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The Effectiveness of Corticosteroid Usage in Complex Therapy for Severe Sepsis and Acute Respiratory Distress Syndrome in Cases of Severe Traumatic Brain Injury

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article

Abstract

Background. Severe traumatic brain injury (STBI) is an important issue in contemporary medicine and treatment strategies are still in need of improvement. The most dangerous complications of STBI are multiple organ failure and severe sepsis. As many as 80% of STBI patients with multiple organ failure have acute respiratory distress syndrome (ARDS). The need for better treatment strategies for STBI has led to investigations of the positive therapeutic effects of corticosteroids (CS). About 10 to 15 years ago research showed the inexpediency of CS in STBI therapy, but there were also contradictory findings showing their effectiveness. STBI is frequently followed by severe sepsis, which is not usually treated with CS. No scientific papers investigated the usage or non-usage of CS in patients with STBI followed by severe sepsis and ARDS.
Objectives. The aim of the study was to investigate the influence of CS usage on treatment results in patients with STBI followed by severe sepsis and ARDS.
Material and Methods. The study involved an analysis of the treatment results in 267 patients with STBI followed by severe sepsis and ARDS, who were treated with and without CS.
Results. The study showed that patients' mortality decreased 1.24 times with CS use (500 mg/day of Solu-Medrol® for three days, followed by dose reduction by one-half every 3 days). Patients who took CS survived longer than patients without this treatment. The duration mechanical ventilation was shorter in patients who were treated with CS compared to the other group.
Conclusions. Further research into CS use is needed to improve treatment strategies for STBI followed by severe sepsis and ARDS (**Adv Clin Exp Med 2016, 25, 6, 1223–1226**).

Key words: acute respiratory distress syndrome, corticosteroids, severe sepsis, severe traumatic brain injury.

Severe traumatic brain injury (STBI) is the most frequent pathology in trauma cases [1]. It has been stated that the mortality rate in cases of STBI is 80%, which is caused by the development of multiple organ failure and sepsis [2].

STBI is a cause of mortality and disability all over the world. It is also one of the main causes of death up to the age of 40 [3]. In Great Britain, STBI frequency is 1500 people per every 100,000; and 9 patients out of 100,000 population die because of traumatic brain injury [1, 2].

The most severe complication of STBI is sepsis [4]. The mortality rate in cases of severe sepsis is still very high, amounting to 50–60%, and the mortality rate for septic shock is 80–90% [5]. Annually, 1.5 million people die and 2.4 million become disabled because of STBI. Patient mortality has increased 57% over the past 10 years, from

133.7 to 210.3 cases per 100 000 population [2–5]. The problem of STBI treatment is not only a medical issue, but a social problem as well [2–4]. In the USA the costs of treating one patient with this pathology amount to more than 150 000 USD, and if further rehabilitation is considered, the costs rise to 2 million USD. In the United States approx. 5.3 million people are disabled due to STBI and in EU countries the number is 7.7 million [2–4].

Among the complications of STBI, lung injury has a prominent role. It develops in 70–80% of STBI patients, and is one of the factors contributing to the deterioration of the patient's status, with further negative treatment results [4]. Morphological changes in the lungs are detected in 95–97.7% of STBI cases [4]. The most frequent cause of patient mortality on the 3rd through 5th day of STBI is acute respiratory distress syndrome (ARDS) [2], which occurs in 80% of STBI patients with multiple organ failure. Despite the fast development of medical technologies, over the past 20 years there has been a reduction in ARDS patients' mortality [6]. The treatment of ARDS entails the use of expensive medical equipment and drugs, resulting in major costs, averaging from 80 000 USD to 320 000 USD per patient [7].

Respiratory support is a vital technique for temporary compensation of breathing function [8], but it is not always adequate in cases of severe respiratory dysfunction, even with the use of up-to-date respiratory technologies [20].

There have been many attempts to use corticosteroids (CS) for the treatment of ARDS [9–13]. Randomized clinical trials showed the effectiveness of CS usage for the treatment of ARDS [10–13], but the majority of current research indicates that corticosteroids are ineffective or even harmful in ARDS cases [14]. There are also research results that show the inexpediency of CS use in cases of STBI [15]. It can be stated that CS treatment is harmful in STBI followed by ARDS, but it is obligatory to take into consideration that the vast majority of these patients also suffer from severe sepsis [4]. CS are indicated for the treatment of severe sepsis in cases of unstable hemodynamics [21]. That means that STBI patients with severe sepsis and ARDS can take CS when there is a decline in hemodynamics. The question that arises is how it will influence the treatment results. The aim of this study was to find a possible answer to this question.

Material and Methods

The present study is a retrospective analysis of treatment results in patients (n = 267) with STBI followed by severe sepsis and ARDS, who were treated in Ternopil University Hospital (Ternopil, Ukraine) between 2008 and 2014. The development of severe sepsis was followed by unstable hemodynamics in almost all the cases. The instability was corrected by administering adrenomimetic drugs and additional infusion of fluids aimed at achieving stable blood pressure. The most frequent complication during the correction was a rise in blood pressure followed by tachycardia. In order to deal with this, stress doses of Solu-Medrol® (Pfizer Manufacturing Belgium NV, Puurs, Belgium) were used: 500 mg/day for 3 days, followed by reductions in dosage by one-half every 3 days. The treatment results were evaluated in relation to the type of respiratory support and presence or absence of CS in complex therapy. The results were evaluated separately for living and dead patients. As the criteria of treatment effectiveness, the duration of mechanical ventilation was used. Two ventilation modes were involved: forced ventilation with controlled volume; and ventilation with two phases of positive pressure in the airway, known as biphasic positive airway pressure (BiPAP, equivalent to pressure-support ventilation or PSV). For the volume-controlled ventilation the Bryz ventilation device (Kyiv State Enterprise "Burevisnyk", Kyiv, Ukraine) was used. For BiPAP ventilation the Draeger Carina ventilator was used (Draeger Medical GmbH, Lübeck, Germany).

