ABSTRACT

We describe the parameters that can influence the outcome of severe closed cranioencebral injury. Cranioencebral injuries involve two phases: the phase of primary injury, which includes primary cerebral lesions made under the influence of factors that have a direct or indirect impact on the cranium, and the phase that represents secondary injuries, which are the result of the impact of pathophysiological mechanisms (hypoxia, hypercapnia, and hypotension). These mechanisms are initiated by a trauma as well as some specific characteristics of the organism (e.g., age, comorbid conditions, and previous injuries). The aim of the study was to establish factors that significantly influence the outcome after severe closed cranioencebral injury. A total of 182 patients that were treated at the Clinical Center in Kragujevac from 2001 to 2005 were included. The most important prognostic factors for the treatment outcome were: age, oxygen saturation, the Glasgow Coma Scale score (GCS) and level of injury of the cerebral tissue diagnosed by a CT. Morbidity risk raised by 2.6% when only the age parameter increased by one year. When evaluating a 1% increase in oxygen saturation, the morbidity risk rate fell for 10.7% of the patients if other parameters remained stable. According to the aforementioned criteria, a 159.3% increase in morbidity risk rate was observed between mild and severe brain injury when other parameters did not change. In conclusion, a severe closed cerebrocranial injury is a dominant factor for the determination of patient outcome.

Key words: cranioencebral injury, outcome, neurosurgery

INTRODUCTION

Injuries of all kinds are a significant medical, economic and social problem. The injuries of the cranium and brain in overall traumas are very significant. They have an enormous influence on the life of an individual, on close and distant family members, as well as on society, because of their high incidence and the future difficulties they impose.

The annual incidence of head trauma is between 0.2 and 0.3% and is most common between the ages of 15 and 24. The risk decreases by the age of 50 but becomes more frequent in the elderly (1). Head trauma is the leading cause of death in the population under 44 years of age. In the population as a whole, the incidence of head trauma mortality is third after vascular (cerebrovascular and cardiovascular) and malignant diseases. Studies in Great Britain have shown that closed cranioencebral injuries had severe consequences in 91 out of 419 people per 100,000 citizens (2). In the USA,
two million people suffer from cranial injury annually and, after the final treatment, 50,000 people suffer from severe consequences (3). According to the data from the USA, 500,000 people are hospitalised with closed cranial injuries annually, 15% of whom have severe craniocebral injuries (4). The incidence of morbidity is estimated to be 25 per 100,000 citizens (1). In the USA, 56,000 people die from head trauma annually (5). According to the same sources, 20-40% of the total injuries are in traffic accidents and 2/3 of the patients die on the way to the hospital. According to data from Slovenia, 30,000 people were treated for different injuries in 2001 and 29% of these cases suffered from a head injury. In 2001, 570,000 people were treated for various injuries at the primary health care level, cranial injuries accounting for 13% of the cases (approximately 75,000 people).

The classification of craniocebral injuries by severity is based on different criteria. All classifications are made according to a scheme. The most applied criteria are the Glasgow Coma Scale (GCS), coma duration, duration of post-traumatic amnesia, and the results of neuroimaging and electrophysiological diagnostic methods. All classifications are of theoretical, therapeutic and prognostic importance. None of the mentioned criteria are sufficient to show total and precise severity of the cranial and cerebral injury, as this is also influenced by age and other factors. In elderly people, even minor craniocebral injuries can be complicated by haematomas and complications of other systems and organs, increasing the morbidity and making the prognosis less predictable. Previous cranial and brain traumas are also negative factors for prognosis. One previous injury doubles the risk of the trauma and two makes the risk eight times greater (6).

In practice, the most common criterion for the classification of severity of craniocebral injuries is the GCS (7). According to this criterion, craniocebral injuries are classified as a) mild (GCS score from 13-15), b) moderately severe (9-12) and c) severe (3-8). If craniocebral injuries are defined by only the GCS, some mistakes can occur because craniocebral injuries can change due to bleeding that can occur afterwards. The preserved state of consciousness does not guarantee that intracranial lesions, such as contusions or haematoma, will not appear. This can also change the clinical picture and significantly influence the prognosis after craniocebral injury. Intoxication with alcohol or the use of sedatives in the traumatised patient is associated with lower GCS values that do not correlate with the severity of craniocebral injury.

