resection.

2. PATIENTS AND METHODS

Our study was conducted at the Clinical Centre Tuzla, Clinic for Surgery from January 1st 1996 to January 1st 2011 and involved 127 patients who underwent the resection surgery of the pancreas.

Our study did not include patients who had a palliative operation, distant metastases, liver cirrhosis, complicated portal hypertension, hereditary coagulopathy, primary and secondary diseases of extrahepatic bile ducts. We analyzed the obtained results by applying Chi-square, Student's t-test and Kaplan-Meyer's test. If the difference between the value of analyzed parameters was $p<0.05$, it is considered to be statistically significant.

Description of surgical procedures, preoperative and postoperative treatment

CDP with pylorus preserving technique was performed on 21 (16.53%) patients. Surgical approach of median laparatomy in 64 (50.40%) patients, laparatomy according to Orr (bilateral sub costal) in 63 (49.60%) patients. We used abdominal retractor with support on the soft tissues over the abdominal compression. Preoperatively, each patient signed a consent form for surgery and the same procedures for consent had been previously presented to the patients with explanation of potential complications. The form was approved by the Ethical Committee of the University Clinical Centre and the Service for Quality Control. Preoperative urinary catheter was placed in all cases, the venous catheter was placed (central venous catheter) and nasogastric tube. All patients were preoperatively treated by the application of isotonic intravenous fluid (0.90% NaCL, 5%) and substitution of blood derivatives; fresh frozen plasma (SSP), thrombocytes (TS) if the laboratory balance was deficient, in addition to preoperative application of antibiotic prophylaxis (third-generation cephalosporin). Preoperative preparation consists of the ultrasound examination of the abdomen, CT scan of the abdomen with contrast, chest X-ray, X-ray of the abdomen, electrocardiogram and complete laboratory tests. Tumor markers (CEA, AFP, CA 19.9) were determined preoperatively and postoperatively on the 15th day. We had a previously confirmed diagnosis for 58 (45.68%) patients. With the patients with pronounced icterus and previous endoscopic stent placement 41 (32.29%), the operative treatment was scheduled after the stabilization of the general condition and laboratory parameters (the level of bilirubin in the serum below 2mg/l) within 2-4 weeks. We have to repeat surgery in 16 (12.60%) patients with previously done biliodigestive anastomosis (choledochoduodenal) after the unsuccessful attempt of endoscopic stent placement. The operative technique of performing cephalic duodenopancreatectomy with hemigastrectomy and pylorus preservation technique is a standard. The technique of creating pancreaticojejunal anastomosis is termino-lateral Blumgart's method and polydioxanone absorbable monofilament suture 4-0 in one layer with previously placed prosthesis in the joint pancreatic duct in 29 (28.83%) patients. Creating hepaticojejunal anastomosis in one layer individually with the PDS polydioxanone absorbable monofilament suture 6-0 in 29 (28.83%) patients. In 98 (71.77%) patients, the pancreaticojejunal anastomosis was created by Safil suture, polyglycolic acid absorbable 3-0 in one layer and the hepaticojejunal anastomosis was created by prolene suture 4-0 by the technique of continuous suture. Prior to creating pancreaticojejunal anastomosis, we take sample from every patient and send it to bacteriology testing. We closed operative wounds with a continuous suture 2-0 polydioxanone in one layer and the skin with metal clasps.

3. RESULTS:

The results of our study are preoperative procedures that include the diagnosis and assessment of resectability, patient's general condition – ASA score, the level of tumor markers CA-19-9, thromboembolism prophylaxis, antibiotic prophylaxis, correction of metabolic and nutritional disorders, the role of somatostatin, the role of preoperative biliary drainage, adequate analgesia, intraoperative conducted planned surgical strategy with a technique with minimal bleeding that does not require intraoperative transfusion, postoperative intensive monitoring (during the first 24 hours), nasogastric tube (extracted 12 hours after the extubation), abdominal drains (extracted within 3 days of the secretion is minimal), postoperative nutrition (enteral feeding by using nasogastric tube, probiotic-enriched), control of laboratory parameters, analgesia, early mobilization of the patient, vaccination of splenectomized patients (Streptococcus pneumonie and Haemophilus influenzae type B).

The localization of tumor is shown in Table 1.

Localization of the tumor	Number	%
Pancreas head	69	59.78
Papilla Vateri	26	16.30
Distal part of choledocus	8	7.61
Entire pancreas	3	2.17
Pancreas body	3	2.17
Pancreas tail	9	7.61
Infiltration of pancreas by tumors of surrounding organs:		
Tumor of duodenum	3	1.09
Tumor of gastric antrum	4	1.09
Tumor of hepatic flexure	2	2.17
Total:	127	100.00

Table 1. Localization of tumor in patients who underwent the resection of pancreas

The median age of patients was 62 (range 34-81). The types of resection surgery are shown in table 2.

