Sirko A.G., Serdiuk V.M., Skripnik A.F.

CRITICAL THRESHOLDS OF INTRACRANIAL PRESSURE AFTER SEVERE TRAUMATIC BRAIN INJURY

A. G. Sirko, Doctor of Medical Sciences, Associate Professor of Nervous Diseases and Neurosurgery Department of Postgraduate Education Division, State Institution “Dnipropetrovsk Medical Academy of the Ministry of Health of Ukraine”, Chief of Cerebral Neurosurgery Department No. 2, Mechnikov Dnipropetrovsk Regional Clinical Hospital, Ukraine

V. M. Serdiuk, Doctor of Medical Sciences, Associate Professor of Neurology and Ophthalmology Department, State Institution “Dnipropetrovsk Medical Academy of the Ministry of Health of Ukraine”, Director of Municipal Institution "Dnipropetrovsk Regional Clinical Ophthalmologic Hospital", Ukraine

A. F. Skripnik, Medical Statistician, State Institution “Dnipropetrovsk Medical Academy of the Ministry of Health of Ukraine”, Ukraine

Abstract

The article considers the monitoring of intracranial pressure as an important prognostic factor of predicting the treatment outcomes in the cases of severe craniocerebral trauma. Realizing the problem of defining the degree of intracranial hypertension as an urgent issue of neurophysiology and taking into consideration the ambiguity of the methods traditionally used to define this indicator the authors focus on the substantiation of the new threshold values of intracranial pressure maximizing the statistic difference between mortality/survival and favorable/adverse outcomes of treatment and established in the course of analyzing the results of the prospective study conducted on 100 consecutively included patients in the dynamics of the severe brain injury in the intensive care departments of Mechnikov Dnipropetrovsk Regional Clinical Hospital in the period from 2006 to 2012. Obtained with use of the parenchymal sensors for measuring intracranial pressure on the Brain Pressure Monitor REF HDM 26.1/FV500 manufactured by Spiegelberg (Hamburg, Germany) during 11657 recorded hours of observation, the data were processed due to the algorithm of the ROC curve analysis used to establish the most informative parameter of intracranial hypertension. The research revealed the dependance of treatment results in two groups of patients (survived/died and favorable/adverse outcomes) on the five basic indicators of intracranial pressure (dose, duration, intensivity of intracranial hypertension/ average and maximum levels of intracranial pressure). Groups of patients with two different treatment results most likely differ in terms of the intensity of intracranial hypertension, namely, due to the average value of exceeding the threshold of intracranial pressure of 15 mm Hg. The received thresholds of average intracranial pressure for the distribution of treatment outcomes are lower than the indicators accepted in many recent recommendations.

The average value of exceeding the threshold of intracranial pressure of 15 mm Hg which is about 7 mm Hg (7.38 for the results survived/died; 7.06 for favorable/adverse outcomes) should be recognized as the most significant prognostic criterion for the differentiation of patients with different results of treatment.

Keywords: severe craniocerebral trauma, intracranial pressure, intracranial hypertension, prognostic factors, threshold values, dose of intracranial hypertension, intensity of intracranial hypertension, duration of intracranial hypertension, average intracranial pressure.

Introduction

Severe craniocerebral trauma (CCT) is the main cause of disability and mortality of working-age people [1,2]. One of the key tasks in the treatment of patients with the severe CCT is the prevention of secondary brain insults [3] by monitoring intracranial pressure (ICP) [4,5,6,7,8,9], maintaining adequate oxygenation and cerebral perfusion [10,11,12]. Numerous studies [4,6,9] have revealed the influence of the threshold values of intracranial pressure and cerebral perfusion pressure (CPP) on both the treatment prognosis and the peculiarities of correction of their deviations.

According to the fourth edition of the Recommendations of the American Association of Neurosurgeons for the management of patients with craniocerebral trauma [13], the following level of intracranial pressure has been recognized as the critical threshold. The urgent action is recommended if ICP is > 22 mm Hg, because the excess of this level predicts an increase in mortality rates (the level IIB of recommendations). This recommendation is based on the results of a retrospective cohort study including 459 CCT victims [14] and attributed by the authors to the second level of research. Thus for ICP the value of 22 mm Hg was defined as the critical threshold for both lethality and favorable outcome for all victims (Chi square = 58.18, e <0.001 and 18.15, e <0.001). The further analysis of subgroups formed by age and gender revealed that the threshold value for lethality did not change, but it decreased to 18 mm Hg for a favorable outcome for patients over the age of 55 and women of all age groups.

Defining the critical ICP thresholds the authors added two new studies to nine studies of the third grade from the previous third edition of the Recommendations [15,16]. The randomized study performed by Kostic A. Et al. in Serbia and published in 2011 [15] compared the mortality rates in patients undergone the ICP monitoring to the lethality indicators in patients without any monitoring. The study included 61 patients, 52.5% of them underwent the ICP monitoring. The average ICP values for survivors and dead patients were 18 mm Hg and 27 mm Hg respectively. The study of the initial ICP levels during surgery [16] focused on their significance for predicting both favorable and adverse outcomes of treatment assessed against the criteria of the Glasgow Outcome Score three months after the injury. The ICP level for the favorable result was 26.4 ± 10.1 mm Hg and that indicator for the adverse outcome of treatment was 47.4 ± 21.4 mm Hg.

For decision-making on treatment the authors [13] also recommend to use a combination of the ICP values and the results of both clinical analysis and computed tomography (CT) of the brain (the level IIIB of recommendations).