Research has shown that coma duration is correlated with the severity of injury and its outcome. Using this as a criterion, craniocebral injuries can be classified as a) mild, where the coma lasts for 20 minutes (some authors include up to 30 minutes), b) moderately severe, where the coma lasts up to six hours, and c) severe, where the coma duration is over six hours from the point of hospitalization (6). Patients with moderately severe craniocebral injuries suffer from many subsequent problems, such that two-thirds of the injured cannot be professionally rehabilitated (6).

In some studies, a significant part of the estimation of the severity of craniocebral injury is post-trauma amnesiac duration. This mostly correlates with the GCS and lasts four times longer than the post-trauma coma (6). In practice, this fact is very unreliable due to many reasons, such as aphasia, the confused condition of a patient and the fact that the patients are released from hospital before the amnesiac period passes.

There are several issues regarding the definition of severe closed craniocebral injury. Most authors agree that the group of severe closed craniocebral injuries consists of the injuries with GCS score of 8 and lower. The pathological substrate in a severe craniocebral injury is primarily the contusion of the cerebral hemispheres, the brain stem and diffuse axonal lesions.

Severe closed craniocebral injury immediately after trauma is manifested as problems ranging from breathing disorders to apnea and disorders caused by bradycardia or arrest (8). Respiration disorders and apnea induce hypoxia and ischemia in the brain and lead to disturbances of consciousness. If these complications last for a long enough, they can have an adverse influence on the craniocebral injury. The kinetic energy of mechanical devices that cause craniocebral injury induces dysfunction of the respiratory centre in the medulla oblongata (9). Premature respiratory support in these cases is a prerequisite for a positive outcome.

The follow-up of a patient with a craniocebral injury is of crucial importance. There are patients who feel very well between the injury and the moment of worsening. The term for this is “speak or vanish” or “speak and aggravate” (10). This typically occurs in patients with a GCS score of 13 or 14 who were injured while falling down. This is demonstrated by the rule that estimation of an initial condition can be incorrect. After recovering from a coma, these patients are anxious, distressed, disoriented in both time and space or towards people, depressed or euphoric, uncritical, nervous and hypomotoric (11); a condition called post-traumatic delirium. If the brain stem is damaged, dysarthria, unbalance, fatigue, ophthalmoplegia and rare pyramidal defects can be observed. Furthermore, post-traumatic amnesia can still be present (10). By new radiographical methods, we can identify the formation of a new bone in periarticular zones, which can mostly be seen in the proximal extremity of the wrists in over half of the patients who recovered from a coma (12). The precise mechanism of appearance of these changes is unknown, however, it is suspected that prolonged coma, muscle hypotonous, weakness of the extremities and fractures are risk factors.

It is of great interest to identify the factors that influence the outcome of closed craniocebral injury. It is well known that closed craniocebral injuries result in mortality in most cases, with a rate of over 45%, although
some studies suggest that the mortality rate is lower than 40%. Although these are studies from different regions and in different circumstances, the difference is lower than 10%. Premature death in the first 48 hours is a clear consequence of primary cerebral damage. Death occurring later is the consequence of various processes that are related to hypoxia, hypercapnia and hypotension. These factors can become more pronounced when there is a severe and heavy injury of other systems and organs. The aim of this study was to define risk factors for poor outcome in order to allow the introduction of novel, adequate therapeutic measures that could make the outcome of injury more favourable.

PATIENTS AND METHOD

We included patients treated at the Neurosurgical Department and Intensive Care Unit at the Clinical Centre in Kragujevac from January 1st, 2001 to December 31st, 2005. Patients had closed craniocerebral injuries (isolated or together with polytrauma) with GCS scores upon admission of 8 and lower. A total of 111 closed craniocerebral injury patients that had no other injuries were included, along with 71 patients with the severe closed craniocerebral injury coupled with the severe injury to other systems and organs (e.g., rib cage, spinal column, pelvis, abdominal organs or fracture of long bones of the extremities).

The design of the study was set up as previously described (13). We investigated socio-demographic data, anamnesis and heteroanamnesis variables, clinical status at admission, radiological imaging, biochemical tests, treatment modalities, and variables of clinical outcome including the outcome according to Glasgow outcome scale (GOSE).

