It is our honor and great pleasure to invite you to attend The Second Congress of Anesthesiologists and the Reanimatologists of Bosnia and Herzegovina, which will be held from 11 - 13th November 2010 in Hotel Tuzla.

Congress is organized by the Association of Medical Doctors Anesthesiologists - Reanimatologists of Fed eration of Bosnia and Herzegovina and the Associa tion of Anesthesiologists and Reanimatologists of Republic of Srpska, under the sponsorship of the Federal Ministry of Health, Ministry of Health of Republic of Srpska and Ministry of Health ofTuzla Canton.

We hope that the proposed topics will contribute to the development of our profession and our work, and through the numerous studies of participants we will demonstrate our knowledge and professional activity. Our wish is to present our experience and results and with members of Congress from the wider region ex change acquired knowledge and achievements.

We would like to invite the colleagues from other spe cialties, with whom we collaborate, to take part in the Congress.

We will try to show our hospitality, the sights of Tuzla and to make your stay as pleasant as possible.

Tuzla is a city of salt with a long history multicultural and multinational tolerance. The town is located in the northeastern part of Bosnia, at an altitude of 231 m, and there are around 170.000 inhabitants. Tuzla is the economic, medical and university center in the Tuzla canton and one of the major cities in Bosnia and Herzegovina.

We look forward to your visit to Tuzla and hope you will get valuable experience and nice memories from Congress.

Associate Professor
Mirsada Prašo, MD, PhD
Co-President of the Organizing Committee
Guest Editor of the supplemet issue of AMS

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Editorial Team

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ACTA MEDICA SALINIANA

REVIEW PAPER

Monitoring in Anesthesia and Intensive Care Unit

Mirsada Prašo, Jasmina Smajić, Halid Mahmutović

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Monitoring is the dynamic follow up of physiological parameters of patients. Modern monitoring is based on three principles, physical (use of different monitors), chemical (biochemical analysis), and clinical (patient's state assessment based on anesthesiologist's experience and some scoring systems).

Monitoring is the logical thinking about the overall condition of the patient and the subsequent treatment, which represents part of the daily anesthesiologist 's duty .The aim of monitoring is to increase the anesthesiologist's attention and help him in the management of anesthesia and other treatments. Although the largest number of patient data we obtain with the help of devices, basic monitoring we perform with our senses, which are in many situations of daily work irreplaceable.

Keywords: *monitoring; anesthesiologist; device*

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Competing interests
The authors declare no competing interests.

INTRODUCTION

Name of monitoring comes from the Latin word monere meaning warning, directing atention, follow-up. Modern monitoring is based on three principles:

-Physical (use of different monitors)
-Chemical (Biochemical analysis)
-Clinical (patient's state assessment based on anesthesiologist's experience and some scoring systems).

MONITORING OF CARDIOVASCULAR SYSTEM

Assessment of adequacy of perfusion

Maintenance of vital organs perfusion and ensuring adequate tissue oxygenation is one of the main tasks of Anesthesiologists. This is achieved by sufficient cardiac output, hemoglobin concentration and hemoglobin oxygen saturation. Clinical, hemoglobin concentration and oxygen saturation are estimated based on skin color, and minute volume of the heart based on blood pressure and pulse quality. Adequate perfusion depends on venous flow to the heart, the contractile force of the heart and blood pressure. Peripheral perfusion is assessed on the basis of color, warmth and moisture of the skin. Warm, dry and pink skin with well-filled veins and rapid return color nail matrix after previous compression (2 seconds) are good indicators of perfusion. The difference between central and peripheral temperature may also be an indicator of adequacy of perfusion. For this purpose, it is usually considered the difference between the temperature in the nasopharynx and the thumb of feet (1).

Monitoring blood pressure

Arterial blood pressure is proportional to cardiac output when the peripheral resistance is constant. Changes in the intravascular volume, vasomotor tone and cardiac output affect on the value of blood pressure. When blood pressure is inadequate it will affect the tissue perfusion. In critically ill patients selfcontrol mechanisms of the vascular system, especially in the brain and kidneys, may be impaired, and perfusion of these organs will depend on the pressure. Flow to the tissues is directly dependent on mean arterial pressure. Mean arterial pressure is the average value of all the pressures measured at short intervals over a certain period. It is not equal to the middle between the systolic and diastolic blood pressure, because blood pressure during the greater part of the cardiac cycle remains close to the diastolic pressure. The mean arterial pressure is usually determined by 60% and 40% diastolic systolic pressure, and automatically displayed on the monitors that measure blood pressure and cardiac output. Knowledge of mean arterial pressure is needed for the calculation of systemic vascular resistance. Blood pressure can be measured by indirect and direct methods. Indirect:

auscultation, oscillometric and Dopler method; direct-placement of the plastic cannula in the radial, femoral or dorsalis pedis artery, , and connect with the transducer that converts pressure energy into an electrical signal. The presence of air or clots in the system, and blocked cannula can give false values (1,2).

Monitoring pulse rate

One method is palpation of the pulse of the a. radialis, brachialis, temporalis superficialis, carotis. There have been constructed some apparatus for registering the pulse: the digital plethysmography and pulse oximeter (1).

Electrocardiogram

Monitoring of the electrocardiogram is a useful, noninvasive diagnostic method. Anesthesiologists are most interested for changes in frequency and rhythm, the occurrence of extra systoles or interference in the conduction, as well as ST segment depression or elevation, because these changes may precede changes in output, and ST segment changes may indicate myocardial hypoxia. But it should not be forgotten that the ECG reflects the electrical but not hemodynamic activity of the heart does, and that the circulation can be in a serious deficit in spite of relatively normal ECG. Incorporate ECG is not a substitute for palpation of the pulse, which in addition to disturbances of heart rate and rhythm can register changes in blood pressure (2).

Body temperature

Measurement of body temperature can be used to assess tissue perfusion and the amount of blood lost. Central temperature is usually measured on the membrana tympani, the esophagus, bladder or rectum. There is increased difference gradient between central and peripheral temperatures in the states of socks. All modern monitors have incorporated an electronic thermometer (1,2).

Central venous pressure (CVP)

A useful indicator of volume status of the patient. CVP value depends on: contractive force of the heart, the volume of circulating blood volume and vascular capacity and its resistance. Insufficiency of any of these three factors can lead to circulatory failure. CVP is used in the assessment of sufficient blood and fluids volume compensation to patients in hemorrhagic or septic shock, and to treat heart failure (1).

Pulmonary arterial pressure

By placing a catheter into the pulmonary artery (Swan-Ganz) catheter is enabled to obtain hemodynamic monitoring various parameters such as pulmonary artery pressure (PAP), occlusal pulmonary artery pressure or a pulmonary capillary wedge pressure (PAOP or PAWP), cardiac output, oxygen saturation mixed venous blood, and can be obtained and derived value of the systemic and pulmonary vascular resistance.

Swan Ganz catheter has 4 lumens:

- The proximal lumen, which is located approximately 25 cm from the top, and after catheter placement should be located in the right atrium and used to measure CVP
- The distal lumen, which is open and connected to the pressure inverter and allows the reading of the wave on the monitor (after correct placement it is located in the large branche of the pulmonary artery and measure the pressure in it)

- The third lumen is used to inflate the balloon surrounding the catheter tip
- The fourth lumen is connected with thermistor at the top of the catheter and measures the temperature of blood in this place which allows the measurement of cardiac output (1).

Cardiac output

Thermo dilution method of cardiac output measuring is the gold standard in clinical practice. For this purposes pulmonary arterial catheter has to be placed. When a known quantity of solution, chilled at a particular temperature lower than body is injected into the right atrium, changes in temperature of blood in the pulmonary artery is determined by the volume of blood that injected solution has received. This volume signifies the cardiac stroke volume, and temperature change is inversely proportional to its amount. By the proximal end of the catheter should be injected 10 ml of cold solution and then continuously register the temperature of blood that leads to thermistor located near the catheter top. The screen displays the so-called thermo diluted curve that indicates a change in temperature of blood in time. Area under the curve corresponds to the volume of blood that was received injected solution, and its numerical value is calculated by the computer program (1,3).

MONITORING OF THE RESPIRATORY SYSTEM

Clinical monitoring of respiratory function is the basis for vital functions monitoring. It involves observing the movement of the patient's chest, rate, rhythm and depth of breathing, the use of supplementary respiratory muscles, or the occurrence of paradoxical breathing as well as observation of skin color and mucous membranes. Careful auscultation complements the impression of the respiratory function adequacy. Increase respiratory rate, shallow breathing and paradoxical breathing, use of supplementary muscles, tachycardia and excessive sweating indicate inadequate ventilation, and impending respiratory failure. Tidal and minute volume, breathing frequency, partial pressure of CO2 in the expiratory air (capnograph), airway pressure, partial pressure of O2 (Clark oxygen electrode), oxygen saturation of hemoglobin in the arterioles (pulse oximetry), are observed in mechanically ventilated patients. Pulse oximetry is a simple and noninvasive method for oxygen saturation (SpO2) monitoring and used to assess the adequacy of gas exchange.

Gas analysis of arterial blood are useful screening tests in assessing the function of the respiratory system and often the first laboratory signs threatening problems with respiration (4).

MONITORING OF RENAL FUNCTION

Urine excretion in an hour is a useful guide for assessing cardiac output, intestinal perfusion and renal function (while one hour is normally extracted from 0.5 to 1 ml urine per kg body weight). Measurement of specific gravity and osmolality of urine is used to differentiate prerenal from renal kidney failure . For the assessment of renal function are monitored and the values of urea, creatinine, and serum electrolytes (5).

MONITORING LIVER FUNCTION

To monitor liver function, serum proteins, bilirubin, coagulation factors, antithrombin-III, protein C, liver enzymes are analyzed (5).

MONITORING OF THE CENTRAL NERVOUS SYSTEM

The need for the application of sedatives, opioids and muscle relaxants makes it difficult to assess the clinical features of central nervous system. Monitoring of the central nervous system during anesthesia is primarily designed to assess the depth of unconsciousness (lack of awareness), to avoid the presence of consciousness during anesthesia. There are subjective and objective methods for assessing depth of unconsciousness during anesthesia. Subjective methods are based on movement and sympathetic response to the stimulus and depend on the opinions and experiences of anesthesiologists. Objective methods are based on the sensitivity of the monitor. Measurement of intracranial pressure, electroencephalography and cerebral function monitoring is used to monitor the functions of the central nervous system in those critically ill patients in whom that monitoring is necessary. However, the assessment of neurological Glasgow coma score and neurological examination are still the basis in assessing the function of the CNS (1,2).

SCORING SYSTEMS

Monitoring at Intensive Care Unit (ICU) includes observing the patient over several days, monitoring with the most perfect appliances, functioning alarm system, specially trained staff that knows to interpret monitor parameters, a sufficient number of staff in the ICU. Monitoring in ICU includes monitoring the overall clinical condition of patients that result in much information for assessing the degree of organism disease (6).

Identifying critically ill patients or patients who could benefit from treatment in the ICU is largely correlated with the scoring system that assesses the severity of the disease. Scoring systems allow classification of patients in large groups, where with mathematical equations could be obtained the data that objectify and make it easier:

a. assessment of patient's condition at the time of testing,
b.process of the disease,
c. assessment of treatment outcomes

The most commonly used scoring systems in adult patients in ICU are:

APACHE II i III SCORE (Acute Physiology And Chronic Health Evaluation),

LODS (Logistic Organ Dysfunction Score),

MOF (Multiple Organ Failure Score),

MOD (Multiple Organ Dysfunction Score),

SSS (Sepsis Severity Score),

SAPS (Simplified Acute Physiology Score),

SOFA (Sepsis-related Organ Failure Assessment Score),

SICKNESS SCORE,

RAPS (Rapid Acute Physiology Score),

TRS (Adult Trauma Revised Score),

LIS (Lung Injury Score),

GCS (Glasgow Coma Scale)

APACHE II Score

APACHE II Score is a commonly used scoring system in ICU. It represents a modification of the APACHE Score and is used to assess the general health of the patient based on:

1.Acute physiological score APS,

2.Score for patients' age,

3.Score for chronic disease.

Acute physiological score correlates with the severity of disease and consists of 12 parameters. The values for the APS will be taken during the first 24 h of admission to the ICU. Data processing is taking the worst value measured. The results obtained can be used to estimate mortality rates of patients in the ICU (6).

Lung Injury Score

ARDS (Acute Respiratory Distress Syndrome) occurs the most often in the septic syndrome, as result of trauma, direct damage to lung parenchyma and massive transfusion. Criteria for ARDS:

a. acute onset,
b. risk factors,
c. PaO2/FiO2 <200 mmHg,
d. bilateral pulmonary infiltrates,
e. wedge pressure ≤ 18mmHg

In patients with impaired lung parenchyma is commonly used Lung Injury Score. Its use value is the high-

est in patients receiving mechanical ventilation.

The Lung Injury Score can be used to assess the adult patient for the extent of acute pulmonary damage. It can be used both at the onset of a lung disorder and during the course of the illness to monitor changing lung involvement.

Expressed damage to lung parenchyma exists if the resulting value is greater than 2.5 (7, 8).

CONCLUSION

Physical monitoring of patients in conjunction to clinical exam, chemically and radiological monitoring with daily scoring of patients is mandatory, indispensable dynamic control of the critically ill. Many clinicians are of the opinion that the outcome of treatment depends on adequate monitoring because continuous monitoring detects the slightest changes in the organism of patients that can turn the entire course of the disease or in the direction of healing or to a fatal outcome. The aim of monitoring is to increase the anesthesiologist's attention and help him in the management of anesthesia and other treatments. Over time, made the devices (computer monitors) to monitor a range of functions that facilitate the monitoring of patient's condition. But it should be noted that there is no appliance that could replace a careful and conscientious anesthesiologist.

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REVIEW PAPER

Heart Transplantation – Perioperative Evaluation, Intraoperative and Postoperative Treatment

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The authors declare no competing interests.

INTRODUCTION

In late 1990-is nearly 5 million Americans had heart failure (HF), with an incidence of 10 per 1000 population among persons older than 65 years of age. HF is the reason of at least 20% of all hospital admission among older persons. On the other side, HF is largely preventable, due to control of blood pressure and other vascular risk factors.

Recent years, interdisciplinary approach to heart failure treatment has made significant improvement. The staging of HF and combined therapy with ACE inhibitors, angiotensin receptor blockers, beta blockers, aldosterone antagonists, diuretics and neseritide have a direct beneficial effect on the myocardium improving its functional capacity and enhancing reverse remodeling. Cardiac resynchronization therapy with biventricular pacing improves left ventricular function and favors reverse remodeling.

Additional effort was made with different surgical techniques for left ventricular remodeling, with idea to reduce volume overloading and work stress of the left ventricle and to improve work efficacy.

Mechanically assisted circulation is worldwide accepted option for patients with extended heart failure, as a prolonged therapy or as a bridge to heart transplantation.

Heart transplantation is, still, option for end stage heart failure. In Europe, about 2000 heart transplant procedures are performed per year, with the increasing shortage of suitable donors. According to the reports the 1 and 3 years survivals after heart transplantation (HT) in USA, for period 1999-2001, were approximately 85% and 77%, respectively. Despite the innovations in left ventricular assist devices as well as in artificial heart technology, simultaneously with improvement in medical treatment of the heart failure, heart transplantation is still "the golden standard" in the end stage heart failure, resistant to the medical treatment.

PATHOPHYSIOLOGY BEFORE HT

Candidates for HT are usually patients with idiopathic or ischemic cardiomyopathy, with both systolic and diastolic dysfunction. Left ventricular ejection fraction (LVEF) below 20% with increased pulmonary and systemic vascular resistance. Therapy of heart failure consists of: diuretics, vasodilators (nitrates, hydralazine or ACE inhibitors) and incremental β– blockade. Some pts often require inotropic therapy, intravenous infusion of direct β-adrenergic agonists (dopamine or dobutamine) or phosphodoesterase inhibitors (amrinone, milrinone) sometimes combined with mechanically assisted circulation (intra-aortic balloon pump or other mechanical devices).

Preoperative donor evaluation has to assess the stage of heart failure as well as other organs functional reserve.

ANESTHETIC MANAGEMENT

Immediately after the admission to hospital, donor has to be evaluated, his medical records at last examination (renal, hepatic or pulmonary dysfunction) , while some laboratory findings, TEE and chest x-ray should be repeated.

Premedication and induction to anesthesia should be managed according to actual hemodynamics (some hospital patients will be supported with inotropic infusions and/or IABP and should be considered to have a "full stomach". Induction has to provide minimal myocardial depression, (moderate dose of narcotic with short acting hypnotic or high-dose narcotic technique with or without benzodiazepines). Direct β-agonists (epinephrine) should be readily available as well as α-agonists (phenylephrine, norepinephrine) to compensate vasodilatory effects of anesthesia.

Usual invasive hemodynamic monitoring should be used (arterial, central venous and/or pulmonary artery catheter) sometimes with transesophageal echocardiography.

Pre cardiopulmonary bypass period is usu-

ally stabile, with proper volume loading and inotropic support. Most patients will have an excess of intravascular volume, and administration of diuretics with/or hemofiltration may be beneficial.

After the graft implantation has been done, aortic cross clamping released, the period of graft reperfusion starts. In this period of CPB patient has to be prepared for the weaning of CPB. Inotropic support has to be considered. Patients with pulmonary hypertension are at risk of right heart failure, and may benefit from a pulmonary vasodilator (isoprenaline, milrinone, prostaglandin E1). Due to heart denervation, pace maker for rhythm control is mandatory.

Despite to heparin neutralization by infusion of protamine, meticulous attention has to be paid to surgical hemostasis, with empiric administration of platelets, fresh frozen plasma and cryoprecipitate due to coagulopathy, guided by coagulation studies (thrombelastography, platelet function assessment).

PATOPHYSIOLOGY AFTER TRANSPLANTATION

Cardiac denervation is unavoidable during HT. The consequence is substantially altered response to demands for increased CO. So, the maintenance of adequate preload, during perioperative period, is crucial. Denervation has the direct implication on the choice of inotropic support after the transplantation. Agents with direct cardiac effects (epinephrine or isoproterenol) are the first choice, supported by pace maker controlled rhythm if it is necessary.

Early complications after HT include hyperacute and acute rejection, cardiac failure, pulmonary and systemic hypertension, cardiac arrhythmias and renal failure. All of these complications may be part of rejection while hypertension and renal failure may be the consequence of immunosuppressive regimen (cyclosporine).

Acute rejection is a constant threat in the early postoperative period (6 months) and may be presented in different forms (low CO, arrhythmias). Clinical evaluation and regular endomyocardial biopsies are the first step of control. Detection of rejection indicates aggressive treatment, usually with pulse of glucocorticoid with eventual switch from cyclosporine to tacrolimus.

POSTOPERATIVE THERAPY

During the first few postoperative days, principles of treatment are very similar to periopartive strategy. Invasive monitoring of right and/or left ventricle failure, low CO, rhythm disturbances, renal failure and clinical signs of eventual rejection are mandatory. Aggressive immunosuppression and monitoring of its effects is the most important (the signs of rejection on one side and deleterious effects on white blood cells and T-cells on the other side). Prevention and treatment of any infection are of the equal importance. Bacterial pneumonia is frequent in firs days, but patients are susceptible to opportunistic viral and fungal infections in firs several weeks too.

Hypertension and renal failure, impaired by immunosuppression (cyclosporine, tacrolimus) are permanent threat during postoperative period. Allograft coronary vasculopathy remains the most important and frequent complication after heart transplantation in firs 3 to 5 years, with incidence up to 80% after 5 years. Lymphoma of malignant etiology is less frequent, but still often during first years after heart transplantation.

PRELIMINARY EXPERIENCE – DEDINJE CARDIOVASCULAR INSTITUTE

In five year period (1995-2000) 7 heart transplantations in 7 male patients (pts) were done. All pts were in NYHA grade IV, average age 43. Five of them had ischemic and two idiopathic dilated cardiomyopathy. Average ejection fraction (EF) was 13±2,5% with average end/systolic diameter (ESD) 65±3 mm and average end-diastolic diameter (EDD) 74±4 mm. In five of them, mitral regurgitation grade III and tricuspid regurgitation grade II were diagnosed. All pts were premedicated with atropine and midasolam, while anaesthesia was maintained with midasolam, fentanyl and pancuronium. Average extracorporeal circulation time was 129±31 min and average aortic cross clamping time was 65±11 min. protocol of immunosuppressive therapy was: imuran and ATG two hours prior to surgery, methylprednisolone after the induction of anaesthesia and cyclosporine intravenously, after the surgery. In all pts inotropic support with dopamine was needed with infusion of nitroglycerine and furosemid. Infusion of isuprel was used in three pts.

There were no operative deaths. All pts were extubated in 8-12 hours after the surgery. Two were reoperated because of bleeding and one died the 27th day after the surgery, due to hepatorenal insufficiency. One of the discharged pts died the 96th day after the transplantation due to aspirational pneumonia, one died five years later because of extensive coronary disease and one died six years after the surgery due to alcohol abuse and cirrhosis of the liver and one died two years after the transplantation due to tuberculosis.

Our preliminary results and great experience in cardiovascular surgery might be corner stone for better organization of the heart transplantation program with adequate support of the National Health Service and society.

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REVIEW PAPER

Protocol Guidelines for Management of Sepsis and Septic Shock

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Sepsis is a major cause of morbidity and mortality in the intensive care units worldwide. In the USA annually 750 000 people have sepsis, and more than 200 000 patients die. Studies show that 17% patients at the admittance to the ICU had severe sepsis with organ dysfunction, and that group mortality was around 45%.

Studies conducted on the incidence of sepsis and septic shock and survival rate in the last 25 years, found that over the last three decades the incidence of sepsis in the USA had increased – almost tripled, yet the mortality had tendency to drop.

Recently there is an increasing sense of responsibility for intensive care physicians (intensivists) in early detection of sepsis and prompt therapy in the first golden hour of resuscitation, which has great influence on definitive outcome of the treatment.

Aiming to reduce variations, that differed by the range of 100%, in mortality rate of the mentioned pathologic conditions, consensus on defintions of sepsis and septic shock were agreed upon in 2004 and 2008.

Since the time frame to administer optimal therapy is very short, the imperative to initiate antibiotic therapy is 30-60 minutes upon contact with septic patient, when associated survival rate was 79.9%. With effective antimicrobial therapy delay to six hours survival was just 42.0%, and for every additional hour delay in effective antimicrobial initiation survival dropped an average of 7.6%.

In addition to the appropriate antibiotic therapy, fluid resuscitation and other supportive therapy, some patients with septic shock might have better (treatment) outcome when corticosteroids and recombinant human active protein C have been applied.

Keywords: *sepsis, septic shock, diagnosis, treatment, incidence, mortality*

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Competing interests
The authors declare no competing interests.

INTRODUCTION

Sepsis is one of pathologic conditions that dominates in the modern intensive care units (ICUs) and a major cause of morbidity and mortality in the ICUs worlwide [1, 2, 3].

Recently there is an increasing sense of responsibility for intensive care physicians (intensivists) in early detection of sepsis and prompt therapy in the first golden hour of resuscitation, which has great influence on the rate of definitive survival [3].

In order to timely diagnose and implement appropriate therapy, it was necessary to harmonize the definitions of sepsis and septic shock. By consensus sepsis was defined as a suspected or proven infection with two or more parameters of systemic inflammatory response syndrome (SIRS) [1, 4]. SIRS is body's response to various stimuli (burns, pancreatitis, trauma), and not only the inflammatory process caused by bacteria, viruses and rickettsiae [5]. Early signs of SIRS include: increase in respiratory rate > 20/min., an increase in heart rate > 90/min., altered mental status. Late signs (symptoms) of SIRS arise due to lack of oxygen supply to the tissues, and are manifested as folows: reduction of output of urine, an initial rise in diastolic pressure followed by a drop in systolic blood pressure and alterations in body temperature > 38°C or < 36°C, leukocytosis (> 12 000/mm3) or leukopenia (< 4000/mm3) [5, 6]. Severe sepsis is sepsis with at least one organ dysfunction or hypotension (< 90 mmHg) [1, 4, 5, 6]. Septic shock is severe sepsis with multiorgan dysfunction and hypotension present despite adequate fluid resuscitation, and often requires treatment with vasoactive drugs [1, 4, 5, 6].

Subset	Usual pathogen	Preferred IV therapy
Unknown source	Enterobacteriaceae	Meropenem 1 g/8 h/15 d *or* Piperacillin/tazobactam 3,375 g/6h/15 d
Intraabdominal pelvic source	Enterobacteriaceae B. fragilis	Meropenem 1 g/8 h/15 d *or* Piperacillin/tazobactam 3,375 g/6h/15 d *or* Ertapenem 1 g/24 h/1d *or* combination therapy: Ceftriaxone 1 g/24 h/15 d *plus* Metrinidazole 1 g/24 h/15 d
Urosepsis	Enterobacteriaceae E. faecalis (VSE)	Meropenem 1 g/8 h/15 d *or* Piperacillin/tazobactam 3,375 g/6h/15 d

Table 1. Empiric therapy: sepsis, septic shock (taken from Cunha BA, Antibiotic essentials, 7th ed., 2008) [23]

PATHOPHYSIOLOGIC EVENTS IN SEPSIS AND SEPTIC SHOCK

In occurrence of sepsis, key role plays the innate system, primarily macrophages and neutrophils, which in an encounter with bacteria and bacterial toxins lead to the synthesis of proinflammatory mediators (TNF-α, IL-1ra, IL-6, IL-12, IL-18). These events are followed by a synthesis of secondary inflammatory elements from the metabolism of arachidonic acid (prostaglandins and leukotrienes), then activation of the clotting process, where a key role plays tissue factor and activated monocytes/macrophages [1, 2, 4]. At the same time, the synthesis of anti-inflammatory mediators, which are trying to block the inflammatory processes (TGF-β, IL-8, IL-10), runs [1, 2].