Recently the method of calculating the average ICP value has been the most commonly used to define the degree of intracranial hypertension (ICH) [5,7,8]. Although the method is relatively simple, it does not provide the precise definition of the effect of physiological damage caused to the brain by the high ICP level. Nowadays secondary brain injuries are characterized by estimating the overall scope and duration of episodes of ICH. The method involves the calculation of the ICH dose as the area under the curve located over the established physiological ICP threshold. Taking into consideration both intensity and duration of the damage this method reflects the ICH effect on the results more accurately than the previous approaches.

Therefore the topicality of the search for the prognosis-favorable ICP parameters is predicted by the ambiguity of defining the ICP threshold value in the treatment of patients with the severe CCT. The information received from monitors becomes more complex and voluminous predetermining the difficulties of identifying and interpreting the ICH. The further study of the problem is impossible without the detailed computer analysis of the data of the bed monitor.

Despite the long history and fundamentality of investigations in the sphere of studying the critical ICP threshold in the case of the severe CCT, many issues remain urgent and require further research. In this regard we conducted an analysis of our prospectively collected database of severe CCT (2006-2012) to define the threshold ICP values on the basis of both survival and functional effect of treatment.

The aim of the study was to define the ICP parameters probably affecting the final outcome of the treatment of patients with the severe CCT. We tried to distinguish the main and secondary ICP indicators and their critical limit values which should be recognized as the ultimate therapeutic goals in the treatment of patients with the severe CCT.

Materials of Investigation

The prospective study was conducted on 100 consecutively included patients with the severe craniocerebral trauma (SCCT) who were treated in the intensive care departments of Mechnikov Dnipropetrovsk Regional Clinical Hospital in the period from 2006 to 2012.

The criteria for including in the current prospective study were: (1) assessment of the state of consciousness on the Glasgow Coma Scale (GCS) at admission to hospital from 4 to 8 points inclusive; (2) age of patients over 18 years old; (3) availability of the ICP data, the indicator on the five-point Glasgow Outcome Score six months after the treatment; (4) not less than six-hour duration of the ICP monitoring. The criteria for excluding from the study: (1) brain injury incompatible with life; (2) GCS of 3 points; (3) both dilated pupils not reacting to the light.

For the statistical treatment of traumatic consequences the study used the score distribution on the Glasgow Outcome Scale six months after the injury due to the dichotomy of favorable results (moderate disability, good recovery) and adverse outcomes (death, vegetative condition, severe disability) [17, 18, 19].

Characteristics of the Studied Group of Patients

The study included 19 female patients and 81 male patients. The average age of patients included in the study was 36.2 ± 13.8 years. The cause of CCT in 49 patients was the injury in the everyday life. The accident was the cause of CCT in 43 victims, the work injury caused the CCT in 5 patients and the circumstances of damaging 3 victims were not finally cleared up.

According to the mechanism of CCT the following distribution of clinical observations was obtained: a blow to the head was fixed in 21 cases of observation; the fall from a height relative to the patient's size was observed in 18 cases; the fall from a larger height was revealed in 15 cases of observation; a pedestrian impact was observed in 16 cases; acceleration/deceleration of the transport movement was fixed in 11 cases of observation; the falling off scooter/moped was observed in 5 cases; the falling off a bike was revealed in 3 cases of observation; the falling off a motorcycle was fixed in 2 cases of observation; the vehicle accident with a cyclist was observed in 3 cases; the railway accident with a pedestrian was revealed in 2 cases of observation; the vehicle accident with a moped driver was observed in 1 case; the cause of damage was not reliably installed in 3 cases of observation.

The patients' state of consciousness corresponded to 6.2 ± 1.5 scores on average on the Glasgow Coma Scale. Thus, 19 victims received the GCS score of 4 points; 22 patients received the GCS score of 5 points; 10 victims received the GCS score of 6 points; 18 patients received the GCS score of 7 points; 31 victims received the GCS score of 8 points. Puppies of the same size with a live reaction to light were noted in 31 patients, anisocoria with the preserved reaction of one pupil was revealed in 50 victims and bilateral mydriasis with suppressed reaction of the pupils to light was observed in 19 patients.

The closed CCT was noted in 39 victims, the open non-penetrating brain injury was revealed in 40 patients, the open penetrating brain injury was observed in 21 victims. The diffuse CCT was noted in 23 patients, the focal brain injury was revealed in 77 victims. According to L.F. Marshal's classification [20,21] type II of diffuse brain damage was observed in 4 patients, type III was noted in 14 victims, type IV was revealed in 5 patients. Among victims with focal trauma acute epidural hematoma was diagnosed in 10 patients, acute subdural hematoma was revealed in 47 victims, intracerebral lesions were noted in 11 patients, and numerous traumatic intracranial lesions were observed in 9 victims. Due to the volume of intracranial hematoma the patients were divided as follows: 16 victims had hematoma from 25 cm3 up to 50 cm3, 35 victims had hematoma 51-100 cm3, 18 victims had hematoma 101-150 cm3, 5 victims had hematoma 151-200 cm3, 3 victims had hematoma more than 200 cm3.

The distribution of the patients during the hospitalization due to the Rotterdam CT scoring system [22] was as follows: 1 victim received the score of 2 points, 9 victims received the score of 3 points, 17 victims received the score of 4 points, 40 victims received the score of 5 points, 33 victims received the score of 6 points.

Signs of dislocation syndrome were absent only in 5 patients, isolated lateral dislocation was noted in 5 victims, isolated axial dislocation was revealed in 13 patients. The most frequently detected type of dislocation was a mixed dislocation observed in 77 cases.