Type of surgery	no of pat.	%
Cephalic duodenopancreatectomy (CDP)	101	79.53
Total duodenopancreatectomy	4	3.15
Subtotal left pancreatectomy	4	3.15
Distal spleen-preserving pancreatectomy	10	7.87
CDP + subtotal stomach resection	4	3.15
CDP + right hemicolectomia	4	3.15
Total:	127	100.00

Table 2. Types of resection surgery of the pancreas

Abdominal postoperative complications found in our sample are shown in table 3.

The total number of intraabdominal

Complication	Number of patients	%
Pancreatic fistula	15	11.8
Biliary fistula	5	3.9
Intraabdominal abscess	4	3.1
Delayed gastric emptying	6	4.7
Infection of the wound	7	5.1
Total:	37	29.1

Table 3. Postoperative abdominal complications in patients with resection of pancreas.

complications occurred in 37 (29.1%) patients and the most common complication was pancreatic fistula 15 (11.8%). Pancreatic fistula occurred in our sample in all cases as an early complication from 3 to 7 days. We treated it conservatively and successfully in 6 (4.7%) patients by adequate rehydration and enteral feeding with a regular cleaning of the surgical wound. All patients had a postoperative administration of sandostatin – 100 micrograms daily in two doses. Because of the impossibility of adequate cleaning by using conservative methods, we conducted a revision because of pancreatic fistula in 9 (7.1%) patients. Revision was conducted by a repeated relapalotomy, resection of pancreatic surface and jejunal convolutions, with a new anastomosis and external drainage of pancreatic duct by Witzell. We treated biliary fistula only conservatively according to a pattern adequate to a conservative treatment of a pancreatic fistula and all are cleaned within 6 weeks.

We treated abscess collections, as a result of accumulation of pancreatic or biliary secretion components, by placing a drainage catheter in the zone of abscess collection and by administrating of broad-spectrum antibiotics after antibiogram confirmation. We want to emphasize that there is a statistically significant lower number of abdominal complications when we use Blumgart's technique of creating pancreaticojejunal anastomosis with suture PDS 4-0 and hepaticojejunal anastomosis by individual sutures PDS 6-0 in one layer ($p<0.02$). In our sample we showed that there is a statistically significant difference in a number of patients with a better gastrointestinal function ($p<0.05$) and a lower incidence of marginal ulcer ($p<0.01$) after the application of PPPD (pylorus preserving pancreaticduodenectomy). A statistically significant difference in our series is related to oncologic adequacy and delayed gastric emptying ($p<0.05$) with patients after standard cephalic pancreaticduodenectomy. Out of late abdominal complications we emphasize bleeding from the marginal ulcer on the gastrojejunal anastomosis in 2 (1.5%) patients whom we treated operatively after unsuccessful control of bleeding by endoscopic procedures. The operative treatment consisted of an additional resection of stomach and of a part of a jejunal convolution with establishing new anastomosis in one layer.

Pulmonary embolism	2	1.5%
Surface thrombosis	4	3.1%
Deep-vein thrombosis	2	1.5%
Pleural effusion	3	2.4%

Table 4. Extra abdominal complications

We treated extra abdominal complications related to thrombosis preoperatively and postoperatively by administrating low molecular heparin, pleural effusion was treated by thoracic punction. The patient with pulmonary embolism had an intensive monitoring and therapy in the intensive care unit. The reasons for postoperative mortality with patients after the resection of pancreas are shown in table 5.

The cause of mortality	no
Intraabdominal sepsis	6
Intraabdominal bleeding	3
Reoperations because of a bleeding ulcer on the gastrojejunal anastomosis	2
Pleural effusion	1
Total: 9.8%	12

Table 5. Postoperative mortality with patients after the resection of pancreas

The dominant pathohistological diagnosis in our sample is adenocarcinoma in 112 (88.2%) patients. Among other types of tumors in our sample, there were metastatic pancreatic tumors (tail) in the primary cancer of rectum 3 (2.6%), breast cancer (body and tail) 2 (1.6%), solid pseudo papillary tumor 4 (3.1%), serous cystic neoplasms 2 (1.6%), intraductal papillary mucinous neoplasm (IPNM) 4 (3.1%) patients. Intraoperative blood transfusion and immediately after the operation (within 72 hours) was 240-760ml.

4. DISCUSSION:

Good prognostic factors for pancreas resection as a result of malignity include negative margins of resection, the absence of metastases in lymph nodes, good or moderate tumor differentiation, tumor smaller than 2 cm in diameter, the absence of perineural and vascular invasion. Poor prognostic signs are DNA aneuploidy, inactivation of suppressor genes (p16, p53, DPC4). On the basis of previous experience it can be stated that there are no indications for routine stenting of all patients with icterus because of the of the pancreas head cancer. Endoscopic stenting of papilla Vateri can be justified in a smaller number of patients who have cholangitis and a high level of damage of the liver function as well as with patients who for whatever reasons cannot undergo surgery immediately after the tumor of the head of pancreas is diagnosed. It is to be expected that in the following period the controlled prospective studies will clearly define criteria for selective application of both the internal endoscopic biliary drainage and external biliary drainage. Incidence of pancreatic fistula (10-25%) and sepses and bleeding that result in mortality when patients are not sufficiently postoperatively prepared and when patients have early postoperative complications reaches the level between 20 and 40%.