Local activation of the endothelium plays a key role in atempted blockade of infection, resulting in neutrophils adherence to the epithelial cells. Endothelium of blood vessels reacts as damaged, with increased permeability, microvascular thrombosis, tissue ischemia, and apoptosis of cells. This process is also the result of activation of thrombin, procoagulant factor, which leads to activation of multiple inflammatory mechanisms. Activation of fibrinolysis is an attempt to stop procoagulant state [4, 7]. Systemic activation is responsible for development of multiple organ dysfunction (MODS). From pathophysiologic aspect, in the occurrence of sepsis there are three key factors: the damage of the endothelium, activation of coagulation and programmed cell death (apoptosis) [1, 2]

In septic shock, there is increased delivery of oxygen (DO2), higher than normal, and also, due to increased metabolic needs, increased oxygen consumption (VO2) [4, 7].

INCIDENCE AND MORTALITY

Literature data show that mortality in sepsis is 35-70%. Considering that the incidence differs by almost 100%, and in order to get as close percentages of actual deaths, it was necessary to verify by the consensus definitions of sepsis and septic shock, which was done in 2004 [8]. In the USA sepsis develops in 750 000 people annually and more than 200 000 die [2, 3, 9]. Literature data show that already at ICU admission severe sepsis with organ failure exists in 17% of patients, with a mortality rate of around 45% [3]. Data from one large pan-European study that included 198 intensive care units in 24 European countries showed that of total 3147 patients, 1177 (37.4%) had sepsis, 777 (25%) of these patients had sepsis on admission to ICU [9]. There were significant differences in % of sepsis and septic shock in some European countries. Percentage of sepsis ranged from 18% (Switzerland, n = 114) to 73% (Portugal, n = 69), and severe sepsis from 10% (Switzerland, n = 114) to 64% (Portugal, n = 69). Studies conducted on the incidence of sepsis and septic shock and survival rate in the last 25 years, found that over the last three decades the incidence of sepsis in the USA had increased – almost tripled, yet the mortality had tendency to drop (epidemiologic review of more than 10 million sepsis cases) [10].

Table 2. Empiric therapy: urosepsis – additional IV therapy (taken from Cunha BA, Antibiotic essentials, 7th ed., 2008) [23]

	ADDITIONAL IV therapy
Urosepsis (Group D Enterococci)	Ampicillin 2 g/4 h/1-2 wee *or* Linezolid 600 mg/12 h/1-2 weeks *or* **combination therapy with**: Vancomycin 1 g/12 h/1-2 weeks *plus* Gentamycin 240 mg/24 h/1-2 weeks

Subset	Usual pathogen	Preferred IV therapy
Lung source	S. pneumonia H. influenzae K. pneumoniae	Quinolone/24 h/15 d *or* Ceftriaxone 1 g/24 h/15 d
Nosocomial pneumonia VAP	P. aeruginosa K. pneumoniae E. colli S. marcescens	Meropenem 1 g/8 h/1-2 weeks *or* Levofloxacin 750 mg/24 h/1-2 weeks *or* Piperacillin/tazobactam 4,5g/6h *plus* Amikacin 1 g/24 h/1-2 wks
Central IV line sepsis	S. epidermidis S. aureus (MSSA) Klebsiella Enterobacter Serratia	Meropenem 1 g/8 h/15 d *or* Cefepime 2 g/12 h/2 wks
	S. aureus (MRSA)	Linezolid 600 mg/12 h/15d *or* Vancomycin 1 g/12 h/15 d

Table 3. Empiric therapy: sepsis, septic shock (taken from Cunha BA, Antibiotic essentials, 7th ed., 2008) [23].

The management of severe sepsis and septic shock in critically ill patients remains a significant challenge to clinicians. Despite introduction of novel therapeutic interventions in the management of sepsis, mortality rate remains disturbingly high [10].

THE CLINICAL PICTURE OF SEPSIS AND SEPTIC SHOCK

Clinical manifestations of patients with sepsis depend on the both: severity of the patient's condition at admission to the hospital and the affection of individual organs and organ systems. Regardless of the affection of some organs, the clinical picture is dominated by systemic reactions: tachypnoea, tachycardia, hypotension, sweating, weakness, shivering, increased or decreased body temperature, petechial hemorrhages on the skin (referred to thrombocytopenia as a result of DIC), with associated symptoms of organ that is the carrier of infection [4, 5, 11]. When lungs are affected, dispnoa, coughing and pain during breathing appear. If urinary tract is affected, besides general symptoms, dysuria and flank pain emerge [9]. When biliary tract is affected, pain under right rib arch dominates [10].

Objective parameters of sepsis and severe sepsis are as follows: changes in body temperature - usually with parameters of hyperpyrexia (> 38°C) or hypothermia (< 36°C), hyperventilation (> 20/min., PaCO2 < 32 mmHg), tachycardia (> 90/min.), hypotension (< 90 mmHg), change of white blood cell count (> 12000/mm3 or < 4000/mm3), organ dysfunction (at least one organ), increase of serum lactate > 4 mmol/L [5, 8, 11, 12]. Because of tissue hypoperfusion, the clinical picture is dominated by: confusion, cold extremities, skin marblings, oliguria [6, 7].

In the clinical picture of septic shock, in addition to typical signs of severe sepsis, hypoperfusion, leukocytosis with the presence of immature form of neutrophils, or leukopenia accompanied by neutropenia, which indicates a poor prognostic outcome, dominate [5, 11]. In accordance with presence of multiorgan dysfunction, present are the following signs: hyperbilirubinemia, hyperglycemia, thrombocytopenia, increase of transaminases and alkaline phosphatase, azotemia, DIC [5].

DIAGNOSTIC PROCEDURES

It is important that the clinician on time recognize and diagnose sepsis and septic shock, promptly implement appropriate treatment and prevent the possibility of progressing sepsis into septic shock. Changes in the standard hemodynamic parameters are poor predictors of the presence of septic shock, and signs that can be used for diagnosis of this condition are quite subtle: body temperature ≤ 36°C or >38°C, blood pressure: systolic blood pressure < 90 mmHg, pulse frequency < 50/min. or > 100/min., respiratory rate < 6/min. or > 20/min., level of consciousness: anxiety/ lethargy, diuresis <0.5 ml/kg/hrs, an increase of creatinine > 0.5 mg/dL, hyperbilirubinemia, hyperglycaemia (blood glucosa > 8 mmol/L in patient with previous normo-glycemia registered), more than 10% immature forms in the total white blood cell count, two times increased levels of C-reactive protein (CRP) and procalcitonin (PCT) in regard to reference values [8, 11, 12].

In further progression of pathologic condition, the following parameters are registered: mean arterial pressur (MAP) ≤ 65 mmHg, central venous pressure (CVP) < 8 mmHg, arterial blood oxygen saturation (SaO2) < 90%, venous oxygen saturation: central (ScvO2) ≤ 70%, mixed (SvO2) ≤ 65%; the value of serum lactate > 4 mmol/L with a tendency to increase; capillary refill > 3s [8, 12].

In addition to the above mentioned parameters, obtained positive blood culture (at least two BCs) contribute in establishing the diagnosis [8, 11, 12]. In attempts to verify potential sources of infection, it

I) If **Pseudomonas is an unlikely** pathogen	II) If **Pseudomonas is a possible** pathogen
Vancomycin *plus* **one** of the following: **Cephalosporin, 3rd or 4th generation** (eg, ceftriaxone or cefotaxime) *or* **Beta-lactam/beta-lactamase inhibitor** (eg, piperacillin-tazobactam, ticarcillin-clavulanate) *Or* **Carbapenem** eg, imipenem or meropenem	**Vancomycin** *plus* **two** of the following: **Antipseudomonal cephalosporin** (eg, ceftazidime, cefepime) *or* **Antipseudomonal carbapenem** (eg, imipenem, meropenem) *Or* **Antipseudomonal beta-lactam / beta-lactamase inhibitor** (eg, piperacillin-tazobactam, ticarcillin-clavulanate) *or* **Fluoroquinolone with good anti-pseudomonal activity** (eg, **ciprofloxacin**) *or* **Aminoglycoside** (eg, gentamicin, amikacin) *or* Monobactam (eg, aztreonam)

Table 4. Initial selection of empiric antibiotics in severe sepsis or septic shock (taken from: Schmidt GA et al., 2010) [22].

is mandatory to perform imaging studies: ultrasound (US), CT, MRI, if the patient's medical condition allows [8, 11, 12].

BIOMARKERS IN DIAGNOSIS OF INFECTION

In addition to the mentioned diagnostic procedures, determination of biomarkers has a certain acceptable place in establishing the definitive diagnosis [13, 14]. According to the literature data, more than 170 markers were studied in order to establish the diagnosis and prognosis of sepsis and septic shock. However, a biomarker that would satisfy the characteristics of the golden standard in diagnosing these conditions, that is, indicating bacterial infection, has not been found yet [13, 14].

Among the biomarkers it was found that procalcitonin (PCT) and C-reactive protein (CRP), are the most commonly used in the diagnosis of sepsis and inflammation, and in monitoring response to antibiotics, but they also have certain limitations in terms of insufficient sensitivity and specificity [13, 14] .

PROCALCITONIN (PCT)

Procalcitonin (PCT) is a protein produced in the C-cells of the thyroid gland as the precursor of calcitonin peptide. Normal serum PCT concentration is < 1 ng/ml [13, 14].

The increased value of procalcitonin at the beginning of sepsis and its tendency to further increase the value is in correlation with the severity of sepsis and poor prognosis.

The value of procalcitonin also increases in non-infectious medical conditions, such as shock, SIRS and multiorgan failure (MOF) [13, 14, 15, 16, 17]. Presently available assays give findings (results) within one hour [13, 14, 15, 16].

C-REACTIVE PROTEIN (CRP)

C-reactive protein (CRP) is often used in clinical practice to diagnose sepsis. Increased values are in correlation with multiple organ dysfunction and mortality. Monitoring of values during the disease is important to assess response to therapy [14, 15, 17].

BIOMARKERS OF THE COAGULATION SYSTEM

Biomarkers of the coagulation system are: antithrombin III (ATIII), prothrombin time (PT), protein C, D-dimers. They show abnormal values in sepsis and septic shock, but those values are not in correlation with the severity of sepsis and septic shock [15].

Antithrombin III, a glycoprotein synthesized in the liver, decreases in 50% of septic patients and its value falls below 60% of the baseline due to interreactions of platelets with leukocytes and endothelial cells. Ref-

erence values of this biomarker are 5-15 mg/L. Values below the mentioned values increase the risk of thrombosis [15].

Protein C is a natural protein, circulates in plasma, is synthesized in the liver and inhibits inflammation [1, 5, 15, 18]. By thrombin, protein C is converted to its active form, activated protein C (APC) [1, 6].

The increase in D-dimer levels in sepsis predicts occurrence of septic shock [15].

CYTOKINES

Cytokines are important mediators in the pathophysiology of sepsis and recently are increasingly studied as potential biomarkers in routine diagnostics. However, their concentration in the blood during sepsis and septic shock is changing. Alterations of their values during the disease are not in accordance with progress of disease, therefore the examination of their role in terms of diagnosis confirmation continues further [1, 13, 14].

Cytokines are protein-signaling molecules of low molecular weight that can regulate many metabolic processes and biologic responses [13, 14, 15]. Proinflammatory cytokines are TNF-α, IL-1ra, IL-6, IL-12, IL-18 and anti-inflammatory: IL-8, IL-10 [1, 2, 15, 16].

BACTERIAL ENDOTOXINS

Bacterial endotoxins are biomarkers that are determined by measuring, in a kinetic luminometric assay (highly sensitive biologic assay), antibodies directed at lipopolysaccharides of layer of various Gram-negative bacteria [15].

MANAGEMENT OF TREATMENT GUIDELINES IN SEVERE SEPSIS AND SEPTIC SHOCK

It is recommended to adopt and apply in clinical practice internationally recognized protocol guidelines in the treatment of severe sepsis and septic shock, in order to reduce the mortality rate associated with the condition [12].

TREATMENT GUIDELINES

Early detection of sepsis and septic shock, the establishment of diagnosis and prompt implementation of clinical practice guidelines are the key elements of the early goal-directed resuscitation and procedures in the treatment of sepsis and septic shock [12].

Early goal-directed resuscitation of patients with sepsis and septic shock during first 6 hrs [12, 19]:

- *blood cultures prior to antibiotic therapy*
- *administration of broad-spectrum antibiotic therapy within 1 hour of detection of severe sepsis and septic shock (preferably within the first 30 minutes)*
- *fluid resuscitation*
- *monitor serum lactate value*
- *administration of vasopressors (if no improvement despite fluid resuscitation)*
- *dobutamine infusion in the presence of myocardial dysfunction as suggested by elevated cardiac filling pressure and low cardiac output*

Further maintenance of resuscitation within the first 24 hours:

- *administration of steroids/intravenous hydrocortisone in septic shock patients when hypotension remains poorly responsive to adequate fluid resuscitation and vasopressors*
- *administration of recombinant human activated protein C (rhAPC) in severe sepsis when there is a high risk of mortality*
- *monitor blood glucosa value (maintain the value 4-8 mmol/L)*
- *mechanical ventilation with specific respiratory parameters [12, 19]*

ANTIBIOTIC THERAPY

Minimum two blood cultures (BCs) have to be obtained before initiating antibiotic therapy [8, 12].

Intravenous antibiotic therapy should be started within the first hour, even within first 30 minutes of recognition of severe sepsis and septic shock [5, 8, 10, 12].

It is recommended to initiate empirical antibiotic therapy or combination of broad-spectrum antibiotic regimen that have activity against all likely pathogens and that penetrate in adequate concentrations into the presumed source of sepsis [5, 8, 12]. Also, it was recommended to administer empirical antifungal therapy including one or more drugs that have activity against all likely pathogens [12].

Definitely, the strongest predictor of mortality in septic shock is delay to initiation of effective antimicrobial therapy [20].

In the study of Kumar et al., 2006, among 2154 septic shock patients who received effective antimicrobial therapy only after the onset of recurrent or persistent hypotension, it was noted a strong relationship between the delay in effective antimicrobial initiation and poor outcome: the survival rate was 82.7% after initiation of effective antibiotic therapy within the first half hour, and 77.2% in the second half of the first hour. With effective antimicrobial therapy delay to six hours survival was just 42.0%, and for every additional hour delay in effective antimicrobial initiation survival dropped an average of 7.6% [20]. After culture results and antimicrobial susceptibility data return and identify causative pathogens that were not covered by initiated antibiotic regimen, other antibiotic (pathogen- and susceptibility-directed) should be administrated in accordance with obtained antibiogram [8, 12].

The duration of antibiotic therapy is typically 7 to 10 days. Longer courses may be appropriate in patients

Table 5. Clinical Significance of Acinetobacter baumannii (modified from: Cunha BA. Antibiotic Therapy of Multidrug-Resistant Pseudomonas aeruginosa, Klebsiella pneumoniae and Acinetobacter baumanii in Critical Care. 2010) [25].
CAB = catheter-associated bacteriuria; CAP = community-acquired pneumonia; CVC = central venous catheter; NP = nosocomial pneumonia; VAP = ventilator associated pneumonia.

Colonization	Common infections in normal hosts	Infections in compromised / critically ill hosts
Respiratory secretions (ventilated patients) Urine (CAB) Wounds Aqueous medications / irrigant solutions	NP / VAP (sporadic outbreaks only) CVC infections	NP / VAP (sporadic outbreaks only) CVC infections

who have a slow clinical response, an undrainable focus of infection, or who have immunologic deficiencies, including neutropenia [8, 12].

According to study of Vincent JL et al., 2006, the lung was the most common site of infection (68%), followed by the abdomen (22%), blood (20%), and urinary tract (14%) [9].

In the above mentioned study (Vincent JL et al., 2006), cultures were positive in 60% of the patients with sepsis and the most common organisms were as follows: Gram-positive organisms were isolated from 40% of patients, Gram-negative from 38% (Pseudomonas species 14%, Escherichia coli 13%), and fungi from 17% (Candida albicans was involved in 13% of infections), 18% of infections were mixed. Methicillin-resistant Staphylococcus aureus (MRSA) was isolated from 14% of cultures [9].

If the presenting clinical syndrome is determined to be due to a noninfectious cause, the International Protocol Guidelines, 2008, recommended antimicrobial therapy to be stopped promptly to minimize the likelihood that the patient will become infected with an antibiotic resistant pathogen or will develop a drug related adverse effect [12].

A prospective cohort study of Leibovici L et al., 1997, of 2124 patients demonstrated that inappropriate antibiotic selection was surprisingly common (32 percent); mortality was markedly increased in these patients compared to those who had received appropriate antibiotics (34 versus 18 percent) [21].

Poor outcomes are associated with delays in initiating antimicrobial therapy, even short delays (eg. an hour) or inadequate or inappropriate antimicrobial therapy [22].

According to Cunha BA, Antibiotic essentials, 7th ed, 2008, the following guidelines are recommended for the initial empiric therapy in severe sepsis or septic shock [23].

As regards Gram-negative bacilli Pseudomoas aeruginosa, the following guidelines are recommended by Cunha BA, 2008 [24]:

1. *monotherapy: Meropenem (IV) or Cefepime (IV)*
2. *combination therapy: either Meropenem (IV) or Cefepime (IV)plus Amikacin.*

According to study of Schmidt GA et al., 2010, few guidelines exist for the initial selection of empiric antibiotics in severe sepsis or septic shock [22] - table 4.

Choice of antibiotics can be complex and should consider the patient's history (eg, recent antibiotics received), comorbidities, clinical context (eg, community- or hospital-acquired), Gram stain data, and local resistance patterns [22].

There is growing recognition that Methicillin-resistant S. aureus (MRSA) is a cause of sepsis not only in hospitalized patients, but also in community dwelling individuals without recent hospitalization. It is recommended that critically ill patients presenting with sepsis of unclear etiology were treated with intravenous vancomycin (adjusted for renal function) until the possibility of MRSA sepsis has been excluded [22].

Linezolid is a reasonable alternative if there are contraindications to vancomycin [22].

In accordance wth study of Schmidt GA et al., 2010, there was no justification to cover Gram-negative pathogens with two agents from different antibiotic classes, so they recommended use of monotherapy with a third generation cephalosporin or a carbapenem with proven efficacy and the least possible toxicity [22].

Antibiotic regimen with two agents from different antibiotic classes is recommended in patients who are either neutropenic or whose severe sepsis is due to a known or suspected Pseudomonas infection [12, 22].

Therapeutically, the most problematic microorganisms encountered in daily practice in critical care are Pseudomonas aeruginosa, Klebsiella pneumoniae and Acinetobacter baumannii. The aerobic gram-negative bacilli (GNBs) are usually sensitive to a variety of antibiotics, but some strains may become resistant to multiple antibiotics from different classes and are then considered to be multidrug resistant (MDR) isolates [25].

Table 6. Antimicrobial Therapy of Susceptible and MDR A. Baumannii
(modified from: Cunha BA. Antibiotic Therapy of Multidrug-Resistant Pseudomonas aeruginosa, Klebsiella pneumoniae and Acinetobacter baumanii in Critical Care. 2010) [25].
CAB = catheter-associated bacteriuria; MDR = multidrug resistant; PO = by mouth.

Acinetobacter baumannii	Susceptible strains	MDR strains
Serious systemic infection	Meropenem Ertapenem	Sulbactam /ampicillin Colistin Polymyxin B Doripenem
CAB (only PO)	Fosfomycin	Fosfomycin

A historical approach to understanding antibiotic-associated resistance from a clinical standpoint indicates that some antibiotics are more likely to cause resistance than others. These antibiotics may be termed "high-resistance potential" antibiotics indicating the resistance potential is not necessarily high in terms of percentage but relatively higher than those with a "low-resistance potential" [25].

Antibiotics referred to as low-resistance potential antibiotics are those which when used in high volume over extended periods of time have not been associated with acquired resistance to various microorganisms. This distinction is clinically useful and has practical applications. It is always preferable to use an antibiotic with a low resistance potential, in preference to one with a high resistance potential [25].

Acinetobacter baumannii are organisms of low virulence with minimal invasive potential. For these reasons, Acinetobacter baumanni commonly colonize, but may infect critically ill patients (respiratory secretions, urine, catheter) [25].

Clinicians should differentiate colonization from infection before considering empiric antimicrobial therapy [25]. This antibiotic therapy of MDR Acinetobacter baumannii in critically ill patients can be achieved most simply by avoiding the unnecessary treatment of colonized respiratory secretions or urine. Other important measures to minimize the evolution of MDR GNBs are not to use antibiotics in place of abscess drainage or to "cover" surgical drains [25].

Acinetobacter baumannii has, by definition, always been MDR (multidrug-resistant) GNBs (gram-negative bacilli). There have always been fewer antibiotics effective against Acinetobacter baumannii [25].

CONTROL OF THE SOURCE OF INFECTION

It is very important to identify and control the source of infection in the first hours after admission (drainage, debridement, early removal of catheters) [6].

It is recommended that definitive interventions are best delayed until adequate demarcation of viable and non-viable tissue has occurred (i. e. infected peripancreatic necrosis). When sorce control is required, it is recommended to perform the effective intervention associated with the least physiologic insult e. g. percutaneous or endoscopic before surgical intervention [8, 12, 22, 26].

FLUID THERAPY

Immediately after hypoperfusion has been diagnosed, early fluid resuscitaion should be started [2, 4, 7, 8, 12]. The initial infusion of 1000 ml of crystalloid solutions in the period of 30 minutes, and after that administration of crystalloid fluids until haemodynamicaly stability (MAP ≥ 65 mmHg, CVP 8–12 mmHg, urine output

> 0,5 ml/kg/h) with continuous monitoring, to evaluate the response to therapy and prevent the possible occurence of pulmonary oedema, as the patients in septic shock are prone to the development of noncardiogenic pulmonary oedema [7, 8, 12, 22, 27].

In some patients aggressive fluid therapy is required even for 24 hours.

The resuscitation process should be cautious if the tissue perfusion is still low despite the administered fluid therapy due to cardiac dysfunction (confirmed by echocardiography or if the SvcO2 < 70%), the infusion rate of fluids should be reduced and vasopressors should be included [4].

During the first six hours initial therapy is aimed to achieve the following haemodynamic values:

- *Central venous pressure (CVP) of 8-12 mmHg*
- *Mean arterial pressure (MAP) ≥ 65 mmHg*
- *Urine output: ≥ 0,5 ml/kg/h*
- *Central venous oxygen saturation or mixed venous oxygen saturation ≥ 70%, and ≥ 65% respectively [8, 12, 27).*

If the afore mentioned hamodynamic values are not achieved with early initial therapy, the administration of fluids should be continued, transfusion of erythrocytes (to Hct values of > 30), and continuous infusion of vasopressors. There is no evidence that administration of colloid fluids have any benefit in regard to crystalloid fluids [8, 12].

VASOPRESSORS

If the hypotension and tissue hypoperfusion are present despite agressive fluid therapy and there are signs of imminent cardiogenic pulmonary oedema, vasopressors should be included in therapy [4, 8, 10, 12, 22, 28, 29].

The first choice of vasopressors is norepinephrine, which increseas mean arterial pressure because of

the vasoconstrictory effects at α-adrenergic receptors, with moderate changs of heart rate and small increase of stroke volume in comparison with dopamine [12, 22, 28].

The second choice is dopamine, which increases mean arterial pressure and cardiac output, primarily because of increase in stroke volume and heart rate. It is useful in patients with compromised systolic function, but it can result in tachycardia and arrhythmia [12, 28].

In the initial therapy of septic shock, epinephrine (adrenalin) is not recommended (because of increase in myocardial oxygen consumption, elevated serum lactate values, decrease in splanchnic circulation and oxygen delivery) [12, 28, 30].

After initial therapy, if there was no response to norepinephrine or dopamine, the next choice is epinephrine (α-adrenergic and β-adrenergic agens) [12, 28, 29].

INOTROPIC THERAPY

Dobutamine is the inotrope of first choice in the patients with low cardiac output, when the left ventricular filling pressures are adequate (or clinically assessed that the fluid resuscitation is adequate) and the mean arterial pressure is adequate [12, 29].

Septic patients with persistent hypotension even after initial fluid resuscitation, could have low, normal and increased cardiac output. Thus, when it is not posible to measure the cardiac output, it is recommended to give inotropes and vasopressors [12].

When the cardiac output could be measured, vasopressors and inotropes could be administered separately to follow the values of MAP and cardiac output. [12].