According to the data of CT of the brain the displacement of medial structures less than 5 mm was detected in 25 victims, the displacement 5-7 mm was revealed in 14 patients, the displacement 8-10 mm was noted in 19 victims, the displacement 11-15 mm was observed in 28 patients, the displacement 16-20 mm was found in 10 victims, the displacement over 20 mm was defined in 4 patients.

Mesencephalic cistern was compressed in 52 victims, it was not defined in 39 patients, and all its branches were opened only in 9 victims. Dislocation hydrocephalus was detected in 22 patients, hydrocephalus expansion of the right lateral ventricle was revealed in 10 victims, hydrocephalus expansion of the left lateral ventricle was observed in 12 patients.

Treatment Performed

The main purpose of therapy in the acute period of severe CCT was to achieve the following ultimate goals: improvement of the neurological state, regression of both axial and lateral dislocation due to the data of computed tomography, intracranial pressure below 20 mm Hg, cerebral perfusion pressure within 50-70 mm Hg (within 60-80 mm Hg during the operation), elimination of oligemia according to the data of transcranial dopplerography (TCDG), SaO_2 98-100%, PaO_2 100-150 mm Hg, $PaCO_2$ 36-42 mm Hg

Decompressive craniectomy (DC) was performed in 75 patients with severe cerebral edema and intracranial hypertension. Indications for the performation of DC were: pronounced one-sided or two-sided cerebral edema with combined focal lesions, displacement of median brain structures over 10 mm; signs of axial dislocation (compression or absence of mesencephalic cistern), multiple foci of the cerebral contusion with pronounced perifocal edema and ICH.

Registration of the Indicators of Intracranial Pressure

All patients were hospitalized with the insertion of a parenchymal device for measuring ICP. Measurements of ICP were performed using the Brain Pressure Monitor REF HDM 26.1/FV500 manufactured by Spiegelberg (Hamburg, Germany). The ICM monitoring by parenchymal sensors was chosen because of its accuracy, simplicity of catheterizing, safety and low maintenance requirements [23]. The performed comparative analysis of the ICP values, measured simultaneously by parenchymal and ventricular devices for Spiegelberg with a standard ventricular catheter (the "gold standard") showed similar data in the range of measurement from 5 to 50 mm Hg. [24].

The ICP measurement sensor was set in all patients employing Kocher's point. In the case of diffuse brain injury the device was installed in the non-dominant hemisphere of the brain, in the case of focal brain injury it was placed on the side opposite to the side of trepanation.

The ICP measurement monitor was connected to a personal computer with the RS232 interface using the licensed Spiegelberg collection program (version 7). This software provided visual evaluation of the form of the ICP wave, storage and processing of the received data. The ICP values were automatically saved in Excel spreadsheet format. Every minute systolic, diastolic and secondary ICP were recorded. Each value represented a median of 12 ICP values taken with an interval of 5 seconds.

In general 11657 hours of observing ICP were recorded. The duration of the ICP monitoring ranged from 1 to 18 days, it took 116,6 ± 62 hours on a patient on average. The grounds for removing the sensor were normal ICP values during a day (less than 20 mm Hg), positive dynamics of the neurological state and results of control computer tomography of the brain.

Analysis of the Results of the ICP Monitoring

The study revealed the dependence of the outcomes of treatment in two groups of patients (surviving/ died and favorable/adverse result) on the five main ICP parameters (dose, duration and intensity of ICH, average and maximum ICP levels for the whole period of observation). Taking into consideration different thresholds for defining ICH (15, 20, 25, 30 mm Hg), the analysis covered 14 indicators of ICP. To fix the maximum ICP value its measurement was to continue at least for 5 minutes.

The ICH dose was the area of the figure on the ICP timetable. The top border of the figure was the curve of ICP, its button border was the horizontal line on the level of the ICP threshold value. The area of exceeding the ICP thresholds was defined as the integral of the function (mm Hg x Hour).

The ICH dose is the generally accepted indicator determined by the area under the curve (AUC) of the ICP dependence on time. Taking into account both intensity and duration of brain injury this criterion reflects the effect of secondary brain lesions on results more accurately than the ICP average and maximum levels [25].

The ICH duration was defined as the period of exceeding the ICP threshold [26]. The ICH duration was measured in hours.

In our study we proposed to use a new parameter for assessing intracranial pressure, which we called the intensity of intracranial hypertension.

The ICH intensity was equal to the average value of exceeding the ICP threshold for the whole period of ICH. For example, the ICH intensity in the case of the ICP ultimate level of 15 mm Hg was calculated by the formula:

The ICH intensity of the ICP ultimate level of 15 mm Hg = [(sum of ICP values higher than 15 mm Hg) - 15 × (number of ICP values higher than 15 mm Hg)] / (number of ICP values above 15 mm Hg).

For further analysis of the group of indicators responsible for the ICH characteristics (dose, duration and intensity consequently) were coded as follows: A1 marked “the ICH dose” (the area under the curve), A2 indicated “the ICH duration” and A3 denoted “the ICH intensity”. The symbol “ICP” (intracranial pressure) and the ICP threshold value (15, 20, 25, 30, 35 mm Hg) were added to the group code. Thus, the area under the curve in the case of the ICP ultimate level of 25 mm Hg was encoded as A1ICP25.

Statistical Analysis of Research Results

The received data were statistically analyzed in accordance with the requirements for processing the physiological information by the methods of biostatistics using the Microsoft Office programs Echcel-2003 (Microsoft Corporation, USA) and Statistica 7 (StatSoft) in obedience to the main research objectives.