Classification	Definition of pancreatic fistula	no	%
1	more than 10 ml/ day after the 5th postop.day	69	(28.9)
2	more than 10 ml/ day after the 8th postop.day	44	(18.2)
3	more than 25 ml/ day after the 5th postop.day	40	(16.5)
4	more than 50 ml/ day after the 11th postop.day	24	(9.9)

Table 6. Classifications of postoperative pancreatic fistula

Fourth classifications of postoperative pancreatic fistula in the sample of 242 patients with cephalic duodenopancreatectomy are shown in table 6.

Knowing this classification is extremely important to be able to correctly note a complication and apply

an adequate treatment. Important factors for creating pancreatic anastomosis are firmness of pancreatic tissue, type of pancreatic disease, width of pancreatic duct, operative technique, patient's age, associated diseases, and icterus. Prevention of pancreatic fistula includes the choice of adequate anastomosis, stent of the pancreatic duct, somatostatin. It is unclear whether pancreaticogastrostomy changes the endocrine function of pancreas and whether it is preserved in the same way as with pancreaticojejunal anastomosis. The incidence with pancreaticojejunal anastomosis is bigger than with pancreaticogastrostomy and both techniques have an acceptable rate of fistulas with experienced pancreatic surgeons. However, it seems that there is an increased tendency towards using pancreaticogastrostomy.

5. CONCLUSION:

Gentle manipulation and correct mobilization of resected pancreas with precise suturing can have a more important effect on the prevention of forming the pancreatic fistula than the choice of the anastomosis type.

With the choice of the type of anastomosis, anastomosis on resected pancreas created by Blumgart's technique using the PDS polydioxanone monofilament suture 4-0 showed a lower percentage of complications related to pancreaticojejunal anastomosis in our sample. The amount of transfused blood is in a direct correlation with a number and severity of early and late postoperative complications. Patients with a higher amount of transfused blood intra and postoperatively (more than 460 ml) in our sample had a higher percentage of postoperative complications. Patients with hyperbilirubinemia, where the total bilirubin level exceeds 8mg/dl, show a higher percentage of postoperative complications, higher morbidity and postoperative mortality. Preoperative stent placement, decolorization of the patient and a normal level of bilirubin in the serum followed by operative treatment are directly related to better operative results, lower percentage of complications, a lower mortality and morbidity rate. Concomitant chemo radiotherapy in treatment of adenocarcinoma of pancreas is applied as neoadjuvant (often with border resected tumors), adjuvant and for locally advanced disease without proved metastasis. In spite of constant research and discoveries of new chemotherapeutics, neoadjuvant chemo radiotherapy did not succeed to significantly increase the number of resectable tumors. On the other hand, new diagnostic methods managed to increase to a certain extent the number of those patients who are potentially curable by surgical treatment, in addition to adjuvant chemo radiotherapy.

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PROFESSIONAL PAPER

Extracorporeal Fertilization in the World and in Croatia

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Aim: To point out the dangers, side effects and risks of medical assisted fertilization, in vitro fertilization, embryo transfer and injection on sperm in ovum for mother and the child. Results: On the one hand the negative side effects for women of an abrupt rising risk for the development of neoplasia under pharmaceutical therapy are mentioned. Especially under a therapy which has the purpose to stimulate the ovulation of the ovary it lies around 100%. An increased level of certain hormones, as for example HCG, which influences the ovulation, is closely related with the risk of developing ovarial cancer. Clinical studies at more than 12.000 infertile women (primary and secondary acyesis), with an average age of 30 years, show an elevated risk for the development of a malignant tumor of 98%. Also the application of Gonadotrophin is connected with a risk of 146% for the occurrence of cancer after a period of 15 years. FDT involves a risk of about 12% for the occurrence of breast cancer and shows also an aggravation for the risk of cancer of the endometrium from 79% up to 1152%. On the other hand the risk of spontaneous miscarriages under MAF, which is near 20%, and serious illness of the children, including 47% with need of intensive care unit support after birth, need to be realized. Furthermore the investigation of naturally obtained twins and through ART obtained twins shows in the arrangement a slower and poorer development of the children in the ART group with also great differences in physical development. In total the number of inherent malformation of newborns under the use of ART rises from 47 to 177 %. With an installment of 9% we notice that children who came into being by IVF and ICS also fall more frequently ill. (Teething troubles, more hospitalizations and operations, higher frequency of major inherent malformations). Conclusion: All women who want to undergo a medical assisted fertilization should be informed about the side effects and risks for mother and child. Key words: medical assisted fertilization, in vitro fertilization, embryo transfer, injection of sperm in ovum, side effects, risks, dangers, adenocarcinoma, ovarial cancer, breast cancer, birth weight, spontaneous miscarriages, fetal damage, hyperstimulation of the ovaries, inherent malformations on newborns, infantile development

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1. INTRODUCTION

The European Society for Human Reproduction and Embryology (ESHRE) arose through the idea of professor R.G. Edwards, of the Cambridge university, and Dr. J. Cohen, from Paris. In 1985 this Society found the first annual meeting in Bonn, Germany. One of the most important tasks of the ESHRE is the promotion and explanation of Reproductive Biology and Medicine. Among other things, they report about the safety and the quality of assisted reproductive techniques (ART), its morbidity risks, complications and mortality within women and children. Furthermore the ESHRE informs regularly on consequences of ART, concerning hyperstimualtion of the ovary (OHSS), oncogenetics, genetics, inherent malformations on newborns and options of the parents. These reports are published in all sides known journals as for example Human Reproduction.