CORTICOSTEROIDS

According to the International guidelines of 2008:

Corticosteroids are not recommended in sepsis [12, 31, 32]. It is suggested to administer hydrocortison intravenously only in adult septic shock patients after blood pressure is identified to be poorly responsive to fluid resuscitation and vasopressor therapy [12].

RECOMBINANT HUMAN ACTIVATED PROTEIN C (RHAPC / ACTIVATED DROTRECOGIN-A)

Recombinant human activated protein C rhAPC (activated drotrecogin-α) has effect in the coagulation pathway by reducing thrombosis in microcirculation and it has beneficial effect on lowering the incidence of multiorgan dysfunction in sepsis and septic shock [2, 12, 19].

It is recommended for the patients with high risk of mortality (APACHE II > 25, sepsis induced multiple organ dysfunction, septic shock, sepsis induced ARDS) [10, 12, 22, 33].

It is not proscribed for children and pregnant women, patients with haematologic diseases, patients with anticoagulant therapy. The most important adverse effect of rhAPC therapy is bleeding, so it is not administered to patients with thrombocytopenia before the correction of the condition.

If the pateints are planned for an elective surgery, rhAPC is administered 12 h after the operative procedure [33].

GUIDELINES FOR THE ADMINISTRATION OF BLOOD AND BLOOD PRODUCTS

It is necessary to maintain adequate values of haemoglobin and haematocrit in patients with sepsis and septic shock, so the therapy with blood products is recommended when haematocrit ≤ 30%, and haemoglobin ≤ 70 g/L [10, 12].

Fresh frozen plasma (FFP) is not recommended in documented deficit of coagulation factors, except in active bleeding and before surgical procedures [8, 12].

Antithrombin III is not recommended in the therapy of severe sepsis and septic shock.

Clinical trials have shown that high doses of antithrombin did not have benefits in regard to reducing of mortality rates in adult patients with severe sepsis and septic shock, and when given together with heparine, there was a higher risk of bleeding [12].

SUPPORTIVE THERAPY IN SEVERE SEPSIS

Mechanical ventilation

Respiratory support is recommended for patients with lung injury and ARDS and severe sepsis with lower tidal volume of 6 ml/kg per body weight, plateau pressure of ≤ 30 cm H20, and PEEP values of 5 cm H20 [8, 10, 12, 19, 22].

Sedation, analgesia and neuromuscular blockade

During mechanical ventilation, sedation is stopped during the day occasionaly.

Muscle relaxation should be avoided, and if needed the relaxants should be given intermittently. Muscle relaxants given together with steroids could induce critical illness myopathies and neuropathies [8, 12].

Glucose control

The target blood glucose level is about 8 mmol/L, with monitoring blood glucose values every 1-2 h when patients, receiving intravenous insulin, receive a glucose calorie source. Thereafter, when glucose values and insulin infusion rate are stabile, blood glucose values could be monitored every 4 hours [10, 12, 19].

Renal function support

When renal failure is present, early hemofiltration or hemodyalisis should be started as soon as possible to prevent fluid overload and azotemia imbalance [4, 10, 12].

Bicarbonate therapy

Metabolic acidosis induced by hypoperfusion should not be corrected with bicarbonate therapy, but with adequate perfusion [12].

Deep vein thrombosis (DVT) prophylaxis

For the patients with severe sepsis therapy with standard low molecular weight heparins (LMWH) is recommended in the prophylaxis of deep venous thrombosis [12, 22].

Stress ulcer prophylaxis

Therapy with H2-blockers or proton pump inhibitors (PPI) is recommended for the prevention of stress ulcus [12, 22].

CONCLUSIONS

Despite establishing early diagnosis and new diagnostic procedures, the knowledge on the immune response of the host to inflammation, and new therapeutic guidelines in the treatment of severe sepsis and septic shock, mortality rate is still at disturbingly high level.

In the management of therapeutic guidelines it is important to obtain the blood cultures in the first hour, administer the antibiotic in the first hour and no later than three hours (every delay of prescribing antibiotic therapy for next hour increases the mortality rate for 7,6%).

Prompt fluid therapy is necessary until establishing the haemodynamic stability. Steroids (hydrocortisone IV) are suggested in septic shock patients (when hypotension remains poorly responsive to adequate fluid resuscitation and vasopressors), and in patients with severe sepsis and high risk of mortality recombinant human activated protein C (rhAPC) with other supportive therapy.

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REVIEW PAPER

Postoperative Therapy in Patients After Liver Transplantation

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INTRODUCTION

Liver transplantation (LT) is a high-risk procedure that is performed in patients who are in the terminal stage of liver disease. As such, they, in the postoperative period, have the same problems as other critically ill surgical patients. However, immunosuppression and the presence of other risk factors, additionally complicate the postoperative treatment and care of these patients. So here is of great importance a special team work of surgeon, anesthesiologist, intensivists and doctors of other specialties (transfusiologists, hepatologists, immunologists, microbiologists).

Stay in the intensive care unit is necessary in the immediate postoperative period. Determined by the need for mechanical ventilation, maintenance of haemodynamic stability (cardiopulmonary support), liver function, risk of various complications. In addition, the length of stay in intensive care unit (ICU) are determined by the donor and recipient preoperative statu[1]. Increased MELD (Model for End-Stage Liver Disease Score) scores correlates with complications and with length of stay in ICU. While the DRI score (Donor risk index) does not correlate [2]. However, some studies suggest that the age of donor and liver function is very important for the success of transplantation [3.4].

The overall postoperative mortality of LT is about 5.3 to 18.9%. The most common complication resulting in death was infection (62.5%), alograft rejection (15.7%) and nonspecific multiple organ failure (MOF) (8.9%).) Mortality decreases with transplant team experience [5,6]. Post-transplant complications are frequent. Oberkofler in his paper presented the following complications: renal failure and need for renal replacement therapy (RRT) in 21% of patients, sepsis 10.8%, respiratory failure (Acute respiratory distress syndrome (ARDS), pneumonia, reintubation) 10.2%, primary graft nonfunction, retransplantation 2.7%, and alograft rejection during ICU stay in 8.8% [7].

Infections are common complications. One of the reasons for the increased number of infections, in addition to immunosuppressive therapy and many invasive monitoring procedure, is the fact that before transplantation, these patients have cirrhosis, which expressed itself a risk of infection.The reasons for the increased risk of infection in pretransplant cirrhotic patients are these [8]:

a) depressed phagocytic activity of the reticuloendothelial system

b) intestinal bacterial overgrowth

c) altered intestinal motility

d) increased intestinal permeability

e) increased bacterial translocation

f) endotoxemia

There are not many papers on the intensive care management of patients after LT. But from a lot of papers on complications, we can point out the main problems, most visible complications and how to overcome them with appropriate postoperative therapy. The most important therapy points are respiratory support, maintenance of haemodynamic stability, cardiovascular failure, the fight against infection, sepsis, kidney failure, organ rejection and other complications.

RESPIRATORY MANAGEMENT

There is no common stand among physicians in making decisions about the early extubation after LT. Early postoperative extubation ("fast tracking"), which means extubation on the operating table, does not correlate with the number of complications, but reduces the need for postoperative mechanical ventilation. Criteria for extubation on the operating room table are standardized and universally accepted criteria of patient awake (able to follow simple orders, spontaneous eye opening,) clinical evidence of neuromuscular reversal, a tidal volume >6 ml/kg, normocarbia (ETCO2 30-40 mmHg), a respiratory rate of < 25/min and a good oxygenation (SpO2>95%, with

Cyclosporine	Tacrolimus	Corticosteroids
Hypertension Renal dysfunction Hirsutism Hyperkalemia Gingival hiperplasia Hypomagnesemia	Posttransplant diabetes mellitus Nausea, vomiting, diarrhea Hyperkalemia Tremor Hypertension Hypomagnesemia Headache Renal dysfunction Neurotoxicity (encephalopathy,...)	Hypertension Mental status changes Lipid abnormalites Impaired wound healing Hyperglicemia Cushinoid syndrome Ulcers Myopathy Osteoporosis Fluid retention Cataracts

Table 1. Common side-effects of immunosupressive treatment

FiO2<0,5) and under conditions haemodynamic stability. Pre operative Child Pugh severity did not predict rapid extubation, but Model for End - stage Liver Disease (MELD) score of < 11 did [9].

Aduen in his work marked the appearance of pulmonary edema after LT. Immediate pulmonary edema (present at administration to the ICU, resolving within 16 to 24 hour after surgery) in 25%, late pulmonary edema (developing during the first 16 to 24 hours after surgery) in 9% and persistent pulmonary edema (present at admission to the ICU and persisting at 16 to 24 hours after surgery) in 18%. Immediate pulmonary edema has little clinical consequence. Patients with persistent permeability edema had higher mean pulmonary arterial pressure (23 mmHg) and higher pulmonary vascular resistence (103 dyn/second/cm5). Patients with late or persistent pulmonary edema received larger amounts of fresh frozen plasma and total fluids intraoperatively than patients with no or with immediate pulmonary edema. Patients with late and persistent pulmonary edema were prolonged at mechanical ventilation, stayng in intensive care unit and hospital [10].

There are many factors that are shown to affect the continued need for respiratory support. Preoperative body mass index (BMI>32), ascites, encephalopathy, viral hepatitis, team experience, Child Pugh score, the amount of intraoperatively given blood transfusion, time of day when transplantation is done.

Acute respiratory distress syndrome (ARDS) may occur in about 16.3% of patients after LT. The most common reasons for the development of ARDS are fluid overload from crystalloid or massive transfusion. Others are: sepsis, iv use cyclosporine, fast tapering of corticosteroids [11]. Aproximately in 8,8 % LT patients were detected pneumonia. Mortality were much higher among patients with pneumonia (71,4%) then those with other pulmonary complications. They needed mechanical ventilation[12].

Thus, patients with lower MELD scoring, a less amount of intraoperatively obtained blood and blood products and crystalloid, as well as less lower intrapulmonary pressure, are candidates for rapid extubation and they were had less complications. Non-invasive ventilation (NIV) is also an option to overcome the hypoxia. The need for mechanical ventilation can be overcome by using the NIV. The “prophylactic” application represents a valid alternative method of ventilatory assistance to prevent serious deterioration of gas exchange[13].

HEMODYNAMIC MANAGEMENT

Vascular and cardiac changes in liver cirrhosis are in the pathophysiological basis of changes in these patients. Primary it is hiperdinamic condition with decreased mean arterial pressure (MAP), decreased systemic vascular resistance (SVR), and with the increased cardiac output. In the center of this hiperdinamic condition and portal hypertension, as a result of cirrhosis, is the peripheral vasodilatation[14].

Based on this it seems like a hipovolemy, but it is relative hipovolemy. So the fluid compensation, maintaining an adequate circulatory volume and avoiding tissue hypoperfusion are the key points of adequate treatment of patients after LT.

The goal of our therapy in LT patients in many elements are not different from the usual criticaly ill patient therapy. It is necessary to maintain MAP min 70 mmHg. In this way it is preserved organ perfusion, and kidney in the first place. It is required compensation of circulatory volume by colloid to achieve central venous pressure (CVP) of 10 to 12 mmHg. It is recommended, maintenance of pulmonary capillary wedge pressure of 15 mbar. If MAP could not be achieved at 70 mmHg, vasopresors such as norepinephrine should be introduced in therapy[15].

LT alone as well as post-operative therapy to be adequate demand exceptional hemodynamic monitoring. For this reason, central venous catheter (CVC) and pulmonary artery catheter (PAC) are placed. Exceptional attention is paid to parameters which show us more about circulatory volume than the pressure. It is now increasingly used “modification” of pulmonary arterial catheter as PiCCO or Vigileo (FloTracR) systems. They provide a continuous monitoring of cardiac output and various other haemodynamic parameters related to the circulatory volume, peripheral resistance and cardiac contractility. Due to them it is reduced the probability of circulatory volume overload. Maintenance Stroke volume variation (SVV) below 10% in large surgical interventions, and the compliance with other parameters led to a better haemodynamic stability[16,17,18].

It is recommended that the CVP is less than 5 mmHg to prevent congestion of the liver. Study of Sanera and all shows that increased values of CVP up to 10 mmHg caused by PEEP does not lead to significant haemody-

namics changes in patients after liver transplantation. Thus, the potential harm of high CVP is very low compared to the effects of tissue hypoxia[19].

Shroeder said in his work that intraoperatively maintaining CVP less than 5 mmHg reduced intraoperative bleeding and the need for blood, but led to a greater number of postoperative renal complications. The group maintained CVP on 7-10 mmHg had significantly fewer renal complications[20].

RENAL FUNCTION

Renal dysfunction (RD) is often problem in patients after LT. Postoperative renal dysfunction was defined as serum creatinine >1,5mg/dl. Early renal dysfunction (ED) was defined as: serum creatinine >1,5 mg/dl within 3 month posttransplant or, in patients with pretransplant renal dysfunction, serum creatinine level >2x that of pretransplant. Late onset renal dysfunction (LD) is defined as serum creatinine >2mg/dl, beyond 3 months posttransplantation in patients without early renal dysfunction or recovered from early renal dysfunction. ED developed in 64,1%, LD in 5,2% transplanted. As independent predictors for ED appear pretransplant serum creatinine, the amount of transfused bank-red blood cells, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and hospital infection. Mortality in the ED group was 33,5%[21].

Cabezuelo with colleagues monitored the occurrence of renal failure after LT. The patients were classified in two groups: as early postoperative failure (E-ARF) during first week after transplantation, and late postoperative (L-ARF) (second to fourth week). E - ARF had 30,9% patients and L-ARF had 19,1%. The most common etiological factors for the development of E-ARF were ischemic acute tubular necrosis and pre renal ARF. The most common etiological factors for the development of L-ARF were cyclosporine nephrotoxicity and sepsis asociated ARF. Univariant analysis showed that patients with E-ARF were received more blood and blood products, had more intraoperativ complications and they need greater intraoperativ dopamine and norepinephrine support versus patients who had L - ARF. Patients with E-ARF had lower systolic arterial pressure in unhepatic and post-unhepatic phase. As an independent risk factor for the development of E-ARF were found preoperative serum albumin (<3,2g/dl), preoperative ARF, treatment with dopamine >6 days and graft dysfunction. As an independent factors of risk for the development of L-ARF were identified surgical re-operation and bacterial infection[22].

How to prevent renal failure after LT? Begins with maintaning intraoperative haemodynamics, with special atention on MAP[23].

Maintenance of renal functions starts intraoperatively. Improved intra-operative management of patients undergoing LT might help to reduce the incidence of postoperative acute renal failure. It seems that the volume compensation is the most effective preventive measure to avoid pre-renal failure as well as acute tubular necrosis. Monitoring with CVP and if necessary with a PAC and/or volumetric monitoring as well as a PiCCO or Vigileo (FloTracR), may guide the amount of fluid to be administered to optimize volemia and maintain an adequate cardiac output.

Of course, avoiding nefrotoxic drugs (lower doses of cyclosporine at the beginning of treatment, and avoiding aminoglucoside antibiotics.), decreasing the need for blood and blood products, reducing infectious complications[21,22,23,24].

In the case of development of acute renal failure, raises the indication for continuous renal replacement therapy. One of its four types. Most frequently Venovenous Continuous Hemodiafiltration (CVVHDF). If we have the development of liver failure with hepatic encephalopathy and liver - kidney failure in cases of hepato-renal syndrome, there are indications for continuous liver-renal replacement therapy Albumin dialysis - MARS (Molecular Adsorbent Recirculating System).

IMMUNOSUPPRESSIVE THERAPY

The most frequently used immunosuppresive drugs after LT, Tacrolimus (TAC), cyclosporin (CYA) and corticosteroids, are often manifest their side effects, Table 1. A large number of drugs may increase and decrease their concentrations in the blood [25,26]. Prevention of side effects require minimum efficacious doses, oral administration as soon as posible, strict monitoring of plasma levels (including metabolites). Then also, monitoring and corection of electrolyte imbalance (hypomagnesemia, hyponatremia), and hypoalbuminemia, hypertension check and correction and attention to pharmacological interactions [26-29].

ANTIMICROBIAL PROPHYLAXIS

In the first month after LT, infections occurs in the percentage from 53 to 79. The most common causes are various bacteria [30]. Bacteriemia, as a significant complication after LT occurs in 24% to 39% of LT patients [31].

There are a marked variation in the antibiotic prophylactic strategies used for LT recipients. For the type of antibiotic agent used, treatment should be based upon local susceptibility patterns and microbial ecology [30].

FUNGAL INFECTION

Fungal infections are significant problems in solid organ transplant. The incidence of fungal infection after LT is from 7 to 50%., with high mortality rate. The most common pathogens are Candida spp. and Aspergillus spp. In early period after operation (0-30 days), the epidemiology of infections are same types as in the nonimmunosuppressed postoperative patient. Period 30 -180 days is prime time for fungal infections in LT patients. There are two options for antifungal prophylaxis: universal prophylaxis -to all transplant patients (98%) or targeted approach – only to those with an increased risk. The reason for this different approach is uncertain clinical benefits of prophylaxis, potential toxicity, risk of resistantce development, price. Both types

of prophylaxis have been directed against Candida and fluconazole is the most commonly used antifungal agent [32, 33].

ANTI-CYTOMEGALOVIRUS (CMV) PROPHYLAXIS

For the prevention of CMV disease, there are two posible strategies: prophylaxis or pre emptive therapy. Prophylaxis means that the treatment given to all patients during the period when they are at risk. Following are established risk-groups:

CMV+donor/CMV-recipient

CMV+donor/CMV+recipient

Primary graft dysfunction

Large volume transfusion

Anti rejection therapy

Re-operation

Fulminant liver failure

Pre-emptive therapy means that antiviral therapy is given to those patients where the observed early viral replication. Ganciclovir is a safe and effective method for the prevention of CMV disease [30].

Singh in his paper also pointed out that bacteriemia is significant complications after LT (24 to 39%.). According to his data, the most commonly used preoperative prophylaxis consisted of ampicillin and cefotaxime for 24 hours. As prophylaxis for infection caused by Pneumocystis carinii are used trimethoprime with sulfamethoxazole. All patients received acyclovir as herpes simplex virus prophylaxis. Preemptive short-course ganciclovir on detection of CMV shedding was used as prophylaxis for CMV disease [31].

HAEMOSTATIC DISORDER

Deficit of coagulation factors, infections, impair organs functions change coagulation in these patients. All this creates the need for coagulation monitoring, which is not restricted only to the implementation of the classical coagulation tests (APTT, INR, fibrinogen, antithrombin III, d-dimer, Platelet count), but will include on site techniques thromboelastography (TEG) too. It will give us valid information about hypercoagulation or hypocoagulation profile of a patient. So we have a targeted therapy with blood and blood derivatives. In addition, we can affect the coagulation by pharmacological agents (antifibrinolytics).

It is important to find a balance between laboratory findings and bleeding tendency [34,35].

NUTRITIONAL SUPPORT

It is also used early enteral feeding through nutritive jejunostomy tube, a surgical Witzel tube. Kaido in his work, recommended Enteral diet was started at 250 kcal/day on the second or third postoperative day, and 250kcal/day was added up to 1000 kcal / day. Enteral feeding was continued until the oral intake was adequate. If there is a need, total parenteral nutrition should be applied [5].

Official recommendation for feeding after LT is introducing early enteral nutrition . Parenteral nutrition is second choice to enetral nutrition. Normal food and/ or enteral nutrition should be initiated within 12-24h postoperatively. Recommended energy intake 35 - 40 kcal/kgBW/d, protein intake 1,2 - 1,5 g/kg/BW/d. Use nasogastric tube or catheter jejunostomy for early enteral nutrition [36,37].

Continuous monitoring of metabolic parameters (with emphasis on glucose, Na, K, Mg), with a constant correction is required during the postoperative treatment.

Post-operative therapy of patients after LT does not differ greatly from criticaly ill patient therapy. Basically, the maintenance of haemodynamic stability with respect to the specifics related to immunosuppressive and antimicrobial therapy. Therapy must be aggressive with proper monitoring (haemodynamic, respiratory, biochemical, metabolic, microbial,coagulation). Good, useful monitoring, is the basis of successful treatment in these patients.

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PROFESSIONAL PAPER

Ventilator Associated Pneumonia in Intensive Care Unit

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Aim: The aim is to show the influence of different risk factors for inception of pneumonia connected with the mechanical ventilation, the most frequent causes and the importance of bacteriological examination of trachea aspirate in making diagnosis.

Methods: The retrospective study, by method of random choice, included 60 patients who were treated at the Clinic for anaesthesiology and reanimatology of the UKC (University Clinical Centre) Tuzla and were connected to the mechanical ventilation. The test group comprised of 38 patients in whom the microbiological report of the trachea aspirate was positive and the control group comprised of 22 patients in whom the microbiological result of the trachea aspirate was negative.

Results: Co morbidity with the developed clinical manifestations of pneumonia connected with the mechanical ventilation had 41/60 (68.3%) patients of which 35/41 (85.36%) were in the test group and 6/41 (14.63%) were in the control group. X^2 test proved that there is high significance (X^2 = 13.021) between verified VAP and the positive microbiological result of the trachea aspirate to bacteria and fungi and co morbidity of patients. In addition to the insufficiency of the respiratory organs which was the main reason of putting the patient to the mechanical ventilation there were other diseases registered for the patients and X^2 test proved that there is no significant connection with the mentioned diseases and the inception of VAP. The average time of putting the patient to the mechanical ventilation until the development of the clinical manifestations of pneumonia of the whole specimen was 4 days while the average length of stay of the test group was 3 days and control group 4 days. The Pseudomonas aeruginosa 28/116 (24.13%) was the most frequently isolated in the trachea aspirate of the patients from the test group and patients from the control group had the largest number of the sterile samples 15/18 (55.55%).

Conclusion: In the conclusion of the study it is emphasized that given that the sampling of the endotracheal aspirate by aspiration is non-invasive method, and its application according to the results of the other authors and according to our results represents good method for making diagnosis of pneumonia connected with the mechanical ventilation.

Keywords: *mechanical ventilation, pneumonia associated with the mechanical ventilation, trachea aspirate*

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The authors declare no competing interests.

INTRODUCTION

Hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and health care-associated pneumonia (HCAP) represent an important cause of morbidity and mortality in patients despite the positive effects of the applied antibiotic therapy, the existence of different functional appliances and the application of preventive measures. Hospital-acquired pneumonia (HAP) is defined as pneumonia that occurs within 48 hours after admission but that was not present or incubating at the time of addmision.Ventilator-associated pneumonia (VAP) is defined as pneumonia that occurs in 48-72 hours after endotracheal intubation. Health care-associated pneumonia involves patients who were hospitalised in any emergency unit or were in contact with the health care system two days or more within 90 days of infection, e.g. the patient was in a nursing home, or he/she had previously received intravenous antibiotic therapy, or he/she was on hemodialysis or had a wound infection within the past 30 days of infection [1].

The risk of ventilator-associated pneumonia VAP directly depends on the length of mechanical ventilation and is considered to be the highest at the start of hospital treatment. VAP is estimated to develop 3% / day the first 5 days of ventilation, 2% / per day for 5-10 days of ventilation, and 1% / day after that period [2].

The process of intubation influences the increase in the incidence of VAP. It is proved

Types of isolated microorganism	Test group N	%	Control group N	%
Pseudomonas aeruginosa	28	24.13		
Acinetobacter baumanii	26	22.41		
Klebsiella pneumoniae	14	12.06		
Klebsiella pneumoniae ESBL soj	10	8.62		
Proteus mirabilis	8	6.89		
Citrobacter species	6	5.17		
Proteus mirabilis ESBL soj	4	3.44		
Staphylococcus aureus	4	3.44		
Staphylococcus aureus MRSA soj	4	3.44		
Enterococcus faecalis	4	3.44		
Candida albicans	4	3.44		
Escherichia coli	2	1.72		
Stenotrophomonas maltophillia	2	1.72		
Coagulase negative Staphylococcus			6	22.22
Normal flora			6	22.22
Sterile			15	55.55
Total	**116**	**100**	**27**	**100**

Table 1. Types of microorganisms isolated from tracheal aspirate

that when noninvasive ventilation is applied then the hospital-acquired pneumonia is less frequent[3]. Early hospital-acquired pneumonia and VAP (within 4 days of intubation) have significantly better prognosis because they are most likely caused by sensitive bacteria, while late hospital-acquired pneumonia and VAP (within 5 days or more of the intubation) are caused by multiple resistant bacteria[4]. Hospital-acquired pneumonia, VAP and health care-associated pneumonias are caused by the different types of microorganisms. They are usually caused by bacteria but they can also be polymicrobial i.e. caused by certain types of viruses and fungi. Most hospital-acquired pneumonias are caused by gram-negative aerobic and facultative anaerobic bacteria such as Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae and Acinetobacter species and by gram-positive bacterium Staphylococcus aureus, especially methicillin-resistant Staphylococcus aureus (MRSA). In the intensive care units (ICU), pneumonias are more often caused by MRSA and they are more frequent in patients with diabetes mellitus and head injury. In elderly patients with two or three comorbidities HAP and VAP in 29% of cases are caused by Staphylococcus aureus, in 15% of cases with bacteria from the Enterobacteriaceae family, in 9% of cases with Streptococcus pneumoniae and in 4% of cases with Pseudomonas species[5].