We used the receiver operating characteristic (ROC) curve analysis [27] to define the optimal ICP threshold for the patients with the severe CCT. ROC curves reflect the effects of a number of threshold values, not just one of them. They are created when the threshold is changed in the decision-making process in a wide range of values. For each ultimate level sensitivity and specificity are calculated. The sensitivity is marked opposite the specificity, and both axes contain values from 0 to 1. The diagonal in the graph represents the null hypothesis, and the curve along this line shows that the used test can not provide a more correct answer than the randomly selected test. The ideal test line will approach ordinates, and at the point of a specific value it will go to the top of the graph defining both the points below which the test will be very accurate (the low level of false-positive results) and under them the points below which the test will be very sensitive (the low level of false-negative results). It is unlikely that any natural system is an ideal case, so the value of the test can be estimated by the distance between the diagonal and the curve.

The diagnostic accuracy of the test is determined by the area under the ROC curve, which corresponds to the probability that the randomly selected sample with a positive result has a higher value than the same sample with a negative result. Thus, the ROC curve analysis is a useful method for determining the way in which the change of the decision-making level affects both sensitivity and specificity of the test. Since the curve can describe the entire range of sensitivity and specificity pairs for certain thresholds, its level varies over the entire spectrum of possible values.

Therefore for each indicator we calculated the area under the curve (AUC), as well as sensitivity and specificity. The ICP threshold value was chosen on the condition of the maximum AUC, the cut-off for prediction of the consequences was established on condition of the maximum amount of sensitivity and specificity.

The conduct of this study was approved by the local ethics committee. In all cases the inclusion in the clinical study with the insertion of sensors for the ICP monitoring was confirmed with the written consents of the patients' close relatives.

Research Results

Within 6 months from the moment of injury 46 victims with the severe CCT died, accordingly, the mortality in the studied group of patients was 46%. Vegetative status was observed in 6 (6%) victims, deep disability was revealed in 13 (13%) patients, moderate disability was detected in 20 (20%) victims, good recovery was noted in 15 (15%) patients. Thus, a favorable outcome of treatment was achieved in 35 (35%) cases of the severe CCT.

During the insertion of the sensor in the examined patients the average ICP value was 34.8 ± 17.7 mmHg. In the studied group the minimum ICP value was 8.7 mm Hg, the maximum ICP value was 86 mm Hg. The ICH (the ICP value more than 20 mm Hg) was observed in 66 (79%) victims.

We calculated the average ICP score for the whole monitoring period for each patient. In 31% of the full observation impact the average ICP value was 10-15 mm Hg, in 71% of all observations the ICP value was below 20 mm Hg and in 29% of all the observed cases the ICP value was above 20 mm Hg.

For the whole monitoring period the average ICP value was calculated over 24-hour interval; it was designated as the average ICP. The highest average ICP level was observed during the first three days of monitoring. On the first day of monitoring the average ICP was 20.5 mm Hg, on the second day this value was 19.6 mm Hg, on the third day it was 17.1 mm Hg. From the fourth day, the average ICP value did not exceed 16 mm Hg.

We compared the average daily ICP values in surviving patients with the relevant data in those who died – the significant differences were noted only on the first 3 days of monitoring (Fig. 1). Thus, on the first day of monitoring the ICP value in the survivors was 16.1 ± 11.4 mm Hg on average, while the average ICP value in the deceased was 25.3 ± 15.2 mm Hg (E = 0.003); on the second day of monitoring the indicators were 14,6 ± 7,7 mm Hg and 25,2 ± 17,5 mm Hg respectively (E = 0.0003), on the third day of monitoring the data were (14.2 ± 7.4) mm Hg and 21.2 ± 15.2 mm Hg (P = 0.0056) respectively (E=0,0056). From the fourth day after CCT, there were no significant differences in the average ICP in surviving patients and those who died.