Facts on ART are presented to the public in almost every European country; however, they are hardly mentioned in Croatia.

This means that in this matter Croatia is isolated from the rest of Europe and that up to the contemporary day a great number of Croatian physicians and also the general population do not know anything about these procedures.

They remain in darkness, because of a view physicians who draw their benefit from the state of general ignorance.

All aspects should become aware to physicians and patients before they

consider a medical supported fertilization, in vitro fertilization (IVF) or embryo transfer (ET).

1.1. Womens' risks

The general risk for the development of adenocarcinomas in infertile women and its correlation with an increased ovarian activity under a specific therapy

Women in the fertilization-capable age and a continuous infertility, have an increased risk for the development of an adenocarcinoma. Hereof a variety of organs is affected, as for example the ovaries, the fallopian tubes, the breasts, the uterus, the lungs, the thyroid gland and the colon (10, 35, 68).

This increased risk exists independently of a therapy against the sterility. Nevertheless, under a therapy it is soaring up from 30 % to above 1000 % for the development of an adenocarcinoma. (32, 11, 28, 14, 15, 16, 30, 31, 27, 46, 20, 47, 38, 12, 33, 1, 5, 8, 39, 44, 42, 133, 134, 135, 136)

In literature three essential causes which are confirmed by various studies are made responsible for the occurrence of an adenocarcinoma in infertile women: (98, 94, 99, 94, 57, 17, 43, 96)

Repeated ovulations and ruptures of the ovarian surface, which can lead to the development of malignancy.

A continuous ovarial stimulation through the hormones LH and FSH, which have a direct carcinogenic effect and also support, through the increased estrogen level, the processing and the growth of tumors.

The exposure of the ovaries to chemical carcinogenic agents.

In this context the meaning of a positive family history for the development of cancer needs to be mentioned particularly.

The knowledge of a positive family history on cancer diseases or melanomas of the breasts, the ovaries, the fallopian tubes, the peritoneum, the endometrium, the stomach, the bile system, the pancreas, the oropharynx or the esophagus is from great relevance. Obviously in this group of patients a special attention and caution must prevail referring to the question of planning and realizing a therapy against the infertility by extracorporeal fertilization. (2, 49, 51, 50)

Infertile women in the fertilization-capable age show an especially high risk for the development of ovarial cancer

In the year 2000 the United states National Cancer Institute draw the conclusion from several investigations, that a repeated and continuous ovulation during lifetime courses a rising probability for the development of ovarial cancer in general. With regard to this, there is a saved evidence that an increased activity of the ovaries caused by an increased level of certain hormones, as for example under the influence of HCG stimulating the ovulation, is closely related to an aggravated risk for the occurrence of ovarial carcinoma.

The analysis of patients with existing ovarial cancer show, that the risk for the development of this kind of neoplasia is hardly influenced by the use of specific pharmaceuticals for the stimulation of the ovulation (65). Women with use of these pharmaceuticals show a risk of 3-4% for developing ovarial cancer, in contrast to the risk of women without specific ovulation stimulating therapy which is about 1-2%. Accordingly, the risk for women for the development of ovarial cancer under an increased ovarian activity caused by ovulation stimulating pharmaceutical therapy rises about 100% compared with the risk of women without such a medication. (181, 4, 19, 67)

Following conclusion can be derived from that:

- The commitment of pharmaceuticals in the therapy of infertility, which increases the number of ovulations can lead directly to an increased risk for ovarial cancer.
- The hazard for the development of a malignant tumor with a low malignant potential lies at 143 % (18).

Clinical studies at more than 12.000 infertile women (primary and secondary acyesis), with an average age of 30 years, show an increased risk for the development of a malignant tumor of 98 %.

Pharmaceuticals for the therapy of infertility, as for example Clomiphencitrat, make the risk go up onto 48 % after 15 years of application (23).

Also the application of Gonadotrophin is connected with an increasing risk of about 146% for the development of cancer after a period of 15 years. (6, 63, 9, 36, 37)

1.2. Possible risks of harm for mother and child referring to the different medical procedures

In vitro fertilization and the occurrence of ovarial cancer

The utilization of the in vitro fertilization led to the occurrence of aneuploidy in the granulosa lutein cells in 50 to 73 %, that means in the vast majority of cases. Further investigations showed aneuploidy at 17% of the oocytes and it needs to be mentioned that this aneuploidy normally represents the starting point for the development of cancer (40, 77). In scientific literature, there are many discussions about the benefit, the risks and the dangers of IVF (137, 172).