The relationship between the factors of patient's natural defense and tendency of pathogens to colonize and invade upper parts of the respiratory tract influences the initiation of hospital-acquired pneumonia. It occurs when a pathogen takes power of non-specific factors (cilia and mucus in the mucous membrane) and specific (humoral and cellular) immunity of the host[6].

The initial step in colonization is adherence of bacteria to the mucosal surface due to interaction between adhesins on the bacterial surface and receptors on the surface of host cells. After that factors of host's defense, especially those on the mucociliary epithelium of tracheobronchal tree with its active function in removing foreign particles by mechanical means, must be suffi-

ciently damaged to allow prolonged contact of bacteria with the surface of epithelial cells. Microorganisms can colonize the surface of the endotracheal tube due to the existence of a biofilm, which is in fact egzopolysaccharide product of certain types of bacteria that protects them from the factors of specific and nonspecific immunity and effects of antibiotics. Aspiration of oropharyngeal pathogenic bacteria or the passing of bacteria by endotracheal tube cuff is the primary route of entry of bacteria into the trachea. The stomach and sinuses are also described as potential reservoirs for certain bacteria that colonize the oropharynx and trachea, but their importance in the development of VAP is controversial[2]. Inhalation of pathogens from contaminated aerosols and direct inoculation are much less common cause of hospital-acquired pneumonia[7]. In all appropriate antibiotic therapy studies for VAP the imperative is on the detection of causative agents of infection as the outcome of the disease proved negative impact of inadequate treatment. The greatest difficulty in microbiological confirmation of ventilator-associated pneumonia is obtaining an adequate sample to the upper respiratory tract infections due to potential contamination with bacteria that are saprophytic flora. Microbiological confirmation of VAP is based on bacteriological examination of samples obtained from the upper parts of the respiratory tract by noninvasive or invasive methods. The noninvasive methods include endotracheal aspirate samples (ETA) and blood cultures and invasive methods include samples taken with a protected brush (PSB, protected specimen brush), bronchoalveolar lavage (BAL) and lung biopsy. The question which of the above methods is better is still controversial because tracheal aspirate sample is cheaper but the use of invasive methods is particularly useful in patients who do not respond adequately to the initial empirical antibiotic therapy. The main problem in applying either invasive or noninvasive methods is to separate the sample of bacteria that are part of the flora that colonizes the upper respiratory tract. Due to this applying of quantitative culture makes the separation of the state of infection and colonization possible. Threshold which separates the colonization and infection by endotracheal aspirate is > or = 105-106 cfu / mL, the sample obtained from protected brush > or = 10^3cfu/mL and BAL > or = 104 cfu / mL (Ioanas et al, 2001). The aim is to show the influence of various risk factors on ventilator-associated pneumonia, the most common microbial pathogens and the significance of bacteriological examination of tracheal aspirate in establishing its diagnosis.

PATIENTS AND METHODS

The study was conducted at the Department of Anesthesiology and Reanimation of University Clinical Centre (UKC) Tuzla in the period from January to June 2010. A retrospective study randomly included 60 patients who were treated at the Clinic for Anesthesiology and Reanimation Center Tuzla and were connected to mechanical ventilation. Results were obtained from medical histories. Subjects were divided into two groups. The test group consisted of 38 patients whose microbiological findings of tracheal aspirate were positive and the control group consisted of 22 patients whose microbiological findings of tracheal aspirate were negative.

Each patient, apart from giving personal and medical history relevant to the diagnosis of pneumonia, underwent clinical and microbiological examination. Clinical examination consisted of physical examination, lung X-ray examination, basic biochemical findings relevant to pneumonia with complete and differential blood count and acid-base status. Criteria for diagnosis pneuminae was: presence of new or progressive infiltrate on lung X-rays, plus at least two of three clinical signs of pneumonia and those are temperature above 38ºC, leukocytosis or leukopenia and purulentan secretion. To set the etiological diagnosis of pneumonia to each patient tracheal aspirate with aspiration of contents using the original bronchial tube was taken as a sample. For identification of aerobic and anaerobic bacteria microbiological examination of processing samples using standard microbiological procedures was used. From each sample beside the mentioned microscopic preparation Gram stain method was made and the number of desquaminated epithelial cells, white blood cell and the number of morphology results of bacteria and fungi was recorded. On each isolated strain antibiogram was performed. For statistical analysis of data $\chi 2$ test and Student t - test (Computers SPSS for Windows release 6.1., 1994) were used. Differences in values of $\chi 2 >$ of 3.804 and values $p<0.05$ are considered statistically significant and highly significant at $p < 0.01$.

RESULTS

From a total of 60 patients who were treated in this study 19/60 (31.6%) were female patients and 41/60 (68.3%) were males patients. The average age of the patients of the test group was 63.3 years and of the control group 36.7 years. Comorbidity with the developed clinical picture of ventilator-associated pneumonia was present in 41/60 (68.3%) of patients of which 35/41(85.36%) of them were members of the test group and 6 / 41 (14.63%) of the control group. 19/60 (31.6%) patients of the examined group did not develop ventilator-associated pneumonia of which 10/19 (52.63%) were patients from the test group and 9 / 19 (47.36%) were patients of the control group.

$\chi 2$ test showed that there is a high significance ($\chi 2 = 13$ 021) between VAP and positive microbiological findings of tracheal aspirate for bacteria and yeasts as well as the comorbidity of patients. Appart from insuficiency of respiratory organs, which was the main reason for putting patients on mechanical ventilation, other diseases were registred as well,

$\chi 2$ test showed that there was no significant correlation of the mentioned diseases and the development of VAP between patients of the test group and control group. The average stay of the patients in the intensive care unit of the Department of Anesthesiology and Reanimation from the whole sample was 29 days, while the average length of stay of the patients from the test group was 31 days and average length of stay of the pa-

tients from the control group was 23 days. The average time of putting patients on mechanical ventilation to the development of clinical pneumonia was 4 days. In the test group 3 days and in the control group 4 days.

$\chi 2$ test showed that there was no significant correlation between VAP and the length of stay of patients in the intensive care unit as well as mechanically ventilated patients to the development of pneumonia of the test and control groups. From tracheal aspirate from a test group of patients Pseudomonas aeruginosa was usually isolated 28/116 (24.13%) and in patients from the control group sterile samples 15/18 (55.55%) were the most often. Apart from these isolates in tracheal aspirates Gram positive cocoid bacteria, enterobacteria and Gram-negative rod-shaped bacteria were also isolated as indicated in Table 1.

As shown in Table 1 in patients from test group certain types of bacteria resistance were islolated, such as Klebsiella pneumoniae ESBL strain 10/116 (8.62%), Proteus mirabilis and ESBL strain 4 / 116 (3.44%), and Staphylococcus aureus MRSA strain 4 / 116 (3.44%).

DISCUSSION

According to the data from the Center for Disease Control (CDC) pneumonia presents 15% of all hospital infections in units of intensive care of adults and 26% of hospital infections of children. The incidence of hospital-acquired pneumonia is 5-10 cases per 1000 hospital admissions and the incidence of ventilator-associated pneumonia is 6 to 20 times higher[6]. According to numerous studies, it is very difficult to define the incidence of VAP, because they can be concealed with other upper respiratory tract infections such as tracheobronhitis or the diagnosis of VAP is set due to inadequate diagnostic methods. Due to this the incidence of VAP can be two times higher in patients in whom the diagnosis of pneumonia is set using qualitative and semiquantitative cultures of sputum, compared with quantitative culture of secretions obtained from the upper parts of the respiratory tract[6]. The incidence of VAP depending on the severity of the disease and the procedures and criteria used for diagnosis ranges from 9-70%[8]. In our study, diagnosis of VAP is based on lung X-ray examination, relevant biochemical parameters, and microbiological examination of tracheal aspirate. Pneumonia was verified in 41 patients or 68.3%. A high percentage of pneumonia in our study is influenced by the fact that in the total sample of all patients with high significance appart from pneumonia comorbidity with two or more diseases was found as well. The important risk factors which influence VAP are sex, previous existence of lung diseases and functional disorders of several organ systems[9]. In our work, in addition to comorbidity, which is a highly significant factor in the study group were also more male patients 41/60 (68.3%), but we didn't found significantly more patients with previous lung diseases 13/60 (21.6%). Appart from these factors which influence VAP, one of the most important factors appart from staying in a hospital setting, particularly in the intensive care unit is length of mechanical ventilation[2]. Since the majority of mechanical ventilations are short-timed it is considered that the half of all VAP develop during the first 4 days of mechanical ventilation. Analyzing our data we found that the average time of stay of patients in the intensive care unit was 29 days and that the average time from putting patients on mechanical ventilation to the development of pneumonia was 4 days for the entire sample and 3 days for patients who have had a positive microbiological findings of tracheal aspirate.

Our results are identical to those of other authors. Frequency and etiology of HAP, VAP and especially HCAP depend on the type of hospital, patient's age and comorbidity, previous antibiotic exposure, type of intensive care units or staying in the another medical facility. The most common causes of HAP and VAP are multiple-resistant microorganisms such as: Pseudomonas aeruginosa, Klebsiella pneumoniae, Citrobacter, Enterobacter, Serratia marcescens, Stenotrophomonas maltophilia, Acinetobacter, Methicillin-resistant Staphylococcus aureus[10]. In our study from tracheal aspirates of patients of the test group Pseudomonas aeruginosa (24.13%), Acinetobacter baumanI (22.41%) and Klebsiella pneumoniae (8.62%) were the most isolated and Stenotrophomonas maltophilia (1.72%) and Escherichia coli (1.72%) were the least isolated. In the control group of patients sterile samples were found (55.55%). Older patients represent a population which is more prone to hospital-acquired pneumonia and in particular ventilator-associated pneumonia[11]. In his research he found that the result of antibiotic therapy was inadequate in 52 patients aged 72 because the VAP was caused by Methicillin-resistant Staphylococcus aureus in 33% of cases. In our study, from tracheal aspirates of patients of the test group 10 isolates of Klebsiella pneumoniae ESBL strain were isolated, 4 isolates of Methicillin-resistant Staphylococcus aureus, and 4 isolates of Proteus mirabilis ESBL strain and the average age of the same group of patients was 63.3 years, although in comparison to the control group age was not a significant factor.

The imperative of most antibiotic treatment of ventilator-associated pneumonia studies is on etiological diagnosis. The question is which material and method is most suitable for microbiological confirmation of the same. The basic problem in making microbiological diagnosis of VAP is in the use of invasive and noninvasive method to separate a sample of bacteria that are part of the normal flora of upper parts of the respiratory tract. It is proven that the incidence of tracheal bacterial colonization is 16% for medium heavy patients up to 100% in patients with prolonged intubation and mechanical ventilation[12]. The strategy for taking samples for microbiological examination depends on the availability and quality of laboratories and of existing capabilities of clinicians. As in many clinical centers immediate bronchoscopy can not be done especially at night. As an alternative method blind nonbronchoscopic method is used. Samples taken with blind bronchial suction are very sensitive, up to 74-97%[13]. In our study the sample for the etiological confirmation of pneumonia was taken from tracheal aspirate (with the original tube for taking the same) and it was positive for bacteria and

yeasts in 35/41 (85.36%) of patients with verified pneumonia, as compared to 6/41 (14.63%) of patients with normal findings.

In conclusion, the study points out that the tracheal aspirate by aspiration is non-invasive method. Its applicability, according to the results of other authors and our results, represents a good method for diagnosis of ventilator-associated pneumonia. A quantitative culture of endotracheal aspirate obtained from bronchoscopy or without it, with the assumption that for each technique diagnostic threshold is applied as well as methodological limitations, is recommended for making bacteriological strategy for settting the etiological diagnosis of VAP.

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ACTA MEDICA SALINIANA

PROFESSIONAL PAPER

Pain Therapy - Our Experience

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Pain is an unpleasant sensation described by a person suffering it and a symptom which most often patients to see a doctor. Pain affects everyday activities of the diseased and leads to decreasing quality of life in all its spheres. Release or elimination of pain is one of most important problems in medicine.

The research aim is analysis of work in the Pain Center Foca, together with pointing positive results as well as defects and failures in treating patients with acute and chronic pains.

This paper is a retrospective, partly prospective study. The data were collected from the available medical documentation. We have analyzed patients according to the type of illness, sort and intensity of pain, number of medical checks, kind of prescribed medicaments, as well as interventions in pain release. All the data have been statistically elaborated.

The study comprises a group of 845 patients treated in our department because of various painful conditions, in the period 2008 – 2010. The patients were at least twice examined in the medical station and all of them treated with medicaments. TENS and neuroblocks was applied such as additional intervention for pain release. Pain intensity and therapeutic effect assessment was done in regular time intervals, according to known pain scales.

Pain therapy demands multimodal and multidisciplinary approach. Thanks to latest medicaments and pain relieving procedures there are few patients to whom pain cannot be eliminated or life with pain made more dignified.

Keywords: *pain center; pain therapy; analgesics*

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Competing interests
The authors declare no competing interests.

INTRODUCTION

According to definition given by the international association for pain studies, "pain is an unpleasant sensorial or emotional event caused by an existing or possible tissue injury, or a problem described in the words corresponding to such injury" (IASP, 1979)[1]. Release or elimination of pain is one of most important problems in medicine.

All sensations in our organism depend on impulses which develop through corresponding receptor irritation and its farther conducting to the central nerve system (CNS)[1-3]. After a tissue injury, the cells of the damaged area release various mediators which impact free nerve endings.

From a nociceptor sensation is transferred to CNS through fibers of anterolateral spinothalamic tract [1-3]. In sensor cortex a final integration of pain information is performed. Descendent centrifugal system of pain control has a special importance and is known as endogenous system of analgesia1. Integrative processes on the highest cortical level provide control of behavior, thus also of pain, which means that this path provides "allowed" borders of painful reaction manifestation[1-5].

Depending on kind of fibers that pain pathways to CNS, pain is classified into acute and chronic [1,6-7]. The simplest and most easily accepted classification is according to the pain cause. Nociceptor pain occurs through irritation of nociceptors on the periphery (injury) and non-nociceptor pain occurs in absence of nociceptive stimulation as the consequence of changed activity of peripheral or central part of the nerve system (neuropathic pain)[3,7].

PAIN ASSESSMENT

A good pain assessment enables adequate choice of pain treatment method as well as assessment of the applied treatment effect. Pain is a strictly personal experience and every person experiences it subjectively[8]. Valid objective parameters for pain assessment still do not exist. One-dimension scales are mainly used for postoperative pain assessment. Among the best-known are Visual Analog Scale (VAS), Verbal Scale (VRS) and Facial Pain Assessment Scale (FPS)[8-11]. Most frequently used method

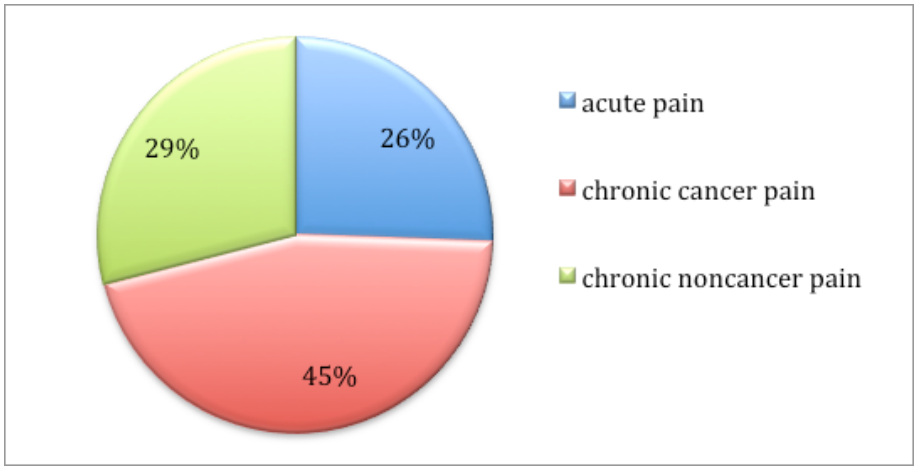

Figure 1. Types of pain within our sample

is pain intensity description. Pain descriptor uses words mild, moderate or intensive – patient chooses the word most corresponding to the intensity of the pain he feels[8].

PAIN TREATMENT

Pain medical service is mainly designed for the treatment of chronic pain and chronic pain syndromes as the biggest and most important public health problems, which diminish life quality, work ability, concentration, mood, sleep, intensifying co-morbidity and leading to chronic pain syndrome[12].

The aim of the research is the analysis of the work in the Pain Center Foca, together with pointing positive results as well as defects and failures in treatment patients with acute and chronic pain.

PATIENTS AND METHODS

This work is a retrospective, partly perspective study. We have analyzed the patients according to type of illness, sort and intensity of pain, number of medical checks, kind of prescribed analgesics as well as interventions in pain release. All data have been statistically elaborated used as measures of descriptive statistics, tabulation and graphical presentation.

RESULTS

The study comprises a group of 645 patients treated in our department because of various painful conditions, in the three-year period (2008/ 2010). Most patients were treated because of chronic pain. 3156 medical examinations were done and the patients were at least twice examined in medical station.

Patients with carcinoma pain were coming more often for repeated and control examination to regulate breakthrough pain (Graph 1). Only lately, market has offered a quick-efficacious peroral solution of morphium (Oramorph), an ideal drug for breakthrough pain[13].

Most frequent carcinoma was lung- and breast cancer. Chronic painful conditions of non-malignant etiology which were reasons of patient, coming to medical station were radiculopathy, osteoporosis, herpes zoster, diabetic polyneuropathy, ischemic illness of legs. Student t-test was obtained statistically significant difference ($p < 0.01$) (Graph 2)

All the patients were treated with medicaments. As additional interventions in pain release were applied transcutaneous electrical nerve stimulation (TENS) and peripheral and central nerve blocks (Graph 3).

From NSAIDs we used mainly ketoprofen (ketonal duo, ketonal amp), and among opioid analgesics, durogesic.

Pain intensity assessment and therapy effect check were done in regular time intervals according to known scales for pain intensity and quality assessment.

DISCUSSION

Latest decades have been showing a dramatic progress in pain researches. Understanding anatomy and neurophysiology of painful response is indispensable in a successful treatment both acute and chronic pain[1, 3-5, 14]. The aim of analgesia is to diminish or remove the sensation of pain and its negative effects. Pain therapy is a multidisciplinary problem, where anesthesiology takes one of leading places, especially in prevention and therapy of postoperative pain. Pain treatment

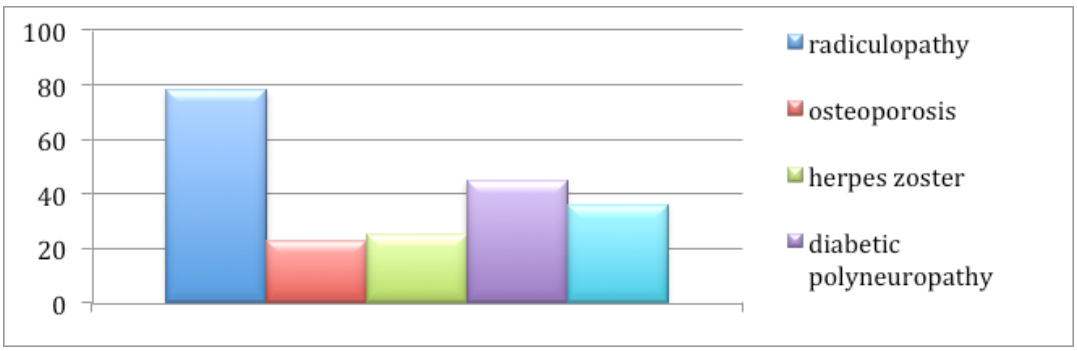

Figure 2. Chronic painful conditions of non-malignant etiology

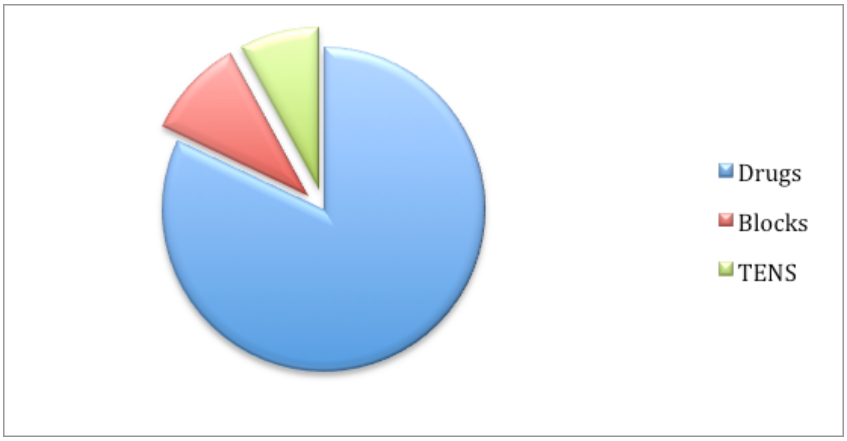

Figure 2. Applied methods of pain treatment

is based on several basic principles: "By mouth", "By the clock", "By the ladder", "For the individual", "Attention to detail" [14-17].

ANALGESICS

Substances applied in treatment of postoperative pain can be divided into three big groups: Opioid analgesics, non-opioid analgesics and adjuvant psychotropic medicaments [1,4,18-20]. Concept of balanced analgesia is based on the fact that combining medicaments and therapeutic procedures builds a regime of synergic pain control[21].

Most frequent reasons for coming to pain medical station is a long-lasting and badly treated neuropathic pain (radiculopathy, diabetic polyneuropathy herpetic neuralgia, central pain after brain stroke, pain after spinal chord injury, phantom pain) carcinoma and malignant pain in palliative medicine, arthralgia, arthritis, osteoporosis and other degenerative changes[1,5-8,21-25]. In chronic pain therapy the biggest importance has the rational pharmacotherapy which includes analgesics (non opiods and opiods) as well as co-analgesics (antidepressants and anticolvusants – mood stabilizers). Ketamin has an effect on NMDA and proved to be effective in preemptive analgesia reducing demand for narcotics. Steroids can be very effective analgesics, too [20-22]. Together with regional blocks, non- pharmacological methods are also at a disposal, which relieve the pain intensity (acupuncture, massage, yoga, psychotherapy etc.). A good anamnesis and physical examination of patient are of great importance [1-4,26-28]. Every patient should, before the examination, fill in a questionnaire related to all details on pain and its impact on quality of life, as well as on eventual earlier analgesic treatment. Pain therapy depends on the kind of pain, so that various groups of medicaments are effective in treatment of various pain sorts [2,13-16, 29].

With regard to neuropathic component which occurs at carcinoma pain and percentage of patients with chronic neuropathic pain, most frequently used drug was amizol (Graph 4). Appearance of neurontin at our market significantly helped and made our neuropathic pain therapy easier and also reduced number of undesirable side effects related to therapy with carbamazepine [1,27-30]. Combination of neurontin and amizol proved to be very successful in therapy of various chronic painful syndromes.

Other interventions done by us were central and peripheral neuroblocks. Mostly applied was epidural block with placing catheter for carcinoma pain therapy, and among peripheral blocks, nervus ischiadicus and lumbosacral block at radiculopathy[1,15-19,28-30].

THE PROJECT

Within the project "COMPREHENSIVE MANAGEMENT OF PAIN IN BH", in January 2009, in Clinic Center in Foca, the Center for pain therapy (SPAMU – satellite unit for pain therapy) was formed. This project was financed by Japanese Government (JICA) under the auspices of the organization "HOPE 87" from Sarajevo. The Project was supported by Ministry of Health B&H and Ministry of Health of Republic Srpska. The project aim was building the net of Centers for pain therapy all over B&H (Sarajevo, Banjaluka, Mostar, Foca), which, through cooperation, should improve pain therapy in these regions.

CONCLUSION

Diagnostics and therapy of pain requires multimodal and multidisciplinary approach.

Insufficient analgesia can, in a very short time, lead patient into sensitization, inflammation and chronic painful syndrome that demands a long-lasting pain treatment. Education of professional personnel ae well as patients and families, with the support of Ministry of Health and whole society, in terms of adequate provision of drugs and corresponding equipment, makes the safe way to a better pain therapy.

With modern medicaments and procedures for pain release, there are not many patients whose pain cannot be eliminated, relieved or, at least, make life with pain more dignified.

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ACTA MEDICA SALINIANA

ORIGINAL PAPER

Bispectral Index in the Assessment of Depth of Anesthesia

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Background: Adequate depth of anesthesia is one of the modern anesthesia aims. Possibility for monitoring of anesthesia depth is one of the modern anesthesia performances. There are subjective and objective methods for assessment depth of anesthesia. PRST score (pressure, rate, sweating, tears) is based on physiological response and can be used for estimating anesthesia depth. The aim of this study was to estimate depth of anesthesia with BIS accompanied by clinical parameters monitoring and ascertain presence of possible intraoperative awareness.

Methods: Bispectral index (BIS) is numerical processed, clinical confirmed electroencephalographic parameter that can be used for assessment depth of anesthesia as objective method.