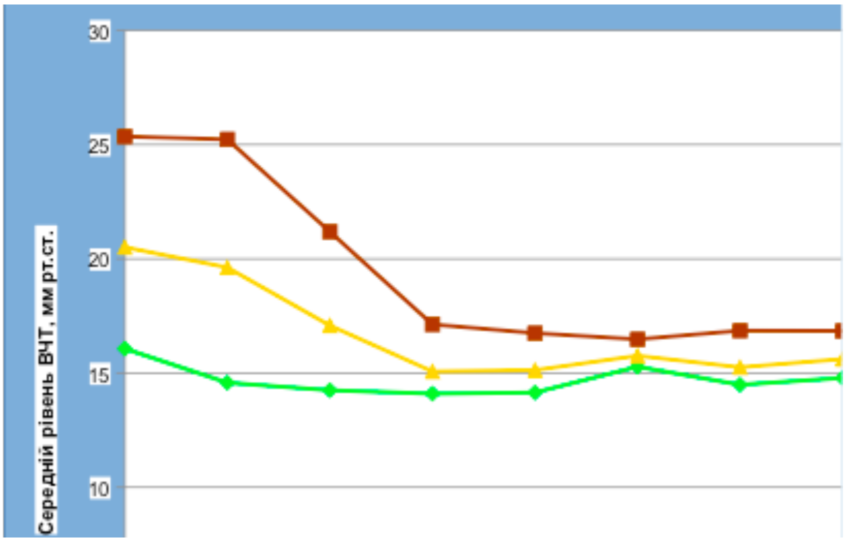

Fig.1 The Dynamics of the Average ICP Level During Monitoring

For the average and maximum ICP values in the definition of the treatment outcomes *survived / died* the ROC curves were constructed. For the average ICP value the study obtained new thresholds, differing from the generally accepted index of 20 mm Hg. Due to the results of the investigation the average ICP value as a classifier has a lower sensitivity than the maximum ICP with the relatively high specificity of the research. On the contrary the maximum ICP has a higher sensitivity with the low specificity of the study. The investigation established the optimal cut-off values for the average ICP against the criterion of the maximum amount of sensitivity and specificity. The cut-off value for the average ICP is 16.9 mm Hg. The sum of Se and Sp equals 1,426. The cut-off value for the maximum ICP is 31.35 mm Hg. The sum of Se and Sp equals 1,378. On the whole it can be concluded that the average ICP value is more significant criterion of both the sum of Se and Sp and the AUC than the maximum ICP value. Thus, we conclude that the average ICP value is considered to be more precise classifier of the patients according to the results of treatment *survived/died* than the maximum ICP value. For the prediction of favorable/adverse outcomes the average ICP value is 16.48 mm Hg.

For the variables of the average and maximum ICP the AUC value is less significant compared to the variables characterizing the ICH dose (A1ICP). Accordingly the quality of the classification of treatment outcomes for the average and maximum ICP variables is lower than the ICH dose.

The ROC curves were constructed separately for the two pairs of treatment results (survived/died, favorable/adverse outcomes). For the ICH duration the AUC value is 0.754, for the ICH dose the AUC value is 0.762, and for the ICH intensity the AUC value is 0.791. Among all variables for which the analysis was performed. The highest AUC value (0.791) was obtained for A3ICP15. Therefore the ICH intensity is the best classifier against the AUC criterion for the ICP threshold of 15 mm Hg. (Fig. 2) The cut-off value for A3ICP15 is 7.38 mm Hg. In this case the sum of Se and Sp is 1.541 (Se = 0.652, Sp = 0.889). Thus the average value of exceeding the ICP threshold level of 15 mm Hg which is equal to 7.38 mm Hg allows to distribute patients due to the treatment results *survived/ died* in the best way.

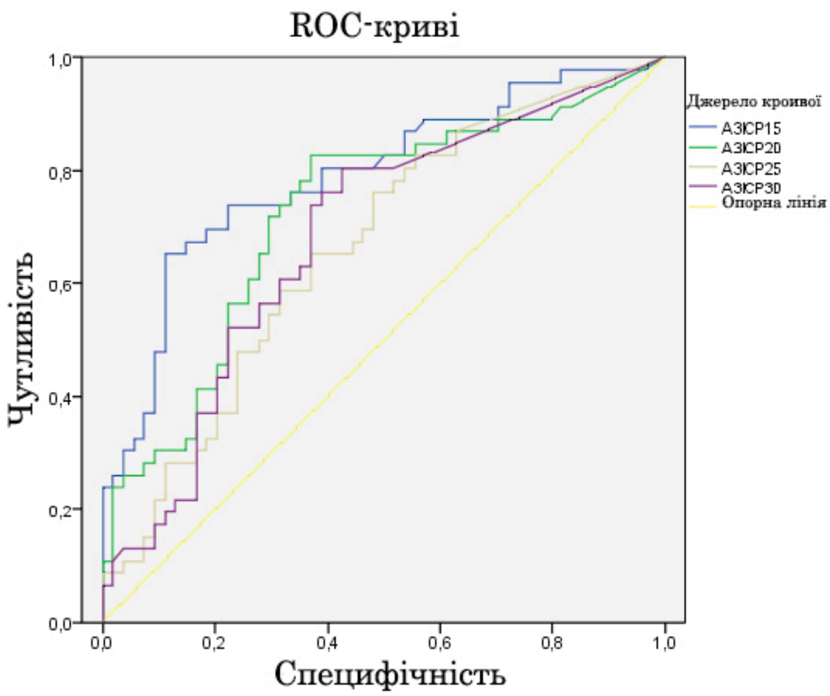

Fig.2. The ROC-Curves of the ICH Intensity for the Treatment Outcomes Survived/Died for Different ICP Threshold Values

For favorable and adverse treatment outcomes ROC-curves were constructed. For the ICH duration the AUC value is 0.713, for the ICH dose the AUC value is also 0.713 and for the ICH intensity the AUC value is 0.721. As well as for the pair of treatment outcomes *survived/died* the investigation established the maximum AUC value (0.721) for the ICH threshold of 15 mm Hg (Fig. 3). The cut-off value for A3ICP15 is 7.06. The sum of Se and Sp equals 1.437 (Se = 0.523, Sp = 0.914). Thus, the average value of exceeding the ICP threshold level of 15 mm Hg, which is 7.06 mm Hg allows to distribute patients due to favorable and adverse treatment outcomes in the best way.

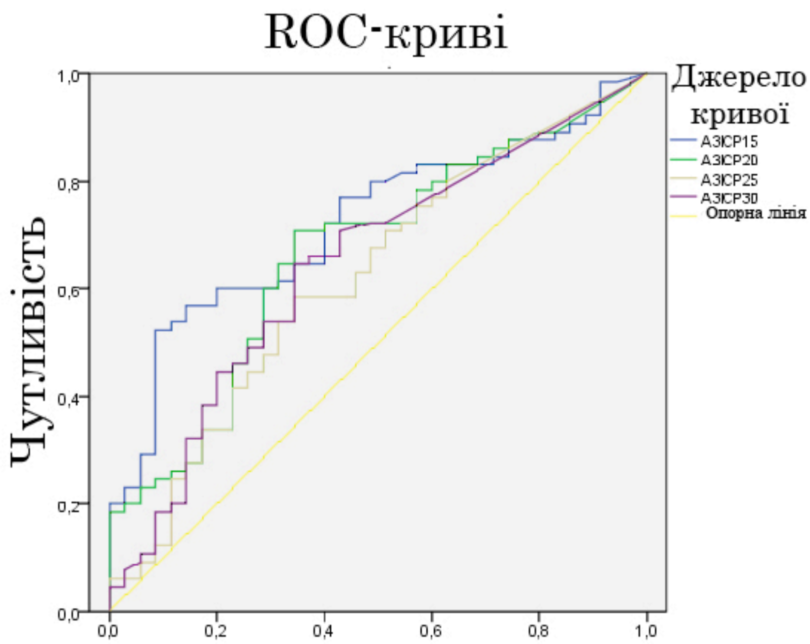

Fig.3 ROC-Curves of the ICH Intensity for Favorable and Adverse Treatment Outcomes