In spite of those ones, who claim that there are no dangers or risks in artificial insemination (45, 13, 138) reliable physicians should clear up their patients about possible complications and make these sign a written consent declaration before they carry out the intervention (41).

Some findings in scientific literature emphasize, that already the first attempt to stimulate the ovulation in the ovary can end in the occurrence of ovarial cancer. The starting point for the development of cancer was probably already available and was overlooked through a lacking anamnesis and preliminary investigation. Others report that more than 10 attempts are necessary until it results in the occurrence of ovarial cancer, so that 10 artificial attempts for the stimulation of the ovulation might serve as a boundary. This can not be acceptable even to the most liberal attitude.

1.3. The effects of the pharmaceutical stimulated ovulation and the rising risk for development of cancer

The utilization of pharmaceuticals for the stimulation of the ovulation in the ovary accelerates the development of clinically unapparent and undiscovered tumors (30, 3, 8). CIS has to be mentioned particularly and also new occurring breast cancer (30, 48, 55, 59, 61, 131). Unkila-Kalio et al. (34) refer in their study, that 15% of the study participants with breast cancer and 85% with ovarial cancer had a preceding stimulation of the ovulation. The higher risk for the development of genetically changed

cells and following the occurrence of cancer, increases with every "stamped" ovulation (94, 97, 98, 99, 173). Furthermore the stimulated ovulation intensifies the status of a systemic inflammation, rise of the CRP for example, and of the implantation (87). Besides the stimulations with Gonadotrophin can increase the risk for the development of cancer in the ovaries, the breasts and the endometrium and therefore lead to malignancy (88, 12, 25, 52, 72).

It was seen, that patients who had used pharmaceuticals for the stimulation of the ovulation (Fertilization Drug Therapy–FDT), and have developed breast cancer which continued far, fall sick with a very aggressive kind of neoplasia that shows a low degree of differentiation (56, 58, 60, 62). Within this group of patients a treatment is extremely complicated and it often results in therapy resistance of the tumor so that an extremely bad prognosis for these women results.

As already mentioned, there is a general risk for the development of ovarial cancer in the course of life of approximately 1,8%, which rises up onto 4-5% under the use of a FDT (69, 137, 140, 178, 179). The risk for the occurrence of breast cancer under FDT is among 12%. For cancer of the endometrium the risk under FDT results in a rise from 79% up to 1152% (130). In this context it is needed to say, that not only the risk for the development of a sarcoma of the uterus does increase under a FDT but also the sarcoma itself shows a higher malignancy than other cancer diseases (28, 20, 24, 26, 29).

Furthermore statistics show, that women who underwent a FDT and nevertheless not became pregnant, have a significant rise of the cancer risk in comparison to women without fertility problems in the anamnesis. (22, 139, 181)

This matter of special importance must be made clear to any women who consider to undergo an IVF.

About the effect of the injection of sperm in ovum (ICSI) onto the infantile development and the mothers' risks

The investigation of naturally obtained twins and through ART obtained twins, showed in the arrangement a slower and poorer development of the children in the ART group, especially great differences in physical development werde observed. Nevertheless no difference in the intellectual development of all children up to the 24th life month was proved (90).

In contrast to this, the study of Bowen (123) demonstrates, that although most of the children received by ICSI ran through a normal physical and sanitary development the MDI (mental development index) shows a slight and significant delay of the intellectual development at more than 85 % of the cases. In comparison to that, the part of delayed intellectual development of children brought to life by natural fertilization is about 2 % ($p<0,0001$).

An investigation at the King Chulalongkorn Memorial Hospital in Thailand also showed, that the use of the ICSI technology caused a multiple pregnancy within 27% of the women, while the part of multiple pregnancies at natural conception was about 0,93%. A quarter of these children were premature infants and 85,7% were born by Caesarean section. 1,3% of them appeared with major inherent malformation and at least 49,3% showed one or some slight malformations (125).

In total the number of inherent malformation of newborns under the use of ART increases from 47 to 177 %. With an installement of 9% children received by IVF and ICS also fall ill more frequently. Examples for this are teething troubles, higher number of hospitalizations and operations and higher frequency of major inherent malformations. (146, 144, 92, 127, 120, 124, 154, 155, 156)

1.4. The childrens' side

Risks of medical assisted fertilization (MAF) for children in general

During the luteinization phase the influence of a surplus of Progestin can lead to an endometric luteinisation and to an unripe appearance of the implantation frame, which complicates the nidation of the embryo. (164, 165, 166, 167, 168, 169, 170) In the case of IVF and ET the human menopausal gonadotropin (hMG) has the ability to interrupt the endometric tendency towards the implantation (86, 114, 113, 118, 117, 115, 112, 157, 159, 160, 161, 162, 175, 176, 177). Beyond this, an ovarial hyperstimulation (OHSS) during IVF influences the gene expression in the endometrium. In this case up to 200 genes can change their expression around 300 %. This means a modification of the gene express around a triple in comparison with a normal menstruation cycle (116, 71, 70, 163, 174). Besides investigations on oocytes and embryos show, that only 6,7% of the embryos have a normal mononuclear blastomer (75, 160, 172).