Results: The mean age of patients was 51, 43 ± 13, 77. Patients were male in 90%, and female in 10%. General anesthesia lasted 54,93 ± 2,14 min. Bispectral index value during general anesthesia was between 35 and 60. There is statistical significant difference of BIS values in all measured periods ($p<0,05$). PRST score value was not higher than 3 in every moment of measuring. The highest PRST score values were immediately after intubation, but there were lower in further general anesthesia process. There is statistical significant difference of PRST score values in t1 and t2, t1 and t3, t1 and t4, t2 and t3. We made conversation with all patients 24 hours after operative procedure. We asked them, following formerly made questionnaire, about their pre, intra and postoperative memory. There was not any patient who replied intraoperative conscious, and most of them had first postoperative remembering associated with operative room.

Conclusion: Bispectral monitoring is significant support for clinical assessment depth of anesthesia.

Keywords: *depth of anesthesia; bispectral index; PRST score*

INTRODUCTION

Surgical anesthesia should be harmless and reversible state of insensibility of the patient, whose characteristics are sleep, analgesia, muscle relaxation and loss of reflexes (1). One of the goals of modern anesthesia is to ensure adequate depth of anesthesia to prevent awareness, but without overloading the patient with strong medications. One of the achievements of modern anesthesia is the possibility of monitoring the depth of anesthesia (1, 2). Adequate depth of anesthesia is present when the concentration of drug is sufficient to provide comfort to patients and perform surgery. There are subjective and objective methods for assessing depth of anesthesia. Subjective methods are based on movement and sympathetic response to the stimulus and depend on the opinions and experiences of anesthesiologists. Objective methods are based on the sensitivity of the monitor (2, 3, 4). Scoring of the patient's response to surgical stimulus, based on autonomous changes occurring in response to surgical stimulation, is a weak indicator of the depth of anesthesia (2, 5). It has been shown that hemodynamic response to stimulus does not always signify vigilance, or the absence of hemodynamic changes guarantee unconsciousness (6, 7). In patients who experienced vigilance during anesthesia, hypertension is reported 15 % of cases, tachycardia in 7%, and only 2% of patients have made a movement (8, 9, 10). PRST score (pressure, rate, sweating, tears) can be used to estimate the depth of anesthesia and is based on physiological response. The control parameter value is the value that was before the induction. Adding up the points of all four parameters determine the total amount which can range from 0 to 8. There is inadequate depth of anesthesia if score is more than three (5).

Electroencephalogram (EEG) can be used to estimate the depth of anesthesia. Anesthetics act on brain physiology and lead to changes in cortical neural activity, resulting in changes in electrical brain activity with a reflection on the EEG. EEG is a noninva-

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Competing interests
The authors declare no competing interests.

Table 1. Pressure, Rate, Sweating, Tears (PRST) score

Parameter	Value	Score
Systolic blood pressure	< control + 15	0
	<control + 30	1
	> control +30	2
Heart rate	< control + 15	0
	< control + 30	1
	>control +30	2
Sweating	Do not sweat	0
	Moist skin	1
	Visible beads of sweat	2
Tears	No tears in the open eyes	0
	The appearance of tears i the opening eye	1
	Leaking tears from closed eye	2

sive indicator of brain function when the patient is unconscious and without vulnerability (11, 12). During general anesthesia, EEG changes imply an increase of average amplitude and decrease in average rate (12, 13). Bispectral index (BIS index) is a numerical processed, clinically confirmed EEG parameter, obtained by combining the more advanced EEG techniques such as bispectral analysis, a powerful spectral analysis and time analysis. These components are combined to optimize the correlation between EEG and clinical effects of anesthesia. BIS index is a number between 0 and 100 arranged to correlate with clinical status during the application of anesthetics. BIS value near 100 is a clinical state of alert, while 0 means the greatest possible effect on the EEG (isoelectric EEG). Administration of hypnotics leads to the fall of the BIS index value of 100 in the waking state. Loss of consciousness occurs at BIS values between 70 and 80. BIS index of 40-60 indicates adequate hypnotic effect of general anesthesia with postoperative rapid return of consciousness. BIS value below 40 indicates a deep hypnotic state. BIS values decline below 70, the possibility of explicit survival is less. With the BIS index values of less than 60 is very small chance of awareness (14, 15).

Table 2. Bispectral index scale

100	Awake – responds to normal voice
80	Light/moderate sedation – May respond to loud commands or mild prodding/shaking
60	General anesthesia – low probability of explicit recall; unresponsive to verbal stimulus
40	Deep hypnotic state
20	„Burst suppression"-
0	Flat line EEG

SUBJECTS AND METHODS

Study was prospective and 30 patients who underwent inguinal hernia surgery at the Department of Surgery, University Clinical Centre Tuzla were analyzed. Subjects were of both sexes, aged 20-70 years, according to the classification of the American Society of Anesthesiologists (ASA) I and II operational risk. We used BIS XP System by Aspect Medical System to estimate the depth of anesthesia. Before the introduction of anesthesia unilateral BIS sensor that records the EEG waves was mounted on cleaned and dried head. BIS sensor is with the appropriate cable connected with the BIS monitor that displays the EEG waves and BIS index value. Using a sensor that is placed on the patient's forehead BIS monitoring translates information from the electroencephalogram in a simple number that is read on a monitor and represents a patient's state of mind. BIS index was monitored continuously, and we recorded the value at the time of intubation (t1), the first skin incision (t2), 20 min after the first incision (t3), and immediately after placing the last suture in the skin. During anesthesia, the BIS index values were maintained in the range 40-60, which is considered adequate depth. With BIS index quotation, it was determined and noted PRST score, too. Before the introduction of anesthesia values of systolic blood pressure and heart rate were recorded (t0). At the time of intubation (t1), the first skin incision (t2), 20 min after the first incision (t3), and immediately after placing the last suture in

the skin (t4), values of blood pressure and heart rate were recorded, also the occurrence of tears in the closed or when opening the eye, and the degree of skin moisture. Each parameter is scored from 0 to 2 and adding up all the points obtained by the PRST score on the basis of which was estimated depth of anesthesia. For an introduction to anesthesia was used propofol (1.5 to 2.5 mg / kg) for muscle relaxation atracurim (0.6 mg / kg), while the anes-

		Differences between pairs			p
		Mean differences	Standard deviation	Central standard error	
Pair 1	BIS t_1-BIS t_2	-7.63333	13.60396	2.48373	**0.00458**
Pair 2	BIS t_1-BIS t_3	-10.73333	13.00115	2.37367	**0.00010**
Pair 3	BIS t_1-BIS t_4	-21.50000	15.22192	2.77913	**<0,0001**
Pair 4	BIS t_2-BIS t_3	-3.10000	7.63996	1.39486	**0.03421**
Pair 5	BIS t_2-BIS t_4	-13.86667	9.87066	1.80213	**<0,0001**
Pair 6	BIS t_3-BIS t_4	-10.76667	7.13265	1.30224	**<0,0001**

Table 3. Differences in bispectral index values in different periods of measurement

thesia was mainatined with 02, N2O and sevoflurane, and analgesia with fentanyl (0, 15 to 0.25 mg). Postoperatively (24 hours after awakening from anesthesia), according to pre-made questionnaire we interviewed respondents to obtain information on whether they heard or felt anything during the surgery:

1. What was the last thing you remember before going to sleep before your surgery/procedure

2. What is the first thing you remember whwn waking up from your surgery

3. Do you remember anything between

4. Did you have any dreams while you were asleep during your surgery

5.What was the most unplesant thing you remember from your surgery and your anesthesia

Statistical analysis was performed by descriptive statistics to calculate the mean and standard deviation, and t-test, χ^2 tests for calculating the materiality established results. Statistical analysis was performed with a confidence interval of 95%, a value of p <0.05 was considered significant.

RESULTS

The average age of respondents was 51.43 ± 13.77. The male were represented in 90% of cases, a female at 10%. General anesthesia lasted 54.93 ± 2.14 min. Bispectral index value during general anesthesia was between 35 and 60. The mean value of BIS at t1 was 38.93, 46.56 at t2, the t3 49.66 and t4 60.43 (Figure 2).

There was a statistically significant difference in BIS index values in all periods of measurement, and is most intensive between t1 and t4, t2 and t4, and t3 and t4 (Table 4).

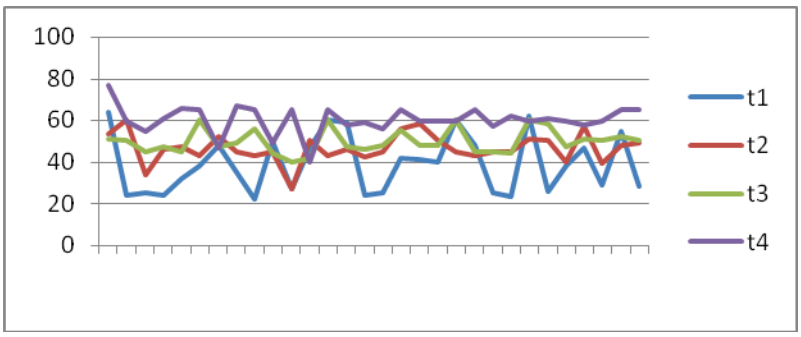

Figure 1. Bispectral index during general anesthesia

In all periods of measurement PRST score values were not higher than 3, which indicated an adequate depth of anesthesia. The highest PRST score values were immediately after intubation, whereas in the further course of general anesthesia were lower (Figure 3).

There was a statistically significant difference between the PRST score value at t1 and t2 (p = 0.00011), t1 and t3 (p = 0.00002), and t1 and t4 (p = 0.00001), t2 and t3 (p = 0.04340).

All respondents were interviewed 24 hours after surgery. According to a prepared questionnaire we asked questions about the immediate preoperative, intraoperative and postoperative memory. None of the respondents did not reply for the existence of consciousness during the intraoperative period, whereas most of them the first postoperative memories tied to the operating room.

DISCUSION

One goal of anesthesiologists is to achieve adequate depth of anesthesia during surgical procedures, to prevent the occurrence of intraoperative awareness. Too deep anesthesia can lead to cardiovascular depression and prolonged awakenings, and light anesthesia to serious physiological consequences for the patient. Moerman et al. (1993) have conducted a study that analyzed twenty six patients who experienced intraoperative awareness (17). Almost 70% later had an uneasy feeling, insomnia, nightmares, re-living the events or feelings of anxiety during the day, while 6% took psychotherapeutic assistance. Before the introduction of muscle relaxants, to achieve adequate depth of anesthesia implied a balance between lack of movement to painful stimuli with maintaining adequate respiration. With the absence of movement on pain it could be safely assessed that the patient is not awake. However, when using muscle relaxants it is necessary to be sure that the applied anesthetic dose is sufficient to prevent awareness. The introduction of new anesthetic techniques, such as intravenous anesthesia, using potent opiate analgesics, newer volatile anesthetics, and the assessment of depth of anesthesia has gained even greater significance. In their daily

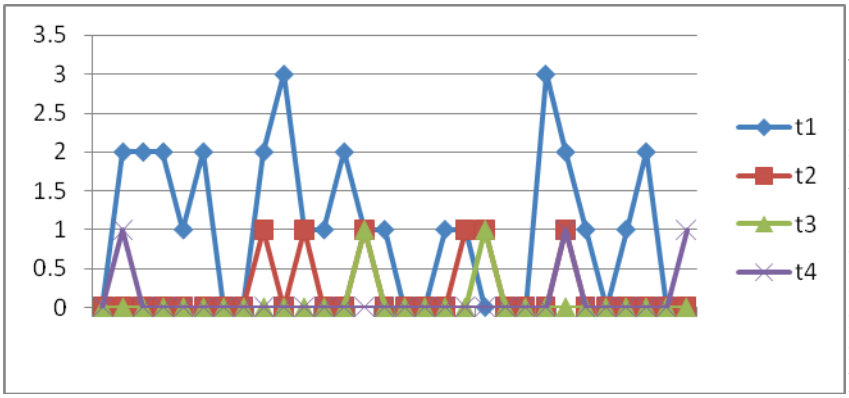

Figure 2. PRST score during general anesthesia

work anesthesiologist assesses the depth of anesthesia based on clinical signs, which represent a response of the autonomic nervous system of the organism to light anesthesia - tachycardia, hypertension, sweating, tearing, and dilation of the pupil. Evans and Davies in 1984 introduced a scoring system for clinical assessment of depth of anesthesia (PRST score). This scoring system may indicate an adequate depth of anesthesia, but patients can be awake during it, or parameters can indicate light anesthesia but patients do not complain later on intraoperative awareness. The signs of increased autonomic activity may be absent when using opioids, cholinergcs a, beta blockers, vasodilators and antihypertensive drugs. Increasing the parameter values of PRST score can cause hypovolemia, inadequate analgesia, hypoxia or hypercapnia. Signs of a light anesthesia often occur, but their correlation with awareness is low. In our study, titration of anesthetics and anesthetic depth assessment were done on the basis bispectral index. Before administration of midazolam BIS index value was between 97 and 100, after administration of midazolam and fentanyl over 80, and after administration of intravenous anesthetics value was below the 60. With continuous monitoring of the BIS index the PRST score was assessed. The lowest mean BIS index was in t1, and the highest in t4, which was expected since we have an intravenous anesthetic for induction of anesthesia titrated to BIS index values below 40, and at the end of surgery reduced the concentrations of volatile anesthetic corresponding EEG and BIS .The greatest value PRST score was in t1. In the further course the mean PRST score values were lower, due to achieving higher concentrations of anesthetics in the central nervous system after turning volatile anesthetics and the administration of additional doses of opioid analgesics. During surgery, we titrated the anesthetic by the BIS index values, keeping it in the range 40-60, which according to an activity level of the central nervous system that is required for general anesthesia. In addition to this objective method nor clinical assessment of depth of anesthesia with PRST score in this group of respondents did not indicate the likelihood of being "shallow" of anesthesia and intraoperative awareness. In our study, 24 hours after surgery the subjects were interviewed according to pre-prepared questionnaires, in order to determine the existence of explicit memory for intraoperative events. All respondents gave a negative response to questions about whether something heard, seen or felt while they were under general anesthesia. Assessing the depth of anesthesia using BIS monitoring is a noninvasive method. The value of BIS index reflects the electrical activity of the brain and the patient's state of consciousness, so BIS monitoring reduces the possibility of intraoperative awareness of the patient and explicit memory for intraoperative events. Ekman and colleagues (2004) conducted a study aimed at analyzing the occurrence of explicit memory in patients who were monitored for BIS monitoring during general anesthesia. The study included 4945 patients who underwent elective surgery. They compared the results of their study with results from earlier studies, but where no cerebral monitoring was used. Two patients (0.04%) who were followed with BIS monitoring had explicit memory, while 0.18% of patients in studies without cerebral monitoring, had explicit memory ($p < 0.038$). In conclusion, Ekman and colleagues have pointed out that the use of BIS monitoring during general anesthesia significantly reduces the incidence of intraoperative awareness (18). Bispectral index allows anesthesiologists directly and accurately monitoring the central nervous system during the application of anesthetics or sedatives, or assessment the hypnotic effect of anesthesia (19). Monitoring Bispectral index monitoring assesses the depth of anesthesia and facilitates titration of anesthetics. In the operating room changes in blood pressure and heart rate are not uncommon, and the task of anesthesiologists in these situations is to make a prompt diagnostic evaluation and timely intervention to eliminate the cause of these changes. BIS monitoring provides new information that can facilitate the anes-

	N	Mean	Standard deviation
PRST t_1	30	1.0333	0.9643
PRST t_2	30	0.2000	0.4068
PRST t_3	30	0.0667	0.2537
PRST t_4	30	0.1000	0.3051

Table 4. The mean value of PRST score in each measurement period

thesiologist in making decisions and treatment of many of these situations (20). BIS monitoring is not a substitute for clinical assessment of depth of anesthesia. However, the use of BIS monitoring with clinical assessment allows anesthesiologists precise decision-making and balancing a dosage of anesthetics and other medicines such as analgesics and cardioactive agents, especially in patients with higher operative risk (21).

CONCLUSION

Evaluation of intraoperative depth of anesthesia is one of the main tasks of anesthesiologists. BIS monitoring is a useful addition to clinical assessment of anesthesia, especially in high-risk patients. BIS monitoring is not a substitute for clinical assessment depth of anesthesia. It is necessary for anesthesiologist to interview patients preoperatively and postoperatively, record the factors and prevent the consequences of intraoperative awareness. Intraoperative vigilance causes permanent damage to the psychic sphere in patients, and liability for anesthesiologists.

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ACTA MEDICA SALINIANA

PROFESSIONAL PAPER

Predisposing Factors for Postoperative Awakening in Patients with Brain Tumors

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Background: Brain tumors account for about 10% of all tumors of the human organism. Depending on localization distinguish supratentorial and infratentorial tumors. Application and effects of mechanical ventilation in patients with brain changes, require knowledge of the influence of mechanical ventilation on ICP and cerebral circulation.

Objective: The aim of our study was to determine the factors that affecting on a prolonged post-operative awaking in patients with brain tumors.

Patients and methods: A retrospective study analyzed 99 patients. We analyzed: age, sex, comorbidity, tumor localization, length of surgery and intraoperative complications. Patients were divided into two groups: the first consisted of those who are awakened within 24 hours, and the other those who are awakened after 24 hours. prolonged awakening patients after surgical treatment of brain tumors occur in high-risk patients, patients with long and complicated surgery, patients with comorbidity, intraoperative or immediate postoperative complications.

Results: The mean age of patients was 52 years (± 17). Supratentorial tumor site was found in 83 patients, and was infratentorial in 16. From patients with supratentorial tumor site was awakened 90% within 24 hours. The remaining 10% is required mechanical ventilation after 24 hours. From patients with localized tumors infratentorially 92% required mechanical ventilation longer than 24 hours, 8% was awakened within 24 hours.

Conclusion: postoperative treatment of patients with brain tumors requires a good understanding of the pathophysiological events in the brain, intensive postoperative monitoring and in particular the regulation of intracranial pressure and cerebral perfusion flow.

Key words: *brain tumor; prolonged awakening; mechanical ventilation*

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Competing interests
The authors declare no competing interests.

INTRODUCTION

Brain tumors account for about 10% of all tumors of the human organism. Depending on location there is supratentorial and infratentorial tumors. At adults are much more common supratentorial and at children infratentorial tumors. There is a difference between primary intracranial tumors (derived from embryonic brain tissue or intracranial residues) and secondary intracranial tumors (derived from metastatic proliferation).[1] Primary intracranial tumors may be histologically benign and malignant, although this division is not sharply defined as in other parts of the body. Malignancy of tumors in the cranium depends on the speed of its growth, the tendency to infiltrate environment and its localization. Tumor that is histologically benign, and located in functionally important regions (medulla oblongata, pons, midbrain, hypothalamus, basal ganglia) malignant behavior.[2] First division of nervous system tumors, the 11 groups have made Cushing and Bailley 1926. The current WHO classification of tumors of the nervous systems are classified into 11 groups:

1.Neuroepithelial tumors (astrocytoma, oligodendroglioma, ependymoma, pinealoma, gangliocytoma, medulloblastoma, glioblastoma)
2. Tumors of nerve sheaths (neurinoma)
3. Tumors of the meninges (meningioma)
4. Malignant lymphomas
5. Vascular malformations (telangiectasia, cavernomas, AV malformation, etc.)
6. Germ cells tumors (germinoma, embryonal carcinoma, teratoma, etc.)
7. Congenital tumors (craniofaringeoma, dermoid, lipoma)
8. Tumors of the pituitary gland,
9. Local expansion from regional tumors,
10.Unclassified tumors,
11.Metastatic tumors.[1]

Symptoms and signs of intracranial tumors can occur suddenly or gradually. Clinically, they can be classified into four groups: symptoms and signs of increased ICP (headache,

nausea, vomiting, stoppage of papilla optic nerve, bradyphsycia, bradycardia, hypertension), focal neurologic signs and symptoms (neurological impairments or neurological irritation as focal seizures, pain syndromes); signs and symptoms of cerebral herniation; specific symptoms and signs (hormonal disorders, signs of cranial nerve compression, such as neuralgia, disesthesia, anesthesia, paralysis, tinnitus, hypacusia, vertigo).[2] Cerebral circulation has its own specifics, which are vital for brain and body as a whole. Specifics of the cerebral circulation are:

1.The ability of the cerebrovascular system to independently regulate the size of cerebral blood flow - cerebral autoregulation;
2. The existence of the blood - brain barrier;
3. Effect of accommodation of the brain in the incompressible cranial cavity on the perfusion of brain tissue.

Cerebral perfusion pressure (CPP), the most important factor in cerebral blood flow (CKP), recovering the difference in mean arterial pressure (MAP) and mean intracranial pressure (ICP). To maintain adequate oxygenation and nutrition of the brain parenchyma is necessary for CPP of at least 50 mmHg. CPP within the range of 50-130 mmHg leads to insignificant changes in CKP. Changes in PaCO2 has an influence on CPP.[3] Application and effects of mechanical ventilation in patients with brain changes, require knowledge of the influence of mechanical ventilation on ICP and cerebral circulation. It is recommended that the application volume-controlled mechanical ventilation, while the application of pressure-controlled ventilation is contraindicated due to variations in output and PaCO2.[4]

OBJECTIVE

The aim of our study was to point out the factors affecting the prolonged awakening in patients with expansive process in the brain. The parameters in this study were length of surgery, tumor site, comorbidities, and intraoperative complications.

SUBJECTS AND METHODS

In a retrospective study analyzed a total of 99 patients, who underwent neurosurgical operative treatment of brain tumors during the period June 2009. - June 2010. at the Clinic of Neurosurgery, UKC Tuzla. Patients were subjected to standard pre-operative preparation. Patients, after completing the operation, were transferred in the Intensive Care Unite at Clinic of Anesthesiology and Reanimation UKC Tuzla. In this paper we have analyzed: gender, age, comorbidity, tumor localization, length of surgery and intraoperative complications. Patients were divided into two groups: the first consisted of those who are awakened within 24 hours, a second group consisted of patients who are awakened after 24 hours. Patients were ventilated by the principles of ventilation patients with brain damage.

RESULTS

The average age of patients was 52 years (+ 17). Of the total number of patients there were 58 female, 41 male. Supratentorial tumor site was found in 83 patients, while infratentorial was found in 16 patients. Number of patients with comorbidity was 54th. Under the comorbidity were assumed patients with hypertension, chronic lung disease, diabetes and obesity. In the group with localized supratentorial tumors were 83 patients. Infratentorial group with localized tumors consisted of 16 patients. From patients with supratentorial tumor site was awakened 90% within 24 hours. The remaining 10% is required mechanical ventilation after 24 hours. From patients with localized tumors infratentorial 92% required mechanical ventilation longer than 24 hours, 8% was awakened within 24 hours. As for the length of surgery, 84% of patients whose surgery lasted longer than 4 hours is required prolonged mechanical ventilation. In relation to age and gender has no statistically significant difference in the need for prolonged mechanical ventilation. Comorbidity, except in 2 cases, did not affect the continued awakening of patients. In both cases it was the unregulated hypertensive disease that required stabilization of the patient first and then awakening. Intraoperative complications in terms of bleeding and brain edema, occurred in 6 patients and all required mechanical ventilation longer than 24 hours.

DISCUSSION

In our study, we showed that age and gender of patients has no influence on the course of postoperative awakening. Comorbidity in a negligible extent be influenced by the prolonged mechanical ventilation. Localization of the tumor is of crucial importance to the length of postoperative mechanical ventilation. Localization of tumors is important because of the length of surgery, and the occurrence of intraoperative complications. Infratentorially tumors that are located on the cranial base are required for long operating procedures and the postoperative recovery was longer and harder, and the possibility of complications is greater. Such tumors and neurosurgical positions require full brain stability in terms of regulation of intracranial pressure and prevention of hemorrhage. This stabilization allows us mechanial ventilation with deep sedation and analgesia.

CONCLUSION

Postoperative treatment of patients with brain tumors requires a good understanding of the pathophysiological events in the brain, and intensive postoperative monitoring of all major organ systems and in particular the regulation of intracranial pressure and cerebral perfusion flow.

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ACTA MEDICA SALINIANA

ORIGINAL PAPER

Effect of Recipients' Arterial Blood Pressure on Renal Graft Survival in Early Posttransplant Period

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Background: In addition to surgical and immunological causes of rejection and reduced renal graft function, there are a number of other risk factors that significantly influence survival of the transplanted kidney. Some of these factors are especially important in the immediate postoperative course, among the factors that are of great importance for graft survival, are donor age, recipient hypertension, immunosuppressive therapy, degree of rehydration and hiperlipidemia.

Aim: The aim of the study was to evaluate influence of blood pressure in recipients on parameters of kidney graft function in the early postoperative period.

Methods: This is an observational cohort study that recruited seventy-four patients who underwent kidney transplantation. Seventy patients received kidney transplant from living donor and four from a deceased donor. Comparing to the values of blood pressure recipient patients were allocated into two groups: normotensive and hypertensive.

Results: There was no statistically significant difference between the value of daily diuresis in normotensive and hypertensive renal graft recipients. The first day after transplantation, there was a statistically significant difference in mean creatinine values. Significantly higher values in hypertensive compared to normotensive patients. In the first two postoperative days, there was no significant difference in creatinine clearance between hypertensive and normotensive renal graft recipients.

Conclusion: Arterial pressure, recipients as well as donors, is a very important factor that affects the function of renal graft. Many studies have shown that improvements in the immunosuppressant treatment and treatment of hypertension significantly reduced the incidence of acute rejection. Although some of the observed parameters of renal function did not show statistical significance, when being compared between hypertensive and normotensive group, tight blood pressure control in the early posttransplant period is an imperative.