For statistical analysis, a Kolmogorov–Smirnov test was used for evaluating variables within normal limits. Other tests were used with the appropriate methods that were consistent with the type and distribution of the original data (14). A t-test and Mann-Whitney test were used for comparison of two means. Frequency of the observations was tested by a chi-square test and Fisher’s exact test. A multifunctional regression analysis was performed to test the relationship between two variables. Univariate and multivariate binary logistic regressions were used for testing the cause-and-effect relationship between treatment outcomes and other variables. The receiver operating characteristic (ROC) curve and area under the curve (AUROC) analyses were used for ensuring that a variable could be the test marker for a fatal outcome prediction (15).

RESULTS

During the study period, 182 patients with the severe closed craniocerebral injury were treated at the Neurosurgical Department and Intensive Care Unit. All patients had GCS scores ranging from 3-8 points. A total of 111 subjects were admitted with an isolated cranio-cerebral injury, and another 71 patients were admitted with both a closed cranio-cerebral injury and at least one more severe injury to other organs or systems.

The mean age of all patients was 49.82 years, with a standard deviation of 21.5 years. The smallest percentages were in the first and fourth decades of life. Men were injured four times more frequently than women (79% vs. 21%). There was a significant difference in age among the groups concerning the outcome (according to GCS total score) (t-test, p<0.001, Table 1). The difference was significant between groups 1 and 2 and between groups 1 and 5. The lack of difference between groups 1 and 3 as well as 1 and 4 was most likely due to the small sample (Table 1).

Statistically speaking, it has been estimated that circumstances of injury, the time spent from the moment of injury until admittance to the neurosurgical institution and the initial loss of consciousness do not influence the outcome. Instead, the outcome is influenced by dynamics in the state of consciousness, medical assistance and arrival at the neurosurgical institution, previous cranial fractures, breathing function upon admission, oxygen blood saturation, and brain stem reflex (reaction of pupils to the light and corneal reflexes). The GCS results were statistically important for predicting the outcome as well as the degree of cerebral tissue damage that was determined during the CT scan. The treatment outcome for cranio-cerebral injury (CCI) and polytrauma is described in Table 2.

Table 1. Influence of the patient age on outcome

<table>
<thead>
<tr>
<th>Group</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td>Well recovery</td>
<td>Average inability</td>
<td>Heavy inability</td>
<td>Prolonged vegetative condition</td>
<td>Death</td>
</tr>
<tr>
<td>N</td>
<td>46</td>
<td>30</td>
<td>10</td>
<td>2</td>
<td>94</td>
</tr>
<tr>
<td>The mean age</td>
<td>36.76±19.31</td>
<td>50.60±29.59</td>
<td>51.40±20.03</td>
<td>45.00±28.28</td>
<td>55.80±19.61</td>
</tr>
</tbody>
</table>

Statistically speaking, it has been estimated that circumstances of injury, the time spent from the moment of injury until admittance to the neurosurgical institution and the initial loss of consciousness do not influence the outcome. Instead, the outcome is influenced by dynamics in the state of consciousness, medical assistance and arrival at the neurosurgical institution, previous cranial fractures, breathing function upon admission, oxygen blood saturation, and brain stem reflex (reaction of pupils to the light and corneal reflexes). The GCS results were statistically important for predicting the outcome as well as the degree of cerebral tissue damage that was determined during the CT scan. The treatment outcome for cranio-cerebral injury (CCI) and polytrauma is described in Table 2.

Table 2. CCI and polytrauma and treatment outcome.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CCI</th>
<th>Polytrauma</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well recovery</td>
<td>32</td>
<td>14</td>
<td>46</td>
</tr>
<tr>
<td>Average inability</td>
<td>17</td>
<td>13</td>
<td>30</td>
</tr>
<tr>
<td>Severe inability</td>
<td>7</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Vegetative condition</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Death</td>
<td>55</td>
<td>39</td>
<td>94</td>
</tr>
<tr>
<td>Total</td>
<td>111</td>
<td>71</td>
<td>182</td>
</tr>
</tbody>
</table>

Treatment outcome does not depend on injury type (p = 0.252, chi-square test)
A multifactorial linear regression showed that the craniocerebral injury outcome depended on age, oxygen saturation, GCS and severity of cerebral tissue damage, where the latter was determined during the CT scan (Table 3). The function representing the linear connection between the outcome and listed factors is shown in the formula: \[ i = 9.95 + 0.02 \times \text{age} - 0.66 \times \text{SATO}_2 - 0.36 \times \text{GCS} + 0.55 \times \text{SCAN}, \]
where \( i = 1, 2, 3, 4, 5 \) (according to the Glasgow Outcome Scale). Multivariate binary logistic regression showed that four separate factors influence the overall outcome: age, saturation by \( \text{O}_2 \), GCS and CT scan (Table 4).