In this context it needs to be made clear, that the modification of mitochondrial genes of the oocytes and the following associated modifications of the embryo have a dominant influence on the further development of the growing up embryo (94, 93, 73, 74, 171).

These variances in the development of the growing up fetus caused by medical assisted fertilization can be named such as variances in the birth weight, fetal malformations, aneuploid chromosomes and syndrome of genetic imprinting (77, 142).

The manipulation of the gametes' and the embryos' under the aid of the IVF technology leads as already mentioned to a prenatal phenotypic modifications of the fetus and also represents an activator of cellular stress, which leads to epigenetic modifications of the genetic expression (143, 76, 122, 53).

In the course of development the incidence of newborns that were received by IVF is about 2% compared with the total number of newborns, while the number of Caesarean sections in this group rises up to 54,3% in contrast to 10,8% of Caesarean sections in the control group.

Added to this, Schieve (91) points in his study, that children who were received by IVF have a 2,6 times higher risk for a low birth weight.

	IVF-Group	control-group
Birth weight less 2500g	57,5%	8,2%
Premature born children	49,9%	8,2%

Special risks for Children received through medical assisted fertilization (MAF)

The special risk for children that were received under the use of MAF to come down with some rare teething troubles lies at 270 to 570 % (143, 145,

106, 104). The in vitro technology, the artificial stimulation of the ovaries or the infertility itself are made responsible as possible reasons for this enormous increase. (81, 78, 82, 80, 79, 121)

As already mentioned the use of medical assisted fertilization, IVF and ICSI technology, causes an increased risk for the fetus to have a low birth weight, cerebral paralysis, injuries of the newborn and inherent malformations (148, 146, 147, 85, 83, 54, 64, 119, 152).

It should also be noticed that the masculine infertility is potentially hereditary and that in 6,4% of the cases hypospadia occurs in children who were received by ICSI.

1.5. Higher frequence of spontaneous abortions, early births and postnatal complications

The risk of spontaneous miscarriages under MAF is near 20% while the normally risk for a spontaneous miscarriage within healthy women is up to 21% (105). Only a few fertile women show a risk of 70% for an early spontaneous miscarriage. Besides, 47% of the children who were received by MAF are in need of immediately intensive care unit support after birth (103, 66).

Studies at 53928 women prove that the incidence of fetal damages is close to 30% in contrast to a number of 19% for fetal damages according to natural conception. Also single-embryo pregnancies achieved through medical assisted fertilization show a lower success as a natural twin pregnancy.

Furthermore in 5,2% of the cases deliveries before the 32nd week appear at women who have been treated with MAF, IVF or ICSI (107, 110, 109, 108, 64, 100, 101, 102).

Helmerhorst even points out, that an early delivery can lie with 227% before the 32nd pregnancy week and with 104% in the 37th pregnancy week. In this case the birth weight lies in average with a risk of 200% under 2500 g and with a risk of 40% under 1500g. In his study 54% of the children needed to be born by Caesarean section and 27% of these newborns needed to be passed over onto the intensive care unit. The perinatale mortality was near 68% (84).

What it all amounts to is, that IVF and ICSI show a 10-times higher risk for a delivery before the 37th pregnancy week and a 7,4-times higher risk for a delivery before the 32nd pregnancy week. The danger for a birth weight of lesser than 2500g is at 1080% and for a birth weight under 1500 g at 440% and 80% of the newborns have an increased risk for cerebral paralysis (RR=1.8). Furthermore there is a rise of the risk for sleep troubles around 100% and a risk for the origin of a malignant hemic disease around 130%. (144, 1, 7, 9, 21, 111, 119, 126, 128, 129, 150, 153)

1.6. Recommendations for the utilization of the ART

Members of the ESHRE recommend the highest transfer to be two embryos or what would be the best thing, to transfer only one embryo (141, 154, 147, 100, 101, 102, 149). A controlled hyperstimulation of the ovaries or an intrauterine insemination should be carried out at most three times (89, 173). It is urgently necessary to create a list in the Croatian Republic in which the morbidity, the complications and the mortality of MFO, IVF and ET are performed.

2. DISCUSSION AND CONSLUSION

More than 200 articles and 150 publications were examined for the circumstances of the case, which emphasize the negative effects of the medical assisted fertilization, IVF and ET on mother and child.

It is necessary to review the method of in vitro fertilization onto the right to live and the dignity of the human being. As an ethical criterion, the human being should not be considered as an object. It should not be allowed to use embryos for experimental purposes, to freeze or to sell them. This was also the conclusion of the supreme court of Costa Rica on 11.10.2000, which led to the prohibition of IVF and ET. The reasons for these decisions lay in the violation of the section four of the Constitution of American Human Rights Convention.