Key words: *renal transplantation; blood pressure; early posttransplant period*

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INTRODUCTION

In addition to surgical and immunological causes of rejection and/or reduced renal graft function, there are a number of other risk factors that significantly influence survival of the transplanted kidney. Some of these factors are especially important in the immediate postoperative course because acute and accelerated graft rejection occur very early post transplant. Among the factors that are of great importance for graft survival, are donor age, recipient hypertension, immunosuppressive therapy, degree of rehydration and hiperlipidemia (1). Posttransplant hypertension is an important issue in kidney graft survival. Factors that cause the occurrence of hypertension after transplantation are renal artery stenosis, immunosuppressive therapy, corticosteroids, graft dysfunction, genetic predisposition. Renal artery stenosis occurs in 2-10% of cases and it should be suspected if there is severe hypertension accompanied by noise during auscultation of the graft (2). Corticosteroids and immunosuppressive agents (particularly calcineurin inhibitors), significantly contribute to the onset of hypertension. Corticosteroids affect the development of hypertension causing hemodynamic and hormonal disorders as well as retention of salt and water (3). Cyclosporine induced hypertension usually occurs after prolonged usage, and in most cases is mild and responds well to treatment (4). The most common and leading cause of posttransplant hypertension is chronic graft nephropathy (5), which is usually the first sign of chronic graft rejection (6).

Table 1. General and demographic data

Variable	Value
Age	32.9 ± 9.7
Gender (m / f)	51/23
Donor age	49. 2±12. 2
CyA	74
Mycophenolate/ Azathioprine	34/40
Basiliximab (yes/no)	33/41
Hypertension	59
Hypotension	1
Normotension	14

PATIENTS AND METHODS

This is an observational cohort study that recruited seventy-four patients who underwent kidney transplantation. Seventy patients received kidney transplant from a living donor and four from a deceased donor. All patients were assessed as ASA IV (American Society of Anesthesiologists) physical status. Balanced anesthesia was used in all transplant patients. In order to assess renal graft function, following parameters were evaluated: glomerular filtration rate (GFR) (ml/min) creatinine clearance (ml/min), 24 h urine output, and from the serum levels of K+, Na++, urea (mmol/L), creatinine (mmol/L). All parameters were assessed daily in first seven post transplant days. GFR was determined using the formula GFR = 270 × Cr -1.007 × Year-0, 18 × Urea-0, 169 × 0.755 (women) (7). Creatinine clearance was determined by a formula given by Cockcroft and Gault 1976 years: Creatinine clearance = (140-year) × tt / (72 × creatinine) (8). Other parameters were determined by using standard methods and procedures in laboratories of Clinical Centre Tuzla. Based on the preoperative blood pressure values recipients were allocated to two groups: normotensive and hypertensive group.

STATISTICAL ANALYSIS

The statistical analysis was performed by using ANOVA and Student t-test, p-value of less than 0.05 was considered statistically significant.

RESULTS

The study was conducted in University Clinical Centre Tuzla and included seventy-four patients with mean age of 32.9±9.7 years. Mean donor age was 49.2±12.2 years; twenty-six donors were older than fifty-five years. All patients received cyclosporine postoperatively; other than with cyclosporine, thirty-four patients were treated with mycophenolate mofetil, and the rest of them with azathioprine. As additional immunosuppressive therapy, thirty-tree patients received basiliximab. Fifty-nine patients were hypertensive, fourteen normotensive and one hypotensive. General and demographic data are shown in Table 1.

Analysis of correlation between values of recipients blood pressure and parameters of graft function

There was no statistically significant difference in daily diuresis between normotensive and hypertensive recipients' (Table 2).

Evaluation of correlation between of recipient's arterial tension and serum creatinine values showed no significant difference on the first posttransplant day. Significantly higher values of serum creatinine were found in hypertensive compared to normotensive patients on the second postoperative day (472.6 ± 223.4 vs. 382.8 ± 118.2, p = 0.04). Equalization of these values occurred on the third postoperative day (282.5 ± 79.1 vs. 282.2 ± 176.4 p = 0.99), and after that followed a significant fall in the value of creatinine in the group of hypertensive compared to normotensive patients (181.5 ± 64.5 vs. 289.3 ± 222.6 p <0.001) (Table 3).

Examination of average values of GFR in relation to the recipients of blood pressure values showed no significant difference between hypertensive and normotensive group (Table 4).

Comparing average creatinine clearance values to recipients blood pressure in the first two days showed no significant difference in creatinine clearance between hypertensive and normotensive renal graft recipients (19.9 ± 7.1 vs. 21.6 ± 9.9 p = 0.46). After the third posttransplant day there was a statistically significant increase in creatinine clearance in a hypertensive compared to normotensive patients (48.6 ± 20.5 vs. 31.9 ± 11.9, p <0.0003) (Table 5).

Values of serum potassium were significantly higher in hypertensive group only on the first postoperative day (Table 6).

Statistically significant difference in average sodium values between normotensive and hypertensive group was found on the first and the fourth posttransplant day. In the following days, no statistical significance concerning mean sodium values were established (Table 7).

In both normotensive and hypertensive group values of blood urea were elevated, but significant difference between the groups was not registered. On the seventh posttransplant day values of blood urea normalized in both groups (Table 8).

Table 2. Correlation of average values of diuresis between normotensive and hypertensive patients

Day	Normotensive patients	Hypertensive patients	p
1.	5066±4291	5125±3859	0,96
2.	5037±3270	6161±3118	0,22
3.	4455±2897	5411±2198	0,24
4.	3688±1736	4684±2220	0,16
5.	3522±1547	3762±1841	0,25
6.	2869±793	3233±1765	0,11
7.	2600±663	2961±1759	0,07

Table 3. Average values of serum creatinine in relation to the value of blood pressure

Day	Normotensive patients	Hypertensive patients	p
1.	382,8±118,2	472,6±223,4	0,04
2.	381,2±190,5	418,9±195,9	0,50
3.	282,5±79,1	282,2±176,4	0,99
4.	238,1±113,7	207,3±93,4	0,28
5.	289,3±222,6	181,5±64,5	0,001
6.	208,5±126,3	156,9±66,7	0,03
7.	174,8±105,5	137,7±49,3	0,05

Table 4. Average values of GFR in relation to the value of blood pressure

Day	Normotensive patients	Hypertensive patients	p
1.	18,4±4,5	16,9±7,9	0,353
2.	21,9±10,9	20,4±13,8	0,681
3.	25,2±8,8	31,9±18,5	0,055
4.	33,2±14,4	40,4±20,8	0,137
5.	38±24,5	43,2±20,6	0,466
6.	46,8±26,5	52,1±24,8	0,505
7.	58,2±38,6	57±24,5	0,915

Table 5. Average values of creatinine clearance in relation to the value of blood pressure

Day	Normotensive patients	Hypertensive patients	p
1.	19,9±7,1	21,6±9,9	0,465
2.	22±10,8	25,1±13,2	0,359
3.	25,8±10,2	38,8±18,5	0,001
4.	31,9±11,9	48,6±20,5	0,0003
5.	35,5±20,9	51,5±17,9	0,016
6.	43,1±20,8	61,2±22	0,008
7.	50,8±23,2	66,8±21,3	0,029

Table 6. Average values of serum potassium in relation to the value of blood pressure

Day	Normotensive patients	Hypertensive patients	p
1.	5,1±1,2	4,6±0,7	0,04
2.	4,4±0,6	4,6±0,6	0,14
3.	4,2±0,6	4,2±0,6	0,99
4.	4,1±0,5	4,1±0,5	0,99
5.	4±0,6	4,1±0,5	0,99
6.	3,9±0,4	4±0,4	0,99
7.	3,9±0,5	3,9±0,4	0,92

DISCUSSION

Blood pressure (systolic, diastolic and mean) in the recipient as well as in the donor of renal graft is a very important factor affecting function of transplanted kidney, occurrence of delayed graft function, acute rejection and long-term graft survival. This study examined the effect of recipient's blood pressure in early posttransplant period, on the renal graft function. The results showed that there was no statistically significant difference between the value of diuresis in normotensive and hypertensive renal graft recipients. From the first to the third postoperative day, no statistically significant difference between the value of serum creatinine in normotensive and hypertensive renal graft recipients was found. Fourth to seventh postoperative day, significantly lower values of serum creatinine were detected in hypertensive compared to normotensive group. The values of GFR were not significantly different between hypertensive and normotensive renal graft recipients. On the first two days, there was no significant difference in creatinine clearance between hypertensive and normotensive renal graft recipients. Nevertheless, after the third day there was a statistically significant increase in creatinine clearance in a group of hypertensive patients compared to normotensive patients. There was no statistically significant difference between levels of serum potassium, sodium and urea in normotensive and hypertensive renal graft recipients. Slow and delayed graft function after renal transplantation, especially in the early recipients, in the early postoperative period is associated with reduced long-term graft survival; however, the whole mechanism is yet to be elucidated. Ozdemir et al. analyzed the possible risk factors associated with the emergence of slow and delayed renal graft function in young recipients from a living donor. They examined the influence of donor age and gender, recipient age and gender, systolic and diastolic blood pressure, lipid profile and biochemical parameters. The results of their study showed that the value of systolic blood pressure <120 mm Hg is a significant risk factor for the development of slow or delayed kidney graft function in the postoperative period (9). Opelz and Döhler analyzed the impact of systolic blood pressure of renal transplant recipients regarding long-term survival of renal grafts and patients. Their research has shown that the recipients of kidney transplant who were treated and brought into a state of normotension had a better function and longer graft survival, compared to those who were hypertensive (10). Fernandez-Fresendo et al. analyzed the impact of the value of GFR in the early postoperative period on the occurrence of posttransplant hypertension; their research has shown that lower values of GFR in the early posttransplant period lead to the development of posttransplant hypertension. Those with normal GFR did not develop posttransplant hypertension. In addition, they showed that there is a negative correlation between GFR and hypertension, on the one hand and survival of renal graft from the other. Therefore, patients with lower values of glomerular filtration rate are more prone to develop secondary hypertension and poorer renal graft survival (11). Multiple stud-

ies have analyzed the effect of hypertension on renal graft function. Mange et al. examined the relationship between hypertension and renal graft survival. This study proved that elevated systolic, diastolic, and mean arterial pressure decreased renal graft function and shortened its survival (12). Mitsnefes et al. observed effect of hypertension in the early postoperative period on renal graft survival in children. Their research has shown that elevated systolic and diastolic blood pressure associated with poor kidney graft survival rates. Children with systolic hypertension in the early post-transplant period had poorer survival rates of kidney graft. Early posttransplant systolic hypertension is a strong and independent predictor of poor survival rates of kidney graft (13). Kasiske et al. examined the influence of blood pressure on kidney function and graft outcome of kidney transplantation. They found that elevated systolic blood pressure was associated with an increased relative risk for kidney graft failure (14). Casio et al. univariate analysis found that acute renal graft rejection associated with delayed graft function, higher serum levels of creatinine, and a high systolic and diastolic blood pressure after transplantation. Hypertension is also associated with previous episodes of acute rejection. Patients with hypertension have a high risk of impaired function and acute rejection of kidney graft (15).

Table 7. Average values of serum sodium in relation to the value of blood pressure

Day	Normotensive patients	Hypertensive patients	p
1.	137,7±3,8	140,3±3,4	0,03
2.	141,4±3,2	140,5±3,1	0,34
3.	140,3±3,6	140,8±2,9	0,35
4.	139,5±3	141,7±2,4	0,04
5.	141,4±3,3	141,9±2,8	0,63
6.	140±4,4	140,2±3,4	0,58
7.	139,6±3,9	140,2±3,2	0,36

Table 8. Average serum values of blood urea in relation to the value of blood pressure

Day	Normotensive patients	Hypertensive patients	p
1.	14,1±6,4	12,5±3,7	0,38
2.	14,3±8,5	12,1±4	0,16
3.	12,7±7,4	11,7±4,3	0,36
4.	13±8,3	10,6±4,4	0,50
5.	13,2±9	10,5±4,5	0,62
6.	11,7±7,3	9,3±3,7	0,13
7.	9,6±5,2	8,8±3,1	0,30

CONCLUSION

Although some of the observed parameters of renal function compared between hypertensive and normotensive group, did not show statistical significance, tight blood pressure control in the early posttransplant period is an imperative. Normotension and mild hypertension are proven to contribute stability of renal graft function in the early postoperative period, and posttransplant hypertension to worsen prognosis for kidney graft survival.

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ACTA MEDICA SALINIANA

PROFESSIONAL PAPER

Bacterial Infections in Intensive Care Unit

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Background: Nosocomial infections is defined as a disease that developed after 48 hours of hospitalization, and did not exist, or had its incubation in the admission to the examination and / or treatment. It is estimated that nosocomial infections occur in 5-10% of hospitalized patients.

Patients and Methods: Retrospective-prospective study involved 268 patients who were admitted for elective surgery, patients with stroke and patients with head trauma. Samples were taken and analyzed by standard methods in microbiological laboratories. Aim: To describe the incidence of nosocomial infections and the sensitivity and resistance to antibiotics.

Results: Of 268 patients analyzed, 343 samples were taken, of which 282 samples showed signs of nosocomial infections. In the aspirates of the trachea was dominated: Klebssiela pn., Staphylococcus aureus, Acynetobacter species. The most common bacteria present in the urine culture findings were: Proteus mirabilis, Escherichia coli, Acynetobacter sp. In the majority of samples from blood was found: Coagulasa negative staphylococcus.

Discussion: The isolated strains showed an extremely high degree of resistance to standard antibiotics, making infections and treatment was difficult. The group causes respiratory tract infections showed the greatest sensitivity to imipenem and pathogens from urinary tract infections in the meropenem. Conclusions: The nasocomial infections are causing morbidity and mortality in the ICU-in. Targeted antimicrobial therapy on the basis of the antibiogram is the only choice to reduce the frequency of nasocomial infectios.

Keywords: *nosocomial infection; sensitivity; resistance*

INTRODUCTION

Nosocomial infections is defined as a disease that developed after 48 hours of hospitalization, and did not exist, nor had its incubation in the admission to the examination and / or treatment. It is estimated that nosocomial infections occur in 5-10% of hospitalized patients. Nosocomial infections are a global health problem particularly in hospitals that treat acute deseases [1]. It is impossible to make a hospital without risk to the patient. The risk of nosocomial infections by entering the patient's informed consent before different kind of surgery, particularly surgical. The frequency and types of nasocomial infections depend on many factors: the profile of the hospital, the immune status of patients, hospital hygiene, staff training, doctrine adopted or unadopted, use of antibiotics in preventive and curative purposes, etc. Their appearance can complicate the course and outcome of underlying disease (increased morbidity and mortality), extending the treatment time and significantly increases the material costs. Nosocomial infections challengers can be finished in all microorganisms: bacteria, viruses, fungi and parasites. The types of bacteria that cause infections, they changed over time depending on the antibiotic use and application of new diagnostic and therapeutic, often aggressive procedures that lead to the break / mucosal and skin lesions. The essential characteristics of bacteria causing nasocomial infections are: resistance to antibiotics (and often multiple resistance), depending on the appearance of resistance to antibiotics and disinfectants. The most common causes of nasocomial infections are: Escherichia coli, coagulase-negative staphylococci and Staphylococcus aureus (especially methicillin-resistant staphylococcus), Enterococcus sp. Psuedomonas aeruginosa, Acinetobacter spp, Klebsiella pnuemoniae, Enterobacter sp., Proteus mirabilis, Serratia sp., and anaerobic gram positive bacteria (Propionibacterium sp., Bacteroides sp.). In recent years, nasocomial infections agents are Legionalla sp., Clostridium difficile, Corynebacterium jejunum and Micoplasma hominis [2].

Unfortunately, some bacteria are difficult

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to treat with antibiotics because they have developed resistance / resistance. These bacteria are commonly called "superbugs". Bacteria MRSA (Methicillin - Resistant Stapyhilococcus Aureus) is "old hospital bacteria, known to the world since 1960. year. This is an important hospital pathogen, and since 1981, in and out [3,4].

ESBL organisms cause a wide spectrum of diseases and conditions ranging from colonization to serious infections. The most common cause of urinary tract infections, peritonitis, cholangitis and intra-abdominal abscesses. Infection or colonization with ESBL bacteria (Enterobacteriaceae) commonly occurs in intensive care units.

β lactam drugs are among the safety and most commonly used antimicrobial drugs. However, their use in clinical practice significantly affects resistance developed by some pathogenic microorganisms [5]. Treatment of infections caused by β lactamase bacteria that are resistant to penicillins, early cephalosporins derivatives, a new generation of relatively stable enzyme and broad spectrum cephalosporin derivatives is very difficult to treat. These enzymes were discovered in late 1970 and early 1980 and among the gram-negative bacteria, dominated in Escherichia coli and Klebsillae pneumoniae.

The most common are urinary tract infections, which are normally associated with implantation catheter and according to most statistics they make up about 40% of nasocomial infection. Generally accepted and proved attitude is that the length of catheter in a blood vessel is directly proportional to the development of infection. According to the results of several surveys safe period, or period in which the infection does not develop until 3 days from the time of catheter insertion [6]. When it comes to urinary catheters, the infection is almost certain in all patients who had catheter 30 days [7]. Followed by lower respiratory infection, about 20%, postoperative wound infections from 16%, septicemia 8,5% and various other infections (skin, gastrointestinal, etc.). Manifest catheter infections in patients occur very often accompanied by significant morbidity. The diagnosis of symptomatic urinary tract infection is confirmed positive urinoculture.

Pneumonia is the second most common nosocomial infections. Most patients had risk factors such as mechanical ventilation (high risk), age, neonatuses, chronic diseases, immunodeficiency, affection CNS, cardiopulmonary disease. A special place among nosocomial pneumonia occupies ventilator-assisted pneumonia (VAP) with a high mortality rate (more than 40%), and serious complications such as acute respiratory distress syndrome (ARDS). In patients receiving mechanical ventilation cumulative risk of pneumonia increases with the duration of ventilation.

PATIENTS AND METHODS

Retrospective-prospective study involved 268 patients in the period from november 2009. year to september 2010. the intensive care unit of the Clinic for Anesthesiology and Reanimatology -objective "Blue Hospital" UKC Tuzla. A total of 343 samples taken for microbiological treatment, of which 282 were the findings showed the presence of agents of infection. Routinely, we take the material for microbiological treatment: once a week we took tracheal aspirate or bronholavat (for patients on a program of artificial ventilation) and urine samples to antibiogram. Of the samples that were taken as needed, were: blood culture (in febrile states), the peak CVK catheter (when replacing or at discharge), smear op. early (by early signs of infection), smear of ulcers, stool analysis (for diarrhea), smear of the nose, throat, arm and inguinal in patients from other institutions. Analysis of samples was done in the laboratories of the Institute of Microbiology, University Clinical Centre Tuzla by standard microbiological techniques. Antibiogram was done by disk diffusion method.

RESULTS

Analysis of samples from tracheal aspirate and bronholavata shows the following results:
Klebsiella pneumoniae ESBL-type (11)
Klebsiella pneumoniae (11)
Pseudomonas aeruginosa (9)
Staphylococcus aureus MRSA type (7)
Acynetobacter spec (7)
Staphylococcus aureus
Escherichia coli
Proteus mirabilis
Acynetobacter Baumani

Analysis of urine samples showed the following results:
Proteus mirabilis (3)
Acynetobacter species (3)
Enterococcus faecalis (2)
Escherichia coli (2)
Proteus mirabilis ESBL-type
Pseudomonas aeruginosa

The analysis of blood cultures were obtained the following results:
Coagulase negative Staphylococcus (8)
Pseudomonas aeruginosa
Enterobacter species

Analysis of the peak CVC catheter shows the following results:
Acynetobacter spec
Klebsiella pneumoniae
Coagulase negative staphylococcus
Enterobacter spec

Analysis of stool in patients, we found the presence of clostridium difficile in 4 patients.

Sensitivity bacterias usually present in the tracheal aspirate

1. Klebsiella pneumoniae ESBL-type	meropenem, imipenem
2. Klebsiella pneumoniae	meropenem, imipenem, amikacin
3. Pseudomonas aeruginosa	imipenem, cefepim
4. Staphylococcus aureus MRSA-type	vankomicin, amikacin

Sensitivity of bacterias commonly present in urine

1. Proteus mirabilis	meropenem, cefepim
2. Acynetobacter species	amikacin, imipenem
3. Enterococcus faecalis	xyclav, vankomicin

Sensitivity of bacteria commonly isolated in chemoculture

1. Coagulase negative staphylococcus	vankomicin, imipenem
2. Pseudomonas aeruginosa	meropenem, imipenem

Resistance of bacterias usually present in the tracheal aspirate

1. Klebsiella pneumoniae ESBL-type	ampicillin, xyclav, cenin
2. Klebsiella pneumoniae	ampicillin, xyclav
3. Pseudomonas aeruginosa	ampicillin, imipenem
4. Staphylococcus aureus MRSA-type	penicillin, gentamycin

Resistance of bacterias commonly present in urine

1. Proteus mirabilis	amoxycilin, norfloxacin
2. Acynetobacter species	xyclav, norfloxacin
3. Enterococcus faecalis	eritromycin, norfloxacin

Resistance of bacteria commonly isolated in chemoculture

1. Coagulase negative staphylococcus	penicillin
2. Pseudomonas aeruginosa	ampicillin, xyclav

DISCUSSION

The results of this study that included 268 patients, of which 343 samples were taken were obtained in 282 findings of which confirmed the presence of pathogens. The analysis of samples from tracheal aspirate following results were obtained: Klebsiella pn .- ESBL type - 11 findings, Klebsiella pn. - 11 findings, pseudomonas aeruginosa - 9 findings, Staphylococcus aureus (MRSA type) - 7 results, acynetobacter sp., - 7 results. Similar results are described in American literature, where the strains Acynetobacter are developing and becoming immune to existing antibiotics. "In many respects it is far worse than MRSA," said an expert at Case Western Reserve University. Corresponding bacteria was also dominant in the urine samples in this study. On wards where MRSA is endemic, especially in the ICU in which patients are at high risk for developing serious infections of MRSA, it is necessary to make a risk assessment and implement appropriate preventive measures. Measures to control MRSA infection include: screening of patients and staff, hand washing, use of topical and systemic antibiotics, patient hygiene, isolation of patients with MRSA, use of protective gear and gloves, and hygiene equipment and facilities. These preventive measures are described in many world famous conductors [8].

Especially prevalent in hospitals and the New York-re-

sistant gram-negative bacteria, Klebsiella pneumoniae. It is estimated that more than 20% of Klebsiella infection in Brooklyn hospitals and are resistant to almost all modern antibiotics and is now spreading across the world. One third of nosocomial infections can be prevented considers Center for Disease Control and Prevention (CDC) and estimated that 2 million people are infected annually in the United States of which is 20,000 deaths. The most common are urinary tract infections, wound infections at the site of surgery and a variety of pneumonia [9]. The isolated strains showed an extremely high degree of resistance to standard antibiotics, making infections and treatment was difficult. The group causes respiratory tract infections showed the greatest sensitivity to imipenem, while a group of agents of urinary tract infections sensitive to imipenem and meropenem. A study conducted in Italy of 2010 also showed that the most common bacteria isolated from tracheal aspirate Klebsiella pneumoniae, which is resistant to most antibiotics used to date, shows a sensitivity to imipenem and meropenem [10].

CONCLUSIONS

These results suggest that the most common bacteria isolated from tracheal aspirate sensitive to imipenem and resistant to penicillin preparations. While the bacteria from urine samples is also sensitive to imipenem and meropenem, and resistant to penicillins and quinolone preparations. The same was confirmed in bacteria isolated from blood cultures: sensitivity to imipenem, and resistance to penicillin preparations. Nosocomial infections are the cause of morbidity and mortality in the ICU. Result in increased costs and extend hospitalization. Sufferers often require additional research and treatment. Targeted antimicrobial therapy on the basis of the antibiogram is the only choice to reduce the incidence of nosocomial infections in addition to basic preventive measures. Successful strategies for the prevention of nosocomial infections must combine all measures to ensure the participation of all health workers.

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ACTA MEDICA SALINIANA

PROFESSIONAL PAPER

Treatment of Critically Ill Patients with Influenza A H1N1 in University Hospital Banja Luka

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Backround: The majority of confirmed cases of influenza A (H1N1) infection were admitted to the University Clinical centre Banja Luka, Bosnia and Herzegovina during time period from November 2009 until March 2010. Some of these patients experienced rapidly progressive lower respiratory tract disease resulting in respiratory failure, development of acute respiratory distress syndrome (ARDS), and prolonged stay at intensive care unit (ICU).

Aim: The aim of this study was to describe baseline characteristics, management and outcomes of critically ill patients with influenza A (H1N1) infection who were treated at ICU.

Methods: We performed a retrospective observational study which included 20 critically ill patients with influenza A (H1N1) infection admitted to ICU between 23rd November 2009 and 15th March 2010. The primary outcome measure was mortality. Secondary outcomes included the rate of 2009 influenza A (H1N1) - related critical illness and introduction of mechanical ventilation as well as intensive care unit (ICU) length of stay and hospital length of stay.