Discussion of Results

We constructed ROC curves for several ICP threshold values. In our analysis there are two cut-off levels for each curve: one of them is related to the ICH definition, and the second level is connected with each individual variable, as in any ROC analysis. For each observation the research selected the threshold value of the corresponding variable, provided that the maximum amount of the test sensitivity and its specificity was established. The study used the area under the ROC curve as an indicator of the quality of classification for each observed case selecting for each variable the ICH threshold value correlated with the construction segment where the area under the curve was larger. The curves were constructed for two categories of treatment results marked by the taxonomies *survived/died* and *favorable/adverse* outcome.

Thus, we constructed the ROC curves for five groups of variables (dose, duration, intensity of the ICH, average and maximum ICP). The evaluation was carried out according to the AUC value. The best characteristics of the classifier (the maximum AUC) in the ICH intensity was revealed with the ICP threshold of 15 mm Hg. This ICP level defines the concept of ICH in this case. Groups of patients with two different treatment results (survived/died and favorable/adverse outcomes) most likely differ in terms of the ICH intensity, namely, due to the average value of exceeding the ICP threshold level of 15 mm Hg. The average value of exceeding the ICP threshold level of 15 mm Hg which is about 7 mm Hg (7.38 for the results *survived/died*; 7.06 for *favorable/adverse* outcomes) should be recognized as the most significant prognostic criterion for the differentiation of patients with different outcomes of treatment.

The results of both ROC analysis and determination of odds ratios testify that the average ICP values for the distribution of treatment outcomes are lower than the indicator established earlier (20 mm Hg). As a result, the therapeutic concept based on 20 mm Hg as an established but not proven threshold for intensive care should be reviewed, and the further studies require thresholds based on evidence.

The received ICP level ranged from 16.48 mm Hg. (for *favorable/adverse* outcomes of treatment) to 16.9 mm Hg (for the results *survived/died*). As the achievement of favorable treatment outcomes is more important than the avoidance of lethal effects, the average ICP level of 16.5 mm Hg may be chosen as a new therapeutic endpoint. But the received data do not yet prove that the reduction of the ICP level below the proposed level is clinically useful.

It was really unexpected that the average ICP values for both groups *survived/died* and *favorable/adverse* outcomes were less than 20 mm Hg. In general, it is recommended to use the ICP threshold of 20-25 mm HG as an ultimate, above which the additional therapy should be considered as a complementary program of treatment. However, the evidence of Level 1 is not sufficient to formulate the highly proved recommendations because of the lack of studies. Nevertheless, we are confident that our study has produced reliable and exhaustive data on the significance of different parameters and thresholds of ICP and will provide an impetus for further in-depth studies of this topic.

Our research offers new perspectives on the changes in existing recommendations for the definition of the ICP thresholds in the treatment of patients with the severe CCT. Having performed the in-depth analysis of both results of our own research and literature data, we found that one of the reasons for the relatively low ICP values in the studied group of patients was the high percentage of patients who had undergone decompressive craniectomy in the acute period after CCT. Patients with DC accounted for 77% of observations. Decompressive craniectomy is a surgical method for the correction of intracranial hypertension, which is currently experiencing its second birth [28, 29].

The interesting results of studying this issue were presented by Sauvigny T. [30]. The researchers analyzed the average ICP values in the first 168 hours after decompressive craniectomy in patients with the severe CCT. In the group with favorable outcomes (the estimation on modified Renkin's score (mRS) ≤4) the average ICP value was 10.9 mm Hg compared with 15.8 mm Hg in the group of adverse treatment outcomes (mRS 5-6) (E <0.001). Moreover, the average ICP level was lower than 20 mm Hg in patients with favorable and unfavorable results of treatment after DC for a heart attack in the basin of the middle cerebral artery. Having found the extremely low ICP values in both groups of patients after DC, the authors emphasized the lack of a reassessment of the ICP threshold values that would be used as the recommended ICP thresholds in future studies.

A low ICP level predicted by DC may result in the lack of evidence in favor of both ICP monitoring and intensive care aimed at maintaining certain ICP values [31, 32, 33]. Despite the fact that the lower ICP thresholds had been already discussed as the endpoints in post-DC patients, this discussion did not have a significant impact on existing recommendations and further studies [28, 34, 35, 36].

Since the ICP values may differ significantly in patients with unharmed skull in the future the critical ICP thresholds should be separately analyzed in the subgroups of patients undergone the DC and not undergone the decompressive surgical interventions. As a result, this approach may lead to the individualization of the ICP thresholds depending on whether the DC was performed or not. In addition, the ICP threshold value for each individual patient may not be the same throughout the period of observation. For each patient the optimal decision is the definition of the time-dependent ICP threshold, which can be confirmed by other indicators of the multimodal neurophysiological monitoring (cerebral oxygenation, cerebral perfusion pressure, PRx-index).