Table 3. Variables influencing the treatment outcome.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Coefficient</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 (Constant)</td>
<td>9.9470</td>
<td>0.000</td>
</tr>
<tr>
<td>AGE</td>
<td>0.0215</td>
<td>0.000</td>
</tr>
<tr>
<td>SATO(_2)</td>
<td>-0.0641</td>
<td>0.014</td>
</tr>
<tr>
<td>GCS</td>
<td>-0.3620</td>
<td>0.000</td>
</tr>
<tr>
<td>SCAN</td>
<td>0.5500</td>
<td>0.034</td>
</tr>
</tbody>
</table>

By employing the ROC and AUROC measurements, we found that patient’s age (AUROC=0.667, \( p<0.001 \)), SATO\(_2\) (AUROC=0.649, \( p=0.001 \)), GCS (AUROC=0.740, \( p<0.001 \)), CT scan findings (mild and severe injuries seen on CT) (AUROC=0.641, \( p=0.001 \)) can be used as markers for the fatal outcome prediction (Figures 1 to 5). Using a linear model, we found that the combination of these variables made a better predictor of the fatal outcome (AUROC=0.813, \( p<0.001 \)) compared to the individual variables alone. The cut-off for the model was 3.21, meaning that values were positive if higher than 3.21 and negative if lower. In 75% of the cases, we found positive results for the fatal outcome. Sensitivity (i.e., the relation of the number of those who did not survive to the number of those who survived) of this test was 79.79%. Specificity (i.e., the relation of the number of those who survived to the number of those with a negative test) of this test was 70.45% (Table 5).

Table 5. The test results (in groups, number of patients).

<table>
<thead>
<tr>
<th>Test results</th>
<th>Dead</th>
<th>Survived</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive test (( &gt;3.21 ))</td>
<td>75</td>
<td>26</td>
</tr>
<tr>
<td>Negative test (( \leq 3.21 ))</td>
<td>19</td>
<td>62</td>
</tr>
</tbody>
</table>

DISCUSSION

Statistics have shown that 37% of all injuries are closed craniocerebral injuries, and that 60% of patients with craniocerebral injuries have another injury. Polytrauma is of particular importance, as people with multiple traumas typically suffer an injury to the head. Studies have found that the mortality rate of patients with an isolated cranial injury was 11%. If the patient suffered from polytrauma, however, this increased to 21.8% (10). The most common craniocerebral injuries are caused by traffic accidents, falls, industrial injuries, sports injuries, as well as intentionally inflicted injuries (punches to the head, war injuries).

In Serbia, as well as in the former Serbia, Montenegro and Yugoslavia, complete data regarding the incidence of cranial injuries do not exist. The inconsistency in the data was influenced by the political climate over the last 15 years. In former Yugoslavia, 70 thousand people were injured annually, with a morbidity outcome of 4500-5000 people. Data from 1995 showed that 781 people died due to head injury, which is 7.4 per 100 thousand citizens. Furthermore, 5500 people, that is, 50 and 100 thousand citizens, were hospitalised in 1995, which means that the incidence of injury was 200 per 100,000 (10).

In addition to the symptoms of high intracranial pressure, the clinical definition of cranial injury is characterised by the focal symptoms that depend on the localisation and size of the contusion or haemorrhage. An acute cerebral oedema with hyperventilation and the signs of decerebration is characteristic of younger age (8). This is because of blood congestion in the white cerebral matter during the disturbance in vasoregulation. The patients with the most severe craniocerebral injuries also have severe injuries to other organs and organ systems in various combinations. Severe injuries to other systems and organs are responsible for secondary cerebral damage.

The clinical picture can be different for different patients. A cranial injury can result in a deep coma, with dilated, atonic pupils, light insensitivity, silent corneal reflexes as well as other brain stem reflexes, atonic muscles and problems ranging from difficulties breathing to apnea. This condition is defined as an irreversible coma.
the case that this condition lasts too long, it is followed by hypothermia, tachycardia, then hyperthermia, circulatory collapse and distress, ultimately leading to a lethal outcome. This condition can last for several hours to several days (10). After patients with slightly milder cranioencebral injuries come out of the coma, there is the risk of complications and aggravation during a period of at least three weeks (8). Monitoring of these patients is necessary so that the aggravation signs can be noticed on time. Symptoms such as an increase of the perifocal oedema, development of ischemic cerebral lesion, enlargement of some intracranial haematomas, aspiration pneumonia, acute respiratory distress syndrome (non-cardiogenic lung oedema due to the enlargement of permeable lung blood vessels) and haematemesis are most the common aggravation signs to look for.