Results: We observed 16 (80%) male and 4 (20%) female patients. Mean age was 43.35 year, SAPS II was 49.8, Mechanical ventilation received14 (70%) patients and mortality was 5 (25%) patients.

Conclusion: Critical illness due to 2009/2010 influenza A (H1N1) infections at ICU, University Clinical centre of Banja Luka occurred rapidly after hospital admission, often in young adults, and was associated with severe hypoxemia, multisystem organ failure, a requirement for prolonged mechanical ventilation, and the frequent use of rescue therapies.

Keywords: *Influenza A H1N1, critical care*

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Competing interests
The authors declare no competing interests.

INTRODUCTION

The occurrence of influenza A (H1N1) at the beginning of 2009 awoke memories of the influenza pandemic which happened at the beginning of the 20th century (1918) when several million people died. The highest number of persons affected by H1N1 has been confirmed in the USA, Mexico, Canada, Chile and Australia. Mexico and Canada experienced the most serious explosions of this disease. The disease manifested itself by acute respiratory illness with signs of general weakness, fever, dry irritating cough, myalgia, joint pains and sometimes abdominal symptoms.

Some patients developed severe respiratory failure which required an extended mechanical ventilation as well as prolonged stay in Intensive Care Units (ICU).

The objective of our study is to analyze the principles of treatment as well as the outcome of treatment of critically ill patients (mortality rate, duration of mechanical ventilation and length of hospitalization) in the Intensive Care Unit of the Clinical Centre Banja Luka [1 -9].

MATERIAL AND METHODS

The study was designed as a retrospective study and it included all patients who were critically ill with Influenza A (H1N1) and who were treated in the Intensive Care Unit of the Clinical Centre Banja Luka in the period from 23 November 2009 to 15 March 2010. An analysis of the Complement Binding Reaction (CBR) was performed for all patients admitted to the ICU, which definitely confirmed diagnosis of influenza A (H1N1).

The following patients were defined as critically ill:

- *Patients who had severe clinical condition and who needed respiratory support –MV (ALI/ARDS)*
- *Patients with multiple bilateral infiltrates confirmed by CT*

The severity of the disease was assessed based on SAPS II score (Table 1). All data were statistically processed.

Table 1. Anthropometric characteristics and SAPS II score

Average age	43.35 years
Number of men	16 (80%)
Number of women	4 (20%)
Number of affected health professionals	1
Number of vaccinated (in the last two years)	0
SAPS II	49.8

RESULTS

20 critically ill patients were hospitalized between 23 November 2009 and 15 March 2010. The majority of patients with confirmed influenza were young adults with long period of MV and stay in the ICU. The average age was 43.45 years. 4 patients were women (20%) and 16 patients were men (80%). None of the cases got ill due to hospital infection. Among the ICU staff, an H1N1 infection was confirmed for one doctor. The average value of SAPS II score was 49.8. Comorbidity was present for 12 patients, representing 60%. The most frequent individual comorbidities were chronic pulmonary diseases (10%), obesity (25%), hypertension (10%) and smoking (15%). Three patients were extremely obese (10%). The most frequent symptoms accompanying this disease were fever, respiratory difficulties, abdominal problems with feeling of weakness and myalgia. Other accompanying symptoms were occurring as a part of complications due to bacterial superinfection with pneumonia, sepsis and septic shock. Out of 20 critically ill patients with H1N1, five have died. (Graph1). Of that number, 1 patient was a young obese woman, 4 were men. Only one health professional was affected whose disease was manifested by a mild clinical condition. The average time spent in the ICU was 6.68 days for the survivors and 10 days for the patients with fatal outcome. The average duration of MV was 7.5 days.

DISCUSSION AND CONCLUSION

The average time from the onset of symptoms until admission to the hospital was 4.65 days and from hospitalization until admission to the ICU was 1.2. days. These data correspond to findings of other authors who were monitoring similar patients affected by H1N1 influenza [1-11]. None of the patients was vaccinated against seasonal flu during the last two years. The majority of patients, 75% of them had radiographically verified bilateral pulmonary infiltrates, while 72.6% had acute respiratory distress syndrome (ARDS) from the onset of the disease. Of all admitted patients, 15 were placed on mechanical ventilation (MV) from the first day of admission to the ICU. Of that number, 14 patients had invasive and 4 had non-invasive support, while 2 patients had oxygen support.

On the first day, the average value of pO2/FiO2 ratio for patients who were on MV was 153mm Hg. The average FiO2 value was 73%, and average PEEP value was 10.8 cm H2O. The average PEEP daily value during MV was higher than 10. During the first two weeks of the disease, the TV value was about 6.5-7.5 ml/kg of ideal body weight. Barotraumas occurred in 3 patients (15%).

Vasopressors were included in the therapy for 3 patients, immediately upon their admission to the ICU. Mechanical ventilation was initiated by IPPV mode with Vt adjusted to PIP (lower than 30 cm H2o) FiO2 -1 (with progressive decrease below 0.6) high values of PEEP. When the clinical condition allowed, patients were shifted to one of the supporting modes BIPAP CPAP) [12–14]. All of them were analgosedated and if needed relaxed. All patients were taken off MV through NIV, which enabled an easier shift to spontaneous breathing. A drug therapy included neuraminidase inhibitors for seven days (Tamiflu 2x150 mg), antibiotics in the form of de-escalated antibiotic therapy for septic patients upon admission, corticosteroids were used for all patients, mostly Methylprednisolone in small doses. Infusion therapy was strictly applied and constantly adjusted to losses – administered by infusion pumps (ml/kg/h). Nutritive support was introduced on the second day by enteral preparations (Nutridrink, Kabiven) with 25-30 kal/ kg of body weight [1–14].

In the biochemical findings, the following stand out: an increase in creatine kinase with an average value of 1619 U/L until the third day. At admission, white blood cell count was normal, and it maintained that level during the first week upon admission to the ICU (except in patients with complications). Secondary bacterial pneumonia was registered in 5 patients.

The main cause of fatal outcome was acute respiratory distress syndrome (ARDS) with severe hypoxemia and complications such as secondary infections, sepsis and MODS [12–14]. Our experience is that by careful monitoring and selection of ventilation modes in accordance with the respiratory parameters, with extremely restrictive fluid therapy and permanent supervising of infection parameters, as well as performing a microbiological testing, it is possible to improve the outcome of treatment and especially reduce mortality in patients with influenza A (H1N1).

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Parameters of mechanical ventilation (X)	
Average time of mechanical ventilation	6.68 days
VT (respiratory volume)	6.5 – 7.5 ml / kg / pred.body weight
FiO_2	73%
PEEP	10,8 cmH_2O
Total number of patients on MV	14

Table 2. Parameters of mechanical ventilation in patients critically ill with influenza A (H1N1)

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ACTA MEDICA SALINIANA

PROFESSIONAL PAPER

Use of Caudal Anesthesia in the Pediatric Population in the Cantonal Hospital Dr. Irfan Ljubijankić in Bihać

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Background: Caudal block is today the world's most commonly performed regional technique in the child population. It was made in 1933 for the first time, in the last 30 years it survived its repopularization due to the changes in the approach to the „surgical" pain at children.

Aim: The aim of the paper is to show the experience achieved during the performance of the block in our institution.

Patients and Methods: Twenty patients at the age from four months to eight years underwent a surgery procedure such as hernioplasty, orchidopexia, circumcision and uretheral reconstruction in the hypospadias. After the induction of the general anesthesia, the patients are applied 0,25% levobupivacain in the dose determined by the Armitage scheme. The time is measured after which it was postoperatively necessary to ordinate the analgetic, and the possible residual motor block was followed which was expressed in the Bromage scale.

Results: The average time needed for the patients to be „pain-free" was 370 ± 40 min, and the possible use of the analgesics postoperatively was significantly delayed. Residual motor block, 30 minutes after the surgery at only 2 patients, was 1 by Bromage (impossibility of the extension of the lower extremity at the level of the hips). Cases of the urinary retention were not reported.

Conclusion: Caudal block is a method which provides an excellent, affordable and safe analgesia at children.

Keywords: *caudal block, levobupivacain, pediatric anesthesia*

INTRODUCTION

Caudal anesthesia or a caudal block is today world's most often performed regional technique in the child population [1]. By children, in general it is performed as a supplement in a combination with the general anesthesia, by which the consumption of volatile anesthetic and analgetics is reduced, and long lasting postoperative analgesia is provided. It was reported for the first time on its application on children in 1933, in the past 30 years it achieves its repopularisation due to the changes in the way of thinking and approach according to the „surgical" pain at children. Today a caudal block is being performed everyday about 96% of pediatric anesthesiologists in the United Kingdom [2].

Paper objective is to present the technique of performance, choice and dosage of the anesthetics by certain procedures, and the experiences gained during the performance of the block in the CH Bihać on the sample of twenty patients.

PATIENTS AND METHODS

Twenty patients (M/F- 18/2) are at age four months to eight years underwent to the elective operation such as hernia, orchidopexy, circumcisions and urethral reconstruction. The patient was given premedication, atropine 0.015 mg/kg intravenously. And after that in general anesthesia are introduced thiopental 5mg/kg, relaxed with leptosuccin 1mg/kg and pancuronium 0.07 mg/kg. After that anesthesia was continued sevoflurane with fentanyl 2 mcg/kg. At the youngest four months old patient induction to anesthesia was performed by inhalation with escalating concentration of sevoflurane. Patients are routinely monitored during anesthesia for noninvasive blood pressure, heart rate, oxygen saturation of hemoglobin and the main respiratory monitoring.

After intubation, patients were turned on the right side, and the identification and marking sacralia cornua was carried out as well as hiatus sacralis-which gave the basic orientation of the placement of the cannula. As an additional landmark determination of the position of spina iliaca superior

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The authors declare no competing interests.

posterior was used, which with hiatus form equilateral triangle. Then a test dose of anesthetic levobupivacaina 0.25% with adrenaline in the concentration 5mcg/ml in total dose of 0.1 ml/kg was given to exclude the possibility of intravascular application of anesthetic. After that the rest of the anesthetic was given in a quantity that is determined by Armitage's scheme (levobupivacaine 0.5 to 1.25 ml/kg). After awakening from anesthesia in children younger than five years the modified Children`s Hospital of Eastern Ontario Pain Scale(CHEOPS) was monitored, and older children from five years simply asked whether they feel pain and at any point. Possible residual motor block expressed in Bromage's scale was also monitored as well as the possible side effects, particularly urinary retention

RESULTS

The most important patient characteristics and types of surgery are given in Table 1. The table shows that male children dominated, mostly completely healthy. Only one child had acyanogenic congenital heart anomaly without hemodynamic consequences. Considering the surgery, most procedures demanded sensory block which was spread to the lower thoracic segments. In this group of patients 0.25% levobupivacain was given in the amount of 1.0 ml / kg body weight. If orchidopexy is required, necessary block is approximated at the level of middle thoracic segments such as T7; dose by the Armitage's scheme was increased to 1.25 ml / kg. In the case of hypospadias, because of innervation on sacral segments of spinal cord dose decreased to 0,5 ml/kg tt. It should be noted that there are multiple dosing scheme (Loyd-Thomas, Busoni, Shulte-Stainberg) taking into account various anthropometric parameters and that doses being calculated on the basis of these are sometimes very different.

In the second table we see the average duration of analgesia after surgery, which lasted approximately 30-90 minutes. Children older than five generally gave reliable data on the occurrence of pain, where the parents represent a significant help. With younger children was continued with other aspects of analgesia when Ontario pain scale reached a value of 4/12 and more. In two patients had been seen weak motor block, virtually none of whom did not last longer than two hours. There were no other side effects. Under excessive hypotension was considered drop in middle arterial pressure of more than 30% compared to preoperative values.

DISCUSSION

Generally, all children, including premature babies have the necessary level of development of the nervous system to be able to feel and express pain in a a way appropriate to their age. In fact there are number of neurobiological evidence to suggest significant functional differences compared to adult system of nociceptive transmission and modulation in which the perception of painful stimulants in children is even more pronounced with a low possibility of neuromodulation [3].

Table 1. Patients characteristic and types of operation

Number of patients	20
Gender (M/F)	18/2
ASA Status (I/II)	19/1
Age (year)	4,1 (± 3,9)
Type of surgery:	
Hernia surgery	7
Hernia surgery + circumcision	4
Orchidopexy	7
Reconstruction of hypospadias	2

From these results it is evident that patients in average had analgesia, which lasted about six hours postoperatively. The results of other authors are various, they depend on the concentration of anesthetics (bupivacaine,levobupivacaine), and the types of surgery [4]. The duration of analgesia with other authors are generally ranging from three to twelve hours, and the cases that patients after caudal block for minor surgical procedures did not receive any analgesia postoperatively are described. The values obtained in this paper would, from this point, belonged to "the golden middle". During follow-up of patients a shorter duration of analgesia was not observed in patients in whom surgery required a higher level block, which is mentioned in literature [5,6]. The reason may be that patients in the case of a higher sensory block received significantly higher doses of anesthetic, according to Armitage's dosing scheme. Motor block was present in two patients, per-Bromage scale at the lowest possible level (1/3). The existence of severe motor block may be disturbing to a child, and some authors recommend the use of lower concentration of local anesthetic, eg 0.125% bupivacaine [7]. Such concentrations of anesthetic results in lower frequency and intensity of motor block, and possibly, a longer latency period to development of sensory blockade and a shorter duration of surgery.

From the aspect of monitoring side effects during the duration of caudal anesthesia, and particularly excessive hypotension, urinary retention and pruritus were observed. Urinary retention and pruritus are frequently seen in situations in which the caudal block combine a mixture of local anesthetics and opioids, and hypotension is combined with anesthesia with clonidine, all in order to extend postoperative analgesia and decrease the concentration of applied anesthetic [8].

Table 2. Block characteristics and frequencies of adverse effect
**two patients were catheterized prior to surgery*

Duration of analgesia (min)	370± 40
Residual motor block (Bromage scale) 0/1	18/2
Duration of residual motor block (min)	90 ± 20
Urinary retention	0*
Pruritus	0
Hypotension	0

CONCLUSION

Caudal anesthesia 0,25% levobupivacain in pediatric population gives excellent multihour analgesia, with small frequency of motor block and rare appearance of other adverse effect.

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PROFESSIONAL PAPER

The Vibration Response Imaging: Application in Intensive Medicine

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Introduction: Radiological methods provide insight into the anatomy of the airways but with certain restrictions. The development of an electronic stethoscope, conversion of analog audio signals into digital ones as well as images are the foundation of "the device for vibration response imaging (VRI - Vibration Response Imaging). Aim of the research: To review the application of the VRI in intensive care units (ICU) and the localization of pathological processes that alter the function of breathing.

Methods: Retrospective analysis (VRI, X-rays), during a quarterly period of 2009, interdisciplinary ICU. We analyzed the application in: 1. surgical and non-surgical patients "without lung pathology" 2. Pleural pathology, 3. Parenchyma and bronchi pathology, 4. Quality of lung ventilation, compared to existing methods.

Results: The analysis of 44 patients whom the VRI device was applied to: 1. "Without pulmonary pathology (surgical: 7, non-surgical 6); 2 pleural space (pneumothorax 5, hemato-liquidothorax 6, other 4), 3. lungs (inflammation, atelectasis: 11, pulmonary embolism 5). By applying the "VRI", ventilation problems were noticed earlier than they would appear using the X-ray, especially after the surgery and in patients with a longer ICU stay.

Discussion and conclusion: In relation to the X-ray, VRI provides simple, continuous and noninvasive monitoring of lung ventilation at patients´ bedside. It is a good continuous overview of ventilation of different parts of the lungs: the presence of air and fluid in the intrapleural space, the development of atelectasis and inflammatory lung pathology. The method is to complement the existing methods.

Keywords: *Chest X-ray, Lung ventilation, Breath sounds, Vibration Response Imaging.*

INTRODUCTION

Radiological methods provide insight into the anatomy of the airways with certain limitations (radiation, transport, and price). The development of an electronic stethoscope and the conversion of audio signals into the picture are the basis of "device for imaging of vibration signals (VRI-" Vibration Response Imaging) ". This new diagnostic method for the qualitative representation of lungs shows lung dynamic images, and quantitative image shows the distribution of vibration energy in the lungs. Due to these properties, with the possibility of freezing the image at the certain time, recording data and subsequent analysis of multiple images, this method is becoming more and more popular in clinical medicine, [1]. (ICU) and the localization of pathological processes that alter the function of breathing.

METHOD

The retrospective analysis of data (VRI, X-rays) during a three-month period of 2009. in the interdisciplinary intensive care unit of the General Hospital Karlovac, Croatia. We analyzed the application of the VRI in: 1. non-surgical and surgical patients "without lung pathology". 2. Pleural pathology, 3. Pathology of the lung parenchyma and bronchus, 4. Quality assessment of lung ventilation, compared to the existing methods, 5. Patients with the chest pathology: serial rib fracture with no signs of pneumothorax.

Description of the 'VRI devices" and the recording procedures The recording sessions were done in a sitting and supine position. Respondent was deep breathing with frequency of 15-20 per minute. The device filters out vibration signals - corresponding to the frequency of breathing - showing a dynamic picture of the lungs and creating a film that consists of a series of frames. High intensity vibration energy gives a black color and low ones are shown in bright gray. The screen

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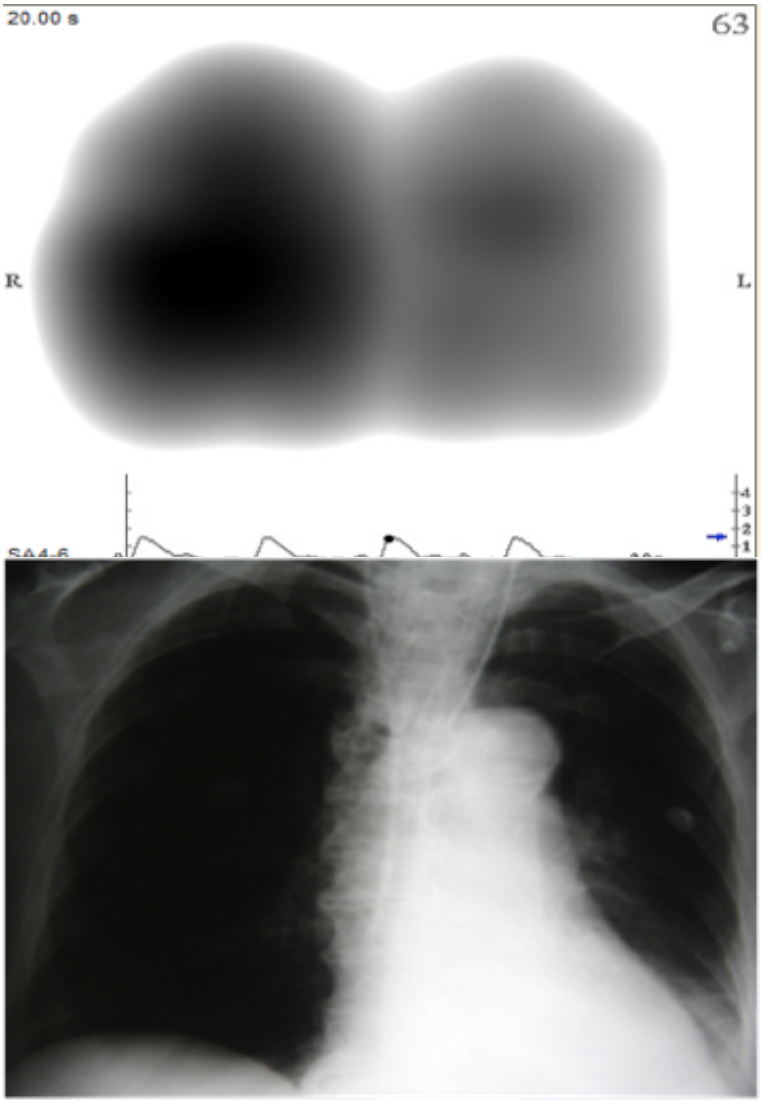

Figure 1a and 1b. Comparation of findings in VRI and lung x-ray - atalectasis

displays the quantitative data distribution of vibration in the lungs as well. Each of the lungs (right 50% and 50% left) are divided into three areas (upper, middle, lower). The intensity of vibration signals is determined for each field. Due to the intrathoracic pathology, the look of the VRI shots are changed. The resulting artifacts are noticed in the recording, and recording and the data are excluded from the analysis.

RESULTS

A total of 44 patients in whom the VRI device was applied were analyzed. Patients were divided into the following groups:

1. *"without pulmonary pathology (surgical patients) - 7 patients, non-surgical patients - 6 patients;*
2. *Patients with pleural space pathology: pneumothorax - 5 patients, hemato-liquido thorax - 7 patients, fibrothorax - 2 patients;*
3. *patients with lung pathology: inflammation, atelectasis - 10 patients, pulmonary embolism - 5 patients, bronchospasm - 1 patient.*
4. *patients with chest conditions: serial rib fracture with no signs of pneumothorax - 1 patient.*

The usage of 'VRI' showed earlier ventilation disturbances then when using X-rays. These observations were more pronounced after the operation, where the VRI enabled us to notice the cause of postoperative respiratory failure and pneumothorax sooner than we would have by using the X-ray images.

CASE DISPLAY

Pathology of the lung - an example of patients with pulmonary atelectasis. By using the 'VRI device' in these patients, we followed the dynamics of lung atelectasis after the bronchial intervention. The first image (Figure 1a) shows the left lung hypoventilation, especially the left upper lung field with respect to the right, 4% to 14%. Lung X-ray images show the shadowing the left lung base with a small sinistral effusion (Fig. 1b).

The figure 2 shows improved ventilation of the left lung. The ventilation of the right and left lung has been eguilised.

Pathology of pleural space: the case of patients with right sided liquidothorax . The "VRI images" show the hypoventilation of a right lung, which correlates with the auscultatory findings and chest X-ray. The hypoventilated right lung basis of 33% compared to the left of 67% (Fig. 3a). The hypoventilated right lung base to the left lung base is 11% to 32%. Note the correlation with X-ray images of the lungs in which it is clearly visible a right sided liquidothorax, which encompasses most of the right hemithorax (Figure 3b)

The following example shows a patient with right sided pneumothorax and subcutaneous emphysema with the acute respiratory failure and COPD (Figure 4a). X-ray image shows a right sided pneumothorax (up to a height of 6. rib: Figure 4b).

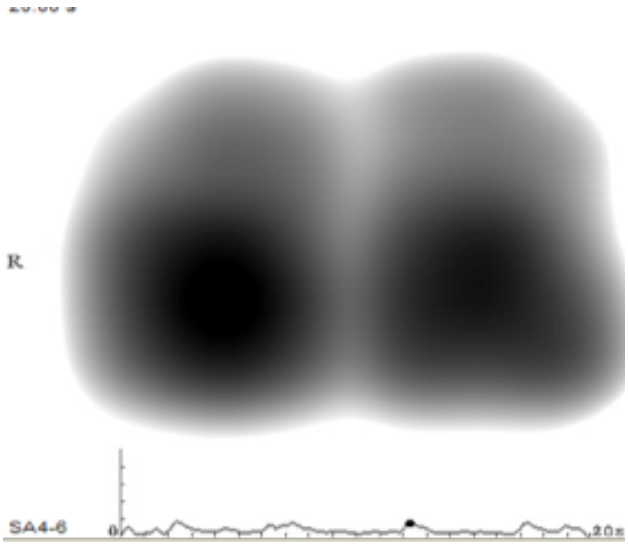

Figure 2. Improvement of ventilation of the left lung - patient from figure 1a and 1b

DISCUSSION AND CONCLUSION

Lung auscultation is a fundamental method of lung tests which involves the chest and listening to the sounds generated inside the body. Today, the indirect method using headphones on a particular scheme is applied. Since the number of pulmonology patients is increasing, this "old" method is regaining importance nowadays. GE Healthcare and Deep Breeze Ltd.. presented a new, non-invasive monitor of lung sounds called Vibration Response Imaging (VRI ICU). We named this method the "vibration imaging signal". The device itself, as shown, provides information on the movement of air in the airways of patients regardless of whether spontaneously breathing or connected to a respirator. The intensity of the vibrations is affected by the properties of the airways (lumen shape, obstruction, discharge) and the properties of lung parenchyma. Each record includes several respiratory cycles, which enables the clinician assessment of lung function in order to improve the treatment methods.

The areas of application of the VRI include different pulmonary pathologies and other functional changes in the lungs. VRI allows simultaneous comparison of vibration curve with the curve of pressure and flow. This helps in assessing the quality of recording as well because the curve of vibration simultaneously changes together with the other two curves. The „VRI recordings" are different in mechanically ventilated patients with different pathologies. Thus, "VRI image" may offer clinicians important information about patients with COPD, [2].

It is the evaluation, which combines qualitative and quantitative changes of lung sounds that shows the difference between individual pathology and thus represents a sensitive method. This way it is possible to see the qualitative and quantitative differences between patients with COPD or asthma. The sensitivity and specificity of 'VRI images" is especially noticeable in large airway obstruction of 97% or 88%, [3].

VRI can safely be applied in the diagnosis of pneumothorax, because the reduction of vibration responses correlates with radiographic findings (sensitivity 100%, specificity 87%). It also showed to be an useful method in the diagnosis of pleural effusions because of high correlation with the X-ray images. In other states, such as the ventilation of one lung, VRI device can be of great benefit, bearing in mind the limitations of applying "classical X-ray apparatus.