We understand that the treatment based upon the new ICP threshold values proposed by us can have a positive effect on the clinical outcomes. This assumption requires the compulsory verification in the future multicenter prospective randomized investigations. An extremely important result of our study is the establishment of the fact that such parameters as the intensity and dose of intracranial hypertension are more informative than the widely used indicator generalizing the average ICP level for the whole monitoring period. The study of these parameters in the acute period of CCT will provide new knowledge in the sphere of pathophysiology of intracranial hypertension defining new therapeutic targets for patients with thesevere CCT.

Conclusion

The threshold value of the average ICP for the prediction of the survival/death rate in our study is 16.9 mm Hg. The average ICP value for the prediction of favorable/adverse results is 16.48 mm Hg. The most prognostic value for the prediction of the treatment outcomes is the ICH intensity during the whole period of treatment (the average excess of the ICP threshold level of 15 mm Hg). The average value of exceeding the ICP threshold level of 15 mm

Hg is the most significant prognostic criterion for the differentiation of patients due to the treatment outcomes. The excess achieving 7.38 mm Hg allows to distribute patients due to the treatment results *survived/ died* in the best way. The excess of 7.06 mm Hg allows to distribute patients due to favorable and adverse treatment outcomes in the best way.

References:

[1] Roozenbeek B., Maas A.I.R, Menon D.K. Changing patterns in the epidemiology of traumatic brain injury. Nat Rev Neurol. 2013; 9: 231–6. https://doi.org/10.1038/nrneurol.2013.22 PMID: 23443846.

[2] Tagliaferri F., Compagnone C., Korsic M., Servadei F., Kraus J. A systematic review of brain injury epidemiology in Europe. Acta Neurochir (Wien). 2006; 148: 255–68; discussion 268. https://doi.org/10.1007/ s00701-005-0651-y PMID: 16311842.

[3] Stein S.C, Georgoff P., Meghan S., Mizra K., Sonnad S.S. 150 Years of Treating Severe Traumatic Brain Injury: a Systematic Review of Progress in Mortality. J Neurotrauma. 2010; 27: 1343–53. https://doi.org/ 10.1089/neu.2009.1206 PMID: 20392140.

[4] ICP management in patients suffering from traumatic brain injury: a systematic review of randomized controlled trials / P. Abraham, R.C. Rennert, B.C. Gabel et al. // Acta Neurochir. - https://doi.org/10.1007/s00701-017-3363-1. -Published online 20 October 2017.

[5] Shen L., Wang Z., Su Z., Qiu S., Xu J., Zhou Y., et al. (2016) Effects of Intracranial Pressure Monitoring on Mortality in Patients with Severe Traumatic Brain Injury: A Meta-Analysis. PLoS ONE 11(12): e0168901.doi:10.1371/journal. pone.0168901.

[6] Han J., Yang S., Zhang C., Zhao M., Li A. Impact of intracranial pressure monitoring on prognosis of patients with severe traumatic brain injury. A PRISMA systematic review and meta-analysis/ Medicine. - Vol. 95. - Number 7. - P. 1-8. http://dx.doi.org/10.1097/MD.0000000000002827.

[7] Talving P., KaraManos T., Teixeira P., Skiada D., lam L., Belzberg G., Inaba K / Intracranial pressure monitoring in severe head injury: compliance with Brain Trauma Foundation guidelines and effect on outcomes: a prospective study // J Neurosurg / August 23, 2013/ http://thejns.org/doi/abs/10.3171/2013.7.JNS122255).

[8] Tang A., Pandit V., Fenkell V., Jones T., Joseph B., O'Keeffe T. et al. Intracranial pressure monitoring in patients with traumatic brain injury / Journal of surgical research. - XXX (2014). P. - 1-6 / http://dx.doi.org/10.1016/j.jss.2014.11.017.

[9] Forsyth R.J., Raper J., Todhunter E. Routine intracranial pressure monitoring in acute coma. CochraneDatabaseof SystematicReviews

2015, Issue 11. Art.No.: CD002043. DOI: 10.1002/14651858.CD002043.pub3.

[10] Adams H., Donnelly J., Czosnyka M., Kolias A.G., Helmy A., Menon D.K., et al. (2017) Temporal profile of intracranial pressure and cerebrovascular reactivity in severe traumatic brain injury and association with fatal outcome: An observational study. PLoS Med 14(7): e1002353.https://doi.org/ 10.1371/journal.pmed.1002353

[11] Dias C., Silva M.J., Pereira E., Monteiro E., Maia I., Barbosa S., et al. Optimal Cerebral Perfusion Pressure Management at Bedside: A Single-Center Pilot Study. Neurocrit Care. 2015; https://doi.org/10.1007/ s12028-014-0103-8 PMID: 25566826

[12] Cerebrovascular pressure reactivity monitoring using wavelet analysis in traumatic brain injury patients: A retrospective study/ X. Liu, J. Donnelly, M. Czosnyka et al. / PLOS Medicine | https://doi.org/10.1371/journal.pmed.1002348. - July 25, 2017.

[13] Carney N., Totten A.M., O'Reilly C., Ullman J.S., Hawryluk G.W.J, Bell M.B. et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Editio// Neurosurgery 0:1–10. - 2016. - DOI: 10.1227/NEU.0000000000001432, www.neurosurgery-online.com.

[14] Sorrentino E, Diedler J, Kasprowicz M, et al. Critical thresholds for cerebrovascular reactivity after traumatic brain injury. Neurocrit Care. 2012;16 (2):258-266.