We approve and support all forms of the medical assisted fertilization within the framework of the natural cycle. In spite of this, we would like to come forward with the proposal that IVF and ET within the uterus should not be applied. This stands in unison with the opinion of his holiness Pope Benedict XVI. and the doctrine of the Holy Catholic Church. Through this the love in marriage in family and the responsibility to the upbringing of our children should be preserved.

We kindly ask the readers of these pages to follow us and to contribute on this discussion, by expressing their opinion and arguments freely. This is from special relevance, because it is about an extremely complex, than also ethical, genetic, medical, biologically sensitive topic. Only by the way of conversation a responsible dealing with this subject and the formation of adequate conclusions and an adequate attitude will be achieved.

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CASE REPORT

Anesthesia for Trans Sternal Thymectomy: Modified Non-muscle Relaxant Technique

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Anesthesia for thymectomy in myasthenia gravis is challenging. Early surgical management is now considered to be an important therapeutic intervention for most of the patients of myasthenia gravis. The anesthetic experience of that technique is quite large. It involves either muscle relaxant or non-muscle relaxant techniques. However, the literature is deficient of standard anesthetic technique for thymectomy. Therefore we present in this report a modified non-muscle relaxant technique for thymectomy. We report one case with thymectomy under general anesthesia using fentanyl and propofol for induction and endotracheal intubation using non-muscle relaxant technique. The intubating, intraoperating and postoperative conditions were excellent. Key words: thymectomy, surgery, non-muscle relaxant anesthesia

corresponding

1. INTRODUCTION

Myasthenia gravis is an autoimmune disorder with an estimated prevalence of 1 in 20,000 (1). The disorder affects females more than males, usually in their third decade and is frequently associated with morphological abnormalities of the thymus. Myasthenia gravis (MG) is an autoimmune disease characterized by release of antibodies against acetylcholine receptor at the neuromuscular junction (1, 2). The techniques of anesthesia for thymectomy in myasthenia gravis could be either with or without muscle relaxants. That warrants revisiting and modifies our anesthetic technique. This report will focus on the modified non-muscle relaxant anesthetic technique for trans sternal thymectomy in patient with myasthenia gravis.

2. CASE PRESENTATION

A 23-year-old female, body weight 54 kg, does not smoke or drink alcohol, known to have myasthenia gravis. The diagnosis of myasthenia gravis was made based on the severity of her symptoms and laboratory findings. She had generalized muscle weakness. The patient was scheduled for trans-sternal thymectomy and preanaesthetic evaluation was carried out. Preoperatively she was treated in Clinic of Neurology, by neurologist, with corticosteroids, pyridostigmine bromide, H_2 blockers, potassium preparations, with marked improvement of her symptoms. Her preoperative laboratory investigations and ECG were within normal limits. Chest CT scan showed in the upper mediastinum, in restrosternal area hyper density with dens metric values of the solid tissue. One dose of plasma (250 ml) was administered preoperatively. On arrival in the operation theatre intravenous line was secured with 16G cannula. Monitoring included, non-invasive monitoring of blood pressure, ECG, pulse oximeter, expiratory CO_2.

Patient was preoxygenated with 100% O_2 over three minutes and anesthesia was induced with Fentanyl 3 mcg/kg i.v. and Propofol 4mg/kg i.v., after which there was loss of all responses. Larynx was sprayed with 10% Xylocaine; she was intubated with no. 7 mm cuffed portex endotracheal tube without use of muscle relaxant and ventilation was continued with 50% N_2O in O_2. There was no haemodynamic response to laryngoscopy and intubation conditions were excellent.

Anesthesia was maintained with bolus doses of Fentanyl 200 mcg after intubation and 100 mcg when was required and Propofol infusion at the rate of 6-12 mg/kg/h. Thymectomy was completed uneventfully and the patient was hemodynamically stable. At the completion of surgery (215 minutes duration), N_2O was switched off; 100 % oxygenation continued, Propofol infusion was stopped. Neostigmine 1.5 mg, and Atropine 0.5mg, were administered. Patient regained consciousness and adequate muscle power and was extubated after 13 minutes of satisfying all clinical criteria, of recovery. She was then transferred to the intensive care unit (ICU), for better post operative monitoring. Post operatively she continued her routine treatment and also atropine was added in her therapy. Postoperative analgesia was achieved with Tramadol 100mg in 500 ml of Sol.NaCl 0.9% and Diclofenac 75mg/iv/12h. The patient was comfortable and analgesia was excellent. Her post–operative x-ray chest showed no abnormality. The patient was discharged from the ward after an uneventful 16 days of stay.

3. DISCUSSION

Neuromuscular weakness and easy fatigability are the hallmarks of myasthenia gravis which results from autoimmune damage to the post synaptic nicotinic receptors (3). There is considerable evidence that thymectomy improves survival, rate of remission and accelerates symptomatic improvement in patients with myasthenia gravis (4).So we utilized Propofol with Fentanyl for rapid induction, better relaxation of jaw muscles and for providing adequate depth of anaesthesia. However, we have modified our technique which we present in this report to be non-muscle relaxant without thoracic epidural analgesia. Our current anesthetic technique includes non-muscle relaxant approach, tracheal intubation with endotracheal tube, and continuous infusion of Propofol with bolus doses of Fentanyl on demand.