During the period from 2008 to 2014, 1120 patients with STBI were treated at Ternopil University Hospital. Severe sepsis developed in 325 of the patients (29.01%); 267 patients (82.15%) with STBI followed by severe sepsis also suffered from ARDS, which necessitated mechanical ventilation. ARDS diagnoses were established on the basis of the Berlin criteria [22]. Among the patients with STBI, severe sepsis and ARDS, the number of people who died was 152 (46.7%).

For the statistical analysis, nonparametric methods were used. The hypothesis about the equality of averages was verified using the Mann-Whitney test. Averages and standard errors were calculated. A p-value under 0.001 was treated as statistically significant. The analysis was carried out using STATISTICA v. 10 software (StatSoft Inc., Tulsa, USA).

Results

The patient mortality rate depended on the type of mechanical ventilation used; mortality decreased by 1.24 times when BiPAP mechanical ventilation was used, as opposed to volume-controlled forced ventilation of 5–7 mL/kg. The dead patients who had had forced ventilation with volume control lived for a shorter time than patients on BiPAP ventilation (p = 0.01). Among the patients who survived, the duration of BiPAP ven-

Table 1. The duration of ventilation and the survival of patients with severe traumatic brain injury followed by severe sepsis and acute respiratory distress syndrome in relation to the use of corticosteroids

Ventilation mode	Number of patients		Ventilation period in days	Survival (%)
ACV	alive	16	24.18 ± 5.93	31.3
	dead	35	5.29 ± 1.04	
ACV+ k	alive	22	20.82 ± 3.13 p = 0.000880	37.9
	dead	36	7.5 ± 1.4 p = 0.000001	
BiPAP	alive	30	18.33 ± 1.81	44.7
	dead	37	8.08 ± 1.0	
BiPAP+k	alive	47	16.27 ± 3.11 p = 0.006203	51.6
	dead	44	13.09 ± 1.29 p = 0.004674	

BiPAP is equivalent to pressure-support ventilation (PSV); +k – with corticosteroid treatment; p – probability calculated according to the relevant value (dead or alive) in the previous column.

tilation was 1.32 times shorter than the duration of forced ventilation with volume control.

With both ventilation modes, the use of CS decreased the mortality rate and reliably had a positive influence on the ventilation period. In dead patients it prolonged the ventilation period (in ACV mode: p = 0.000001; in BiPAP mode: p = 0.004674). In the surviving patients the converse was true: the ventilation period was shortened (in forced ventilation mode: p = 0.000880; in BiPAP mode: p = 0.006203).

Discussion

Despite the view that CS usage in case of STBI and ARDS has negative effects [15], there have been clinical trials that proved the positive effect of CS therapy in such patients. In particular, there are some data about the effectiveness of CS based on a reduction in fibrosis activity [12]. Meduri [10, 11, 13] stated that CS use in ARDS reduces leukocyte extravasation, inhibits leukocyte adhesion to endotheliocytes, increases lymphocyte migration from blood circulation to lymphoid tissue, stops macrophage activity and phagocytosis, stops production of interleukin-1, stops expression of cyclooxygenase-2, stops prostaglandin synthesis and also slows down the fever reaction.

The data from the present study also confirms the experience of Ternopil University Hospital during the treatment of patients with the H1N1 influenza virus epidemic in 2009. At that time, 26 patients with flu entered the anesthesiology and intensive care unit within 12 days. In all of these patients the disease was complicated by the development of ARDS. All 26 patients were put on low volume (5–6 mL/kg) mechanical ventilation with volume control. This group of patients died within 3–4 days, after which this mode of ventilation was no longer given. Instead, ARDS patients got BiPAP ventilation with stress doses of CS, and patient life expectancy considerably increased. Even the patients who died had longer survival period, which increased from 3–4 days to 7–10 days. Approximately 50% of the patients that got ventilation in BiPAP mode along with stress doses of CS survived. The total number of flu patients who got ARDS was 80.

The number of cases observed in 2009 was too low to form judgments about the treatment results depending on the type of respiratory support and CS prescription. But based on that experience and the results of the present study the authors have come to the conclusion that stress doses of CS therapy are effective in flu patients followed by ARDS. Additionally, at the beginning of the flu epidemics in the autumn of 2009, CS treatment was not prescribed, based on research pointing to the harmfulness of CS in ARDS [17, 18]. Later, there were also some publications that indicated the harmfulness of CS for treating the flu [19].

The present authors are convinced that the results of this research reveal that there is no final verdict about the effectiveness of CS therapy in cases of STBI followed by severe sepsis and ARDS. The presence of severe sepsis may be an important indication for using CS treatment. Further research analyzing the treatment results of such patients in other clinics is needed.

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