[15] Kostic A., Stefanovic I., Novak V., Veselinovic D., Ivanov G., Veselinovic A. Prognostic significance of intracranial pressure monitoring and intracranial hypertension in severe brain trauma patients. Med Pregl. 2011;64(9-10):461-465. PMID: 22097111.

[16] Kuo J.R., Yeh T.C., Sung K.C., Wang C.C., Chen C.W., Chio C.C. Intraoperative applications of intracranial pressure monitoring in patients with severe head injury. J Clin Neurosci. Feb 2006;13(2):218-223. PMID: 16459087.

[17] Disability after severe brain injury: observations on the use of the Glasgow Outcome scale / B. Jennett, J. Snok, M.R. Bond [et al.] // J. Neurol. Neurosurg. Psychiat. — 1981. — Vol.44. — P.285–293.

[18] Jennett B. Assessment of outcome after severe brain damage. A practical scale / B. Jennett, M. Bond // Lancet. — 1975. — Vol.1. — P.480–484.

[19] Wilson L. Structured interviews for the Glasgow Outcome scale and the Extended Glasgow Outcome scale: Guidelines for their use / L. Wilson, L. Pettigrew, G. Teasdale // J. Neurotrauma. — 1998. — Vol.15, N8. — P.573–585.

[20] A new classification of head injury based on computerized tomography / L.F. Marshall, S.B. Marshall, M.R. Klauber [et al.] // J. Neurosurg. — 1991. — Vol.75, suppl. — P.14–20.

[21] Prediction of outcome in traumatic brain injury with computed tomographic characteristics: a comparison between the computed tomographic classification and computed tomographic predictors / A.I. Maas, C.W. Hukkelhoven, L.F. Marshall [et al.] // Neurosurgery. — 2005. — Vol.57. — P.1173–1182.

[22] Prognostic value of computerized tomography scan characteristics in traumatic brain injury: results from the IMPACT study / A.I. Maas, E.W. Steverberg, I. Butcher [et al.] // J. Neurotrauma. — 2007. — Vol.24. — P.303–314.

[23] Zacchetti L, Magnoni S, Di Corte F, Zanier ER, Stocchetti N: Accuracy of intracranial pressure monitoring: systematic review and meta-analysis. Crit Care 19:420, 2015.

[24] Experimental evaluation of the Spiegelberg intracranial pressure and intracranial compliance monitor. Technical note / Y.H. Yau, I. Piper, R.E. Clutton et al. // J. Neurosurg. – 2000. – Vol. 93. – P. 1072-1077.

[25] Relationship of dose of intracranial hypertension to outcome in severe traumatic brain injury / A. Vik, T. Nag, O.A. Fredriksli et al. // J. Neurosurg. – 2008. – Vol. 109. – P. 678-684.

[26] Time course of intracranial hypertension after traumatic brain injury / N. Stocchetti, A. Colombo, F. Ortolano et al. // J. Neurotrauma. – 2007. – Vol. 24. – P. 1339-1346.

[27] Chambers I.R. Determination of threshold levels of cerebral perfusion pressure and intracranial pressure in severe head injury by using receiver-operating characteristic curves: an observational study in 291 patients / I.R. Chambers, L. Treadwell, A.D. Mendelow // J. Neurosurg. – 2001. – Vol. 94. – P.412–416.

[28] Hutchinson P. Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of intracranial pressure (RESCUEicp). ISRCTN66202560. DOI 10.1186/ISRCTN66202560. ISRCTN Registry 2005; http://www.isrctn.com/ISRCTN66202560.

[29] Cooper D.J., Rosenfeld J.V., Murray L., Arabi Y.M., Davies A.R., D'Urso P., et al: Decompressive craniectomy in diffuse traumatic brain injury. N Engl J Med 364:1493–1502, 2011.

[30] Sauvigny T., Göttsche J., Czorlich P., Vettorazzi E., Westphal M, Regelsberger J. Intracranial pressure in patients undergoing decompressive craniectomy: new perspective on thresholds/ J. Neurosurg. - April 14, 2017. - P. 1-9. https://thejns.org/doi/suppl/10.3171/2016.11.JNS162263.

[31] Chesnut R.M. Intracranial pressure monitoring: headstone or a new head start. The BEST TRIP trial in perspective. Intensive Care Med 39:771–774, 2013.

[32] Chesnut R., Videtta W., Vespa P., Le Roux P. Intracranial pressure monitoring: fundamental considerations and rationale for monitoring. Neurocrit Care 21 (Suppl 2):S64–S84, 2014.

[33] Chesnut R.M., Temkin N., Carney N., Dikmen S., Rondina C., Videtta W., et al: A trial of intracranial-pressure monitoring in traumatic brain injury. N Engl J Med 367:2471–2481, 2012.

[34] Bratton S.L., Chestnut R.M., Ghajar J., McConnell Hammond F.F., Harris O.A., Hartl R., et al: Guidelines for the management of severe traumatic brain injury. VIII. Intracranial pressure thresholds. J Neurotrauma 24 (Suppl 1):S55–S58, 2007 (Erratum in J Neurotrauma 25:276–278, 2008).

[35] Chesnut R., Videtta W., Vespa P., Le Roux P.: Intracranial pressure monitoring: fundamental considerations and rationale for monitoring. Neurocrit Care 21 (Suppl 2):S64–S84, 2014.

[36] Eisenberg H.M., Frankowski R.F., Contant C.F., Marshall L.F., Walker M.D.: High-dose barbiturate control of elevated intracranial pressure in patients with severe head injury. J Neurosurg 69:15–23, 1988.