The estimation of injury severity has not only significant, but also an outstanding prognostic value. Many factors influence the outcome that are not directly correlated with the injury, and are usually unavailable for research or unrecognisable at the time of the initial injury. Reported data and everyday practice have shown that injuries classified as mild can aggravate and have lethal consequences, contrary to the injuries that are, according to the defined criteria, classified as severe and can have a positive outcome. A typical example is an injured person with a brain concussion and cranial fracture. The patient’s consciousness is inhibited and, during the development of an epidural haematoma, his condition deteriorates drastically such that immediate neurological operation is necessary. The classification of injuries by severity is therefore of serious prognostic significance, but what is necessary here is warning before coming to a conclusion. It is clear that monitoring the patient is required so that all signs of aggravation are detected in a timely manner and the reaction can be adequate.

The outcome of severe cranioencebral injury is divided into five grades: good recovery, mild disability, severe disability, prolonged vegetative condition, and death. After completion of treatment, a patient with a severe cranioencebral injury can have long-lasting motor, cognitive, emotional and social disorders. The appropriate rehabilitation that enables these skills can be performed. The term “prolonged vegetative condition” is characterised by the inability to alternate between the sleeping and awake state. These patients are not communicative and they do not have any trace of mental activity. Severe instability means dependence on other persons. These patients are aware, communicative and able to help themselves. Moderate inability means that significant episodes may appear but the patients are able to help themselves and have a certain capability of professional rehabilitation. In patients that show good recovery, subsequent episodes can occur, but these episodes do not significantly influence their professional activity and these patients do not require help from others. The significant prognostic factors are age, coma duration and post-traumatic amnesia duration (11). The most intensive recovery period is during the first six months. There are some cases of unexpected recovery after a longer period, giving greater significance to the use of complex rehabilitation measures (10).

The most important prognostic factors for the treatment outcome are age, saturation with oxygen, GCS score and degree of the cerebral tissue damage visualised on the CT scan. When evaluating an age increase of one year, the mortality risk rises by 2.6% when the other parameters remain unchanged. If only oxygen saturation increases by 1%, the risk of the mortal outcome decreases by 10.7%. When evaluating a 1 point increase in the GCS, the mortality risks decrease by 36.7%, but only if the other parameters remain stable. A 159.3% increase in morbidity risk rate was observed between mild and severe brain injury when other parameters did not change. Finally, we found that the severe closed CCI is a dominant factor for the polytrauma outcome.

Our results are similar to previous findings in which two main prognostic factors were found: the admission status and extent of brain injury (16). To our knowledge, no study has investigated the oxygen saturation status in peripheral tissues following traumatic brain injury. It is well known that the most dangerous factor in brain injury is unresolved tissue hypoxia (17, 18). Neurological injury after brain trauma is directly correlated with severity of primary brain lesion (19). In our study, the mean age of all patients was 49.82 years, with a standard deviation of 21.5 years. The smallest percentages of the injured were in the first and fourth decades of life, which is consistent with previous findings. The percentage of cranial injuries increases at the age of 25. The risk then decreases and rises again after 50 years of age (20). Other studies have shown that the greatest number of injuries occurs up to 25 years of age (21) and that the average age of people suffering from isolated closed cranioencebral injuries was 28.6 ± 17.8 (22). Here, men were four times more at risk than women were (79% vs. 21%). We found that polytrauma occurred more often in accidental injuries (51.65% compared to 41.44%). Furthermore, polytrauma is often developed when falling down from a great height.

In conclusion, the results of our study show that age, SATO₂, GCS and degree of cerebral damage (defined by CT scan results) are predictors for a prognosis of the lethal outcome. The most accurate measure is made by the linear model that combines these variables. The cut-off for this marker is 3.21, meaning that the result is positive if it is higher than 3.21 and negative if it is lower. Finally, the test sensitivity was 79.79% while the specificity was 70.75%.

REFERENCES

1. Frankowski RF, Annegers JF, Whitman S. Epidemiological and descriptive studies. Part 1: The descriptive epidemiology of head
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