In the intensive care units, and during the treatment of patients using respirators, the VRI can be of great benefit simply by providing the insight into the ventilation of both lungs. It is possible, and very easy to determine the "best PEEP": "search VRI snapshot " of where the lungs ventilation is the best. It is possible, moreover, to seek the best mode of breathing, or to apply the device during the period of the separation from the respirator (weaning). One can easily monitor the efficiency of bronchodilators in the treatment of bronchospasm or the application of bronchoscopy for airway obstruction and airway toilette. "VRI" is used in monitoring the development of ARDS and in patients with various unilateral lung pathology, intrapleural space, and in patients with heart failure who are on diuretic therapy. Further research is necessary to monitor lung function in conditions of high intra-abdominal pressure and other pathologies that are "distant" from the chest.

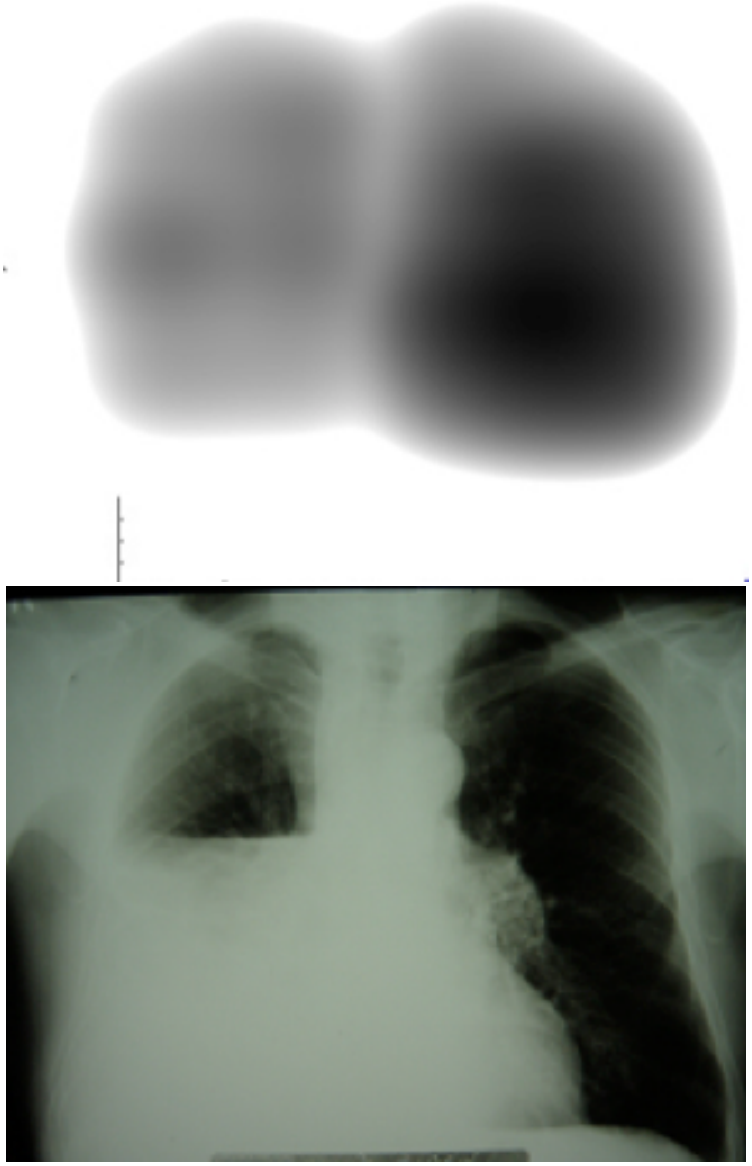

Figure 3a and 3b. Comparation of findings in VRI and lung x-ray - liquidothorax

The application of this method is being tested in perioperative medicine, postoperative monitoring of respiratory function in pulmonology patients and patients with compromised respiratory function due to the extensive operations in the upper abdomen area.

CONCLUSION

Further studies are needed in order to determine the reliability of repeated imaging, sensitivity and specificity in detecting various lung pathologies. In relation to the "classical" X-rays "the VRI method' enables easy, continuous and noninvasive monitoring of lung ventilation at the bedside of patients - in the clinic, the ward

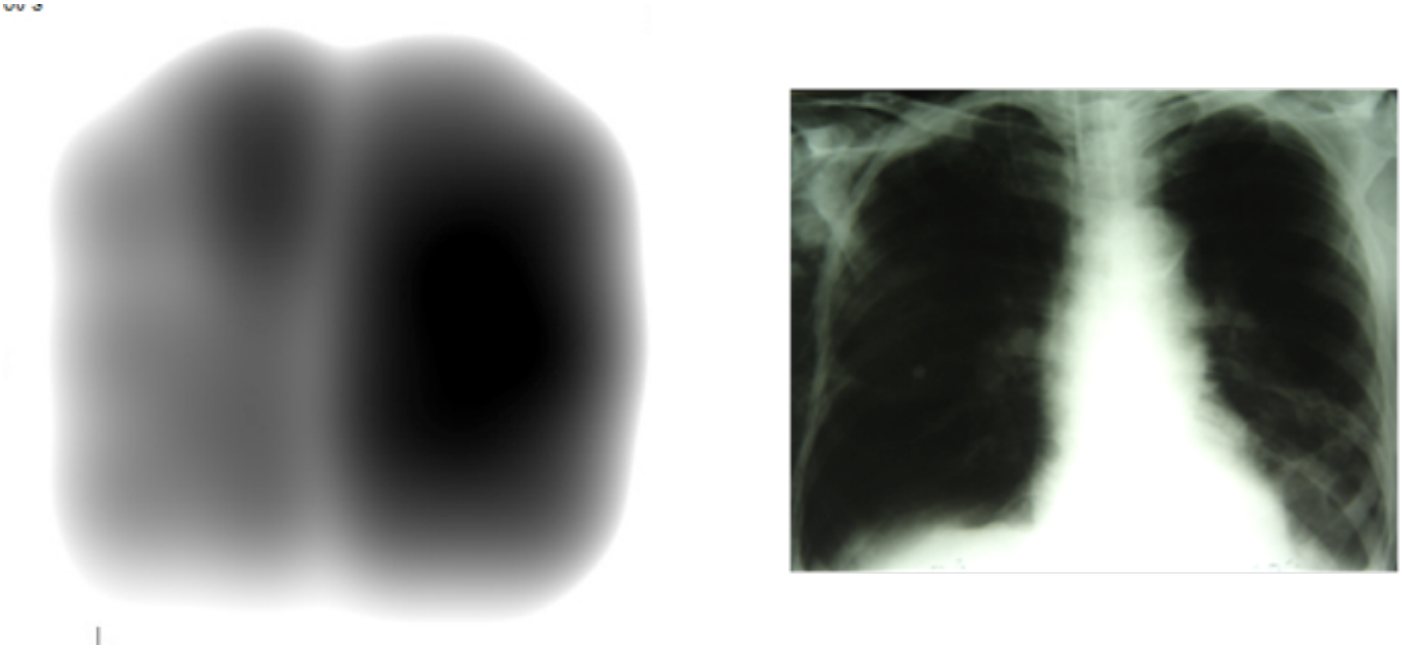

Figure 4a and 4b. Comparation of findings in VRI and lung x-ray - right sided pneumothorax

or intensive care units. At this point, it is necessary to apply this method alongside the other, following the indications, existing imaging methods (X-ray, ultrasound, CT, MRI). Consequently, "VRI device" provides a new perspective of the development of diagnostics, continuous monitoring of the effectiveness of drugs or other therapeutic procedures over a certain time.

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ACTA MEDICA SALINIANA

CASE REPORT

Anesthesiological Complications in Patients with Ankylosing Spondylitis and Crohn's Disease

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Background: Ankylosing spondylitis (AS) is the most common extraintestinal manifestations of Crohn's disease (Morbus Crohn), with a prevalence of between 7% and 25%.

Case report: We describe a case of patient, with immediate preoperative appearance of clot in the placement of peripheral venous cannula which is why it was impossible to establish peripheral venous times, and the impossibility of establishing central venous route via jugular veins and subclavian veins, for men 43 years, with diagnoses of AS, Crohn's disease and cataract. We want to attract attention to possible anesthetic complications in these patients. Last year because of AS, left hip operated on under general anesthesia. During surgery in the perioperative period was not complications. This year was admitted to hospital for surgery right hip. Preoperative examinations showed: limited neck mobility, minimal extension of the head, the mobility of the temporomandibular joint preserved, Mallampati second stage, American Society of Anaesthesiologist Classification (ASA) II/III,cardiopulmonar stable, low-molecular weight heparin administered prophylactically.

Conclusion: Anesthesiologist should pay particular attention in patients with Ankylosing spondylitis in terms of four main aspects; securing the airway, functional disorders of the heart and lungs and neuroaxial access. Thromboembolic disease is a significant cause morbidity and mortality in patients with inflammatory bowel disease that can be monitored states of hypercoagulation.

Keywords: *anesthesiological complications; Ankylosing spondylitis (Morbus Bechterew);Crohn's disease (Morbus Crohn); hypercoagulation*

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Competing interests
The authors declare no competing interests.

INTRODUCTION

Ankylosing spondylitis (AS, Bechterew Morbus), a progressive inflammatory disease that primarily includes the axial skeleton of the patients, sacroiliac joints and extraarticular structures which include eyes, gastrointestinal, cardiovascular and respiratory system, neurological and skin lesions. The first symptoms appear in late adolescence or early adulthood, while after the beginning of 40th was uncommon. Although genetic predisposition is known, the exact cause of the disease remains unknown. The disease is more common in males (5:1) and is correlated with inherited major histocompatibility antigen HLA-B27. Research suggests a possible interaction of histocompatibility antigen HLA-B27 with exogenous factors (bacterial or viral infection) as a possible cause of the disease. The whites in North America overall prevalence of HLA-B27 antigen was 7% and 90% of patients with AS have inherited this antigen. The presence of HLA-B27 antigen was not related to severity of disease, but is a strong component of the multigenic significant in all populations (1,2,3). Evidence links across the HLA-B 27 antigens with other seronegative arthropathies such as reactive and psoriatic arthritis, isolated acute anterior uveitis and inflammatory bowel disease (Inflammatory Bowel Disease, IBD). IBD can be divided into ulcerative colitis and Crohn's disease (Morbus Crohn). Scientists and clinicians have noted that Crohn's disease is often present in patients with AS (4). Proved the presence of HLA-B27 antigen in patients with Crohn's disease suggests a possible genetic link. AS is the most common extraintestinal manifestations of Crohn's disease with a prevalence of between 7% and 25%, and may precede bowel disease for several years (4).

Present a patient diagnosed with AS, Crohn's disease and cataract points to possible anesthetic complications in these patients.

CASE PRESENTATION

A patient man, 43 years, a diagnostics AS, Crohn's disease and cataracts. It is treated by AS, Mb. Crohn 19 years, 2009 and treated in cured of pulmonary TB (per anamnesis). Last year because of AS, underwent surgery left hip operated on under general anesthesia (arthroplastica coxae cum PTC). During surgery and in perioperative period

was not complications. Current therapy of 5-aminosalicil acid (5-ASA), diclofenac, ranitidine. In July 2010th was admitted to hospital for surgery right hip.

Preoperative examination: limited neck mobility, minimal extension of the head, the mobility of the temporomandibular joint preserved, Mallampati second stage, American Society of Anesthesiologists Classification (ASA) II/III, cardiopulmonary stable, low-molecular weight heparin is administered for prophylactic anticoagulation. Laboratory findings: Er: 3.8 x 1012/L, Hb 94 g/L, WBC 20.8 x109/L, SE 65/94mm/h; Platelets: 636x109/L, fibrinogen: 8.4 μmol/L, Protein C: 14, Ferritin: 12.6 μg / L, Folat: 5.9 nmol/L, Vit.B12: 891pmol/L, other laboratory findings were within normal values. Due to present a significant deformity of the spinal column, estimated by the inability to perform subarachnoid and epidural anesthesia, and the intervention is performed under general endotracheal anesthesia. When you try placing the venous cannula in both hands is always coming up to the creation of blood clot, making it impossible to establish peripheral venous access. Due to minimal mobility of the cervical spine and chest wall deformities, it was not possible placement of central venous catheter in internal jugular vein or in subclavia vein. Left femoral vein catheterization was successful after surgical preparation of the same. The presence of a venous catheter 14 Ch in diameter which was used intraoperatively and postoperatively as the only venous access for volume restoration and blood products. Controlled laboratory values two hours after surgery were as follows: Er: 3.74 x1012/L, Hb: 100 g/L, PLT: 693 x109/L, while the other is that they talked about hypercoagulable state are monitored. Applied therapy for prevention of deep vein thrombosis. The patient had no complications from the placed venous catheter was used postoperatively for parenteral therapy and at discharge, when it was taken. In good general condition, the patient was discharged on the twelfth house.

DISCUSSION

The specificity of AS disease in anesthetic practice is reflected in difficult intubation due to limited or completely immobile and limited atlantoaxial joint mobility of the temporomandibular joint, which in 40% of patients can progress to complete ankylosis (5). Subarachnoid or epidural block is usually impossible, but difficult access due to a specific disease, success is possible with paramedial access (6). In patients with Ankylosing spondylitis is an increased risk of the spinal and epidural hematoma which is why the monitoring of these patients in early (24 hours) and late (week) postoperative period (7). There are difficulties in the placement of central venous lines in the internal jugular vein and subclavia vein.

One of the factors of postoperative pulmonary complications was reduced and completely limited by respiratory motion of the chest due to which patients have a pronounced abdominal breathing, especially in cases of fibrous alveolitis, which may occur in only 5% of patients. Lung function tests may show reduce vital capacity of lungs and increase in functional residual capacity. Gas flow is normal, a ventilation function is well preserved. These patients may have developed aortic regurgitation or bundle branch block (1.2).

Patients with inflammatory bowel disease have a three fold higher risk of thromboembolism complications, which affect venous and arterial system (8). The presence of complications in the form throboembolism first described by Bargen and Barker back in 1936th year (9). There is an assumption that several risk factors affect the development of thrombosis in IBD: a) I have inflammation per se is associated with reactive thrombocytosis especially during hospitalization, surgery, immobility, oral corticosteroids, placed cannula and venous catheter, b) hiperhromocitemija, c) vitamin deficiency d) smoking, e) the use of oral contraceptives (10). According to data available in literature, the prevalence of thromboembolism in patients with IBD for deep vein thrombosis was 2.8%, and pulmonary embolism 3.6% (11). A major factor in reducing the risk of thrombosis in patients with IBD is to control of inflammatory process. In the presented patient diagnosed with Crohn's disease and benefits of chronic therapy, and medications used to treat Crohn's disease can be directly inhibit platelet activation, such as 5-aminosalicil acid (5-ASA) containing mesalazine, osalazine (12), azathioprine and its metabolite, 6-merkaptopurine (13) and infliximab (14). The preoperative use of heparin in these patients is contraindicated (15). The patient received a presentation from the low-molecular weight heparin according to the protocol for the prevention of deep vein thrombosis. Hemostatic changes are common in patients with IBD, the precise reasons for the development of thromboembolism is not known to date. In the case presented was diagnosed with a rare set of clinical circumstances in which would be difficult to predict complications in the form hypercoagulable state. It is important to know that in half of patients with IBD in whom developed thromboembolic disease is not reported risk factors (16).

CONCLUSION

AnesThesiologist should pay particular attention in patients with Ankylosing spondylitis in terms of four main aspects; securing the airway, functional disorders of the heart and lungs and access to neuraxis, and prevented unpleasant surprises and unexpected intraoperative and postoperative complications.

Thromboembolic disease is a significant cause morbidity and mortality in patients with inflammatory bowel disease that can be monitored hypercoagulable state, and must pay special attention to preoperative preparation.

Given the lack of other findings, it can be assumed that Crohn's disease a possible causal factor that led to the formation of blood clot and that the phenomena hypercoagulable condition in this patient, which had resulted in difficult vascular access.

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ACTA MEDICA SALINIANA

CASE REPORT

Tetanus in an Unvaccinated Boy: a Case Report

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Background: Tetanus is an acute infectious disease caused by the bacterium Clostridium tetani, whose vegetative spores under anaerobic conditions produce a neurotoxin tetanospazmin. As a consequence of his actions appear muscular hyperactivity, and on the the slightest stimulation, and failure of reflex inhibition. That results in generalized contractions that are called tetanic cramps. There is a harmless enough injury that could open the way for very serious and sometimes life-threatening infection. The aim of this case report is to emphasize the importance of immunization against communicable diseases, especially tetanus.

Case report: We report a case of fourteen year old boy who was hospitalized due to braking of the facial muscles, inability to open the lower jaw, spasms of the whole body, and feelings of suffocation. Heteroanamnestic were obtained data about stab on a peg in the area of his right foot a week ago, and the fact that the boy has never been vaccinated, the wound was not treated, nor was performed with antibiotic prophylaxis. The swab of his foot was taken and sent for microbiological analysis (arrived findings demonstrate the presence of Clostridium tetani). Patient was intensively treated for tetanus, which resulted in complete recovery and removal the patient from the Clinic of Anesthesiology and Reanimatiology (Intensive Care Unit) to the Clinic for Infectious Diseases.

Conclusion: Vaccination against tetanus and its regular update is the only way to prevent this dangerous nfection.

Keywords: *tetanus, Clostridium tetani, infection, braking, spasms*

INTRODUCTION

Tetanus is an acute infectious (anaerobic) infections caused by Clostridium tetani. It is characterized by intermittent tonic spasms of voluntary muscles. Clostridium tetani is a Gram positive anaerobic bacillus that frees mobile neurotoxin called tetanospasmin. It acts on the CNS by inhibiting the release of acetylcholine. However, its most important activity is inhibition of the postsynaptic spinal neurons, preventing the release of inhibitory mediators. As a consequence, appear generalized muscle spasms, hyperreflection, spasms (1).

Tetanus causes about fifty thousand deaths around the world annually. Children, older patients, those with surgical wounds, intravenous drug users more often are ill from tetanus. Infection can occur in utero (pelvic tetanus), and in the umbilical cord of the newborn (neonatal tetanus). Curing the disease leaves no immunity (1). This case should remind us that tetanus is a disease that persists in our areas and with regular vaccinations can be completely preventable.

CASE REPORT

Fourteen-year-old boy was admitted to the Infectious Diseases Clinic, University Clinical Centre Tuzla because braking of the facial muscles, inability to open the lower jaw, full-body convulsions, choking feeling. On admission, patient was spontaneously breathing, conscious, and difficult to answer the asked questions, with visible contractions whole musculature body. Hemodynamic parameters were normal - TA 110/58mmHg, HR 80/min, SpO2 94%. Eyeballs were centered, without nystagmus or diplopia. Pupils were spheral, equal with normal reaction to light. Neck was rigid, motor reflexes lively, balanced. Babinski negative. Controlled laboratory findings did not indicate the signs of infection (Le 9.7 Er 4.81 0.43 Hct Schook TP 5.7 74.2 CRP 0.5 pH 7.43). Heteroanamnestic were obtained data about stab on a peg in the area of his right foot a week ago, and the fact that the boy has never been vaccinated, the wound was not treated, nor was carried out antibiotic prophylaxis. There were consulted orthopedic surgeon for treatment to a wound on foot, a neurologist - indicates a CT scan (benign intracranial hypertension), ophthal-

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mologist (finding at the papilla n. optici was regular).

Appropriate antibiotics were included: the Penicillin G 2 x 6 mil, metronidazol a 400 mg x 4, Tetabulin a 4500 IU im, manitol 50 ml x 3, Diazepam 0.2 mg / kg BW. The following day due to intensifying tonic cramps and difficulty breathing patient is moved to the Intensive Care Unit Department of Anesthesiology and Reanimation. He was placed in a darkened room, continuously monitor the vital parameters. The therapeutic procedure is carried out commenced antibiotic therapy, preservation of electrolyte and metabolic balance, take a smear on his foot and sent for microbiological analysis (arrived findings demonstrate the presence of Clostridium tetani).

On the same day in the evening, the patient becomes tachidispnoic, respiratory insufficient, and that is why he was put on a respirator - a program of controlled mechanical ventilation. The next 21 days patient was connected to a respirator, on continuous sedation with Apaurin, he had occasional tachycardia and hypertensia. Pediatrician cardiologist was consulted and he included appropriate therapy. The biochemical parameters were regularly analyzed and corrected, the material was taken for microbiological analysis, and antibiotic therapy was modified according to the obtained findings. After stabilization of hemodynamic condition of the patient, we started with the gradual awakening and separation from the respirator changing the types of ventilation according to patient's respiratory abilities. Doses of drugs were reduced, metronidazol was excluded from therapy after 14 days, and dose of Apaurin was reduced.

Then the patient was breathing spontaneously, he was aware, hemodynamically stable, with occasional twitching of muscles that do not require therapeutic measures. In consultation with the specialist for infectious disease, patient transferred to the Department of Infectious Diseases for further treatment.

DISCUSSION

Tetanus is an acute infectious, noncontiguous disease caused by Clostridium tetani. The preparations of culture are seen as a long thin stick with a round terminal dispute. Natural source of infection is the gastrointestinal tract of domestic animals and with fecal mass get out in the ground and transform into spores. Human being is usually infected during injury, although infection can occur via nonsteril material in the course of criminal abortion or childbirth. Incubation lasts from two days to several months (1,). The first symptoms are muscle cramps. The earliest simptom is muscle chewing stiffness, the patient hardly opens his mouth (trismus), and speech and swallowing are difficult. Stiff facial muscles produce a characteristic appearance (permanent smile, forehead folded, nostrils dilated, narrow eye wrinkles - risus sardonicus). Involvement of respiratory muscles leads to respiratory failure. The light and noise further provoke the occurrence of convulsions (1, 2). Diagnosis of tetanus is made on the basis of history, clinical signs and microbiological confirmation of Clostridium tetani. In our patient, all these parameters were positive.

Therapy of tetanus is complex: airway management, surgical debridement of the wound, early and adequate use of human immune serum globulin, antibiotics, sedation, maintenance of fluid and electrolyte balance, prevention of super infection and continuous nursing. Patients with tetanus should be treated in the Intensive Care Unit, which significantly reduces mortality.

The patient must be placed in a darkened, quiet room, and problems with respiratory failure should be eliminated by the mechanical ventilation. Antiserum is applied at a dose of 1500-10000 IU. Spasms are declined with benzodiazepines: Apaurin 5-10 mg every 2-4 h or continuous infusion. Antibiotics that are given as Metronidazole 30 mg / kg / day in 4 doses, penicillin G 2 mil every 4-6h. Prognosis is worse if there is a shorter duration of incubation, and if the progression of symptoms is faster. Tetanus has a better prognosis if it is diagnosed early and appropriate medical and supportive care is begun. Overall mortality is 50 % (3).

About 50% of tetanus deaths are associated with respiratory complications arising as a result of muscular stiffness and involuntary muscle spasm that characterize this disease, or as a result of hypoxia due to atelectasis or pneumonia. To secure the airway and ventilation there is performed intubation and implemented mechanical ventilation, and patients is sedated and, if necessary, relaxed. To remove tetanic cramps benzodiazepines are used, and beta blockers to reduce sympathetic tone. If benzodiazepines cannot eliminate spasms and rigidity, apply nondepolarised muscle relaxants (4.5).

Prophylaxis: vaccination against tetanus and its regular update every 5-10 years is the only way to prevent this potentially dangerous infection. Active immunization is compulsory for all children up to 6 years of life. Tetanus infections cases occur in certain so-called risk groups (farmers, ranchers, gardeners, mechanics), and they are the consequences of inadequate or conducted active immunization or not renewed immunization (Buster-dose) against tetanus. The increased risk of disease, at the present time, has persons who enjoy the heroin (6).

If the last renewal of anti-tetanus vaccination carried out in less than 5 years before the injury, and if the cycle of anti-tetanus vaccination in children is a complete (3 doses in the first year, one in the sixth and one after 10 years), there are not necessary other preventive measures than the surgical debridement of wound (6,7). In the case that it passed more than 5 years or if the person is not fully immunized, in that purpose, human tetanus immunoglobulin and tetanus antitoxin should be given twice in a span of one month, and after six months another so called stimulating dose.

In case of violation of actively immunized persons it should be given only antitoxin while the person who is not known whether vaccinated may have a combined passive and active immunization. The so-called passive immunization should be done in all cases of contaminated and extensive injuries and injuries with devitalized tissue, when it comes to those who have not fully vaccinated, or we have unsafe

and untested information about immunization (7). In the present case, emphasis is placed on the fact that patients were not vaccinated; the wound was not treated surgically. Adequate surgical treatment of all wounds is one of the most preventive measures in preventing this type of infection.

At the smallest injury, it is necessary to check how much time has passed since the last renewal antitetanus vaccination and if it is necessary renew.

CONCLUSION

Tetanus is a serious and severe disease.

Early diagnosis and beginning treatment greatly improve prognosis.

Regular vaccination in childhood, as well as vaccination against tetanus at a later age after the injury, prevents the onset of the disease.

Adequate surgical treatment of all wounds is an important measure to prevent tetanus

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