4. CONCLUSION

In conclusion, anesthesia for thymectomy in myasthenia gravis is challenging. Use of modified non-muscle relaxant technique for thymectomy provided excellent intubation, intraoperative and postoperative conditions. With this technique muscle relaxants can be avoided, which facilitates early extubation and avoids postoperative mechanical ventilation.

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NEWS

On the Ocassion of the 50th Anniversary of the Academy of Medical Sciences of Croatia

In Zagreb on 15 June 2011 was celebrated 50th Anniversary of Croatian Academy of Medical Sciences (AMSC). The ceremony took place in the Narodoni dom, the famous architectural structure from the 18th century, which the Count Draskovic richly endowed (do not known if he only equip it or made, order it?) to mark important anniversaries and events of historical significance for Croatia and the capital. The ceremony was attended by the most distinguished political and academic representatives of the Republic of Croatia, over two hundred academics, especially from medical science, whose academic reputation and research results contributed significantly to the reputation of the Republic of Croatia in the development of medicine and health. Distinguished guests were addressed by: Mr. Ivo Josipovic, the President of Croatia, Ms. Jadranka Kosor, Croatian Prime Minister, Mr. Luka Bebic, President of the Croatian Parliament, M.. Darko Milinovic, Croatian Deputy Prime Minister and Minister of Health, Academician Zvonko Kusic, President of the Croatia Academy of Arts and Sciences, and academic Zeljko Reiner, president of the Croatian Academy of Medical Sciences.

After the formal welcome speech, President Mr. Ivo Josipovic awarded the highest state award - the Charter of the Croatian Republic "for outstanding contribution to the Croatian Academy of Medical Sciences during the 50 years of its existence." Mr. Ivo Josipovic, speaking to academics, in his speech said: "The results we've achieved, numerous publications, abroad activities, successes, inventions, patents, new technologies, new medical procedures, are really an important contribution to the quality of our lives." Ms. Kosor point out that Croatia will become the 28th member of the European Union and the Croatian language 24th official EU language, and that Croatia's EU accession brings all the richness of Croatian, including a wealth of work and results achieved by Croatian scientists and experts from all areas including medical and AMSC which has so far published over 100 scientific books by their academics, which is an immeasurable contribution to the development of medical science, not only in Croatia but also in the world.

Otherwise, the main task of the AMSC is to promote biomedical sciences for improving the health of the Croatian population. The Academy has over 300 regular and 50 cooperating members, best scientists in biomedicine chosen by secret ballot. It is the case of experts who stand out within the scientific activity in a specific medical discipline or medical related biomedical sciences and who have contributed significantly to the development medical science in Croatia. AMSC is conducting a series of scientific projects, organized by dozens of scientific researches through annual meetings and the College Board, and a prestigious members for contributions to the development of medicine is awarded respected awards and prizes ("Ante Šercer" the best scientific work in the past year, "Borislav Nakić" the best scientific work by person younger than 35 years of age and the "Laureate of the Academy," a member of AMSC who with their life work in particular contributed to the development of Croatian medicine and AMSC). AMSC is issuing four indexed journals (Acta Medica Croatica, Croatian Medical Journal, Social Psychiatry and AMSC Bulletin) and also new books in the field of medicine, written by its members. AMSC regularly collaborates with others academies of medical science in Europe and worldwide and is a member of numerous international associations.

It was founded in 1961 as the Commission for scientific and research work of the Main Board of the Croatian Medical Association. In 1971 it was renamed into the Medical Academy Assembly, then in 1983 was separated from the Croatian Medical Association and became an independent organization - Croatian Academy of Medical Sciences. Its presidents, academician Asim Kurjak and academic Zeljko Reiner wholeheartedly helped establishment of the Academy of Medical Sciences of Bosnia and Herzegovina (AMSB&H) in 2008. I had the honor and pleasure as the President of Academy of Medical Sciences of B&H to attend this solemn and important event and have useful discussions on future cooperation between our two academies in all areas of activity and express special gratitude for the previous help of AMSC to the development of AMSB&H..

Academcian Izet Masic, MD, PhD

Proslava 50. obljetnice AMZ Hrvatske u Zagrebu, 15. juna/lipnja 2011. godine. U prvom redu sjede, slijeva nadesno: akademik Izet Mašić, predsjednik AMNuBiH; akademik Zvonko Kusić, predsjednik HAZU; mr. sci. Darko Milinović, potpredsjednik Vlade RH i ministar zdravstva i socijalne skrbi RH; predsjednik Sabora RH Luka Bebić; predsjednica Vlade RH Jadranka Kosor; prof. dr. Ivo Josipović, predsjednik RH; i akademik Željko Reiner, predsjednik AMZH

FIGURE 1.

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