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Significance of ICP-related parameters for the treatment and outcome of severe traumatic brain injury

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Abstract

Objective: To analyze the significance of intracranial pressure (ICP)-related parameters on outcome in patients with severe traumatic brain injury. The ICP-related parameters included ICP, ICP dose (DICP), regression of the correlation coefficient between amplitude and pressure (RAP), pressure reactivity index (PRx), and cerebral perfusion pressure (CPP).

Methods: A retrospective analysis was performed using clinical information from 29 patients with severe traumatic brain injury who were admitted to the Department of Neurosurgery from January 2018 to January 2019. All patients underwent ICP probe implantation after admission. Patients were followed up for 6 months after discharge, and were categorized into either the favorable or unfavorable outcome group based on their Glasgow Outcome Scale score. The differences in ICP, DICP, RAP, PRx, and CPP between the two groups were analyzed for their effects on outcome.

Results: The average ICP, DICP, PRx, and RAP values in patients with favorable outcomes were significantly lower than in patients with unfavorable outcomes, while CPP values were significantly higher in the favorable outcome group.

Conclusion: Average ICP, DICP, PRx, RAP, and CPP values may indicate disease status and relate to patient outcomes. It is important to use multiple parameters to predict patients' disease severity and prognosis.

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Introduction

Neurosurgeons play a critical role in managing traumatic brain injury (TBI). TBI has a high disability and mortality rate, and is a major cause of disability and death in young people.[1] Intracranial pressure (ICP) increases during the progression of TBI. This increase in ICP can lead to insufficient effective circulatory blood volume, decreased cerebral perfusion pressure (CPP), and secondary injuries such as ischemia and necrosis of the brain parenchyma; it can also endanger patients' lives.[2] Hence, ICP monitoring may indirectly indicate intracranial disease progression in real time. Information such as ICP, CPP, and cerebrovascular compliance might help to guide treatment strategies and determine patient outcomes.[3,4] However, ICP monitoring in most hospitals currently only focuses on ICP values. This monitoring has shortcomings that include incomplete information about ICP data and external factors affecting ICP values, and information data lag.[5] Thus, a range of ICP-derived values have recently attracted considerable attention, including the ICP dose (DICP), CPP, pressure reactivity index (PRx), and the regression of the correlation coefficient between amplitude and pressure (RAP). Of these, the DICP represents the area below the curve and above the threshold. The PRx represents the correlation between ICP and arterial blood pressure, and the RAP represents the correlation between ICP amplitude and ICP.[6]

The main aim of the present study was to investigate whether average ICP, DICP, CPP, PRx, and RAP values were associated with disease progression, and whether they might contribute to the treatment and outcome of severe TBI.

Materials and methods

Clinical information

A retrospective analysis was performed using clinical information from ICP monitoring and related data. These data were obtained from patients with severe TBI who were admitted to the Department of Neurosurgery in our hospital between January 2018 and January 2019. Inclusion criteria were as follows: 1) patients had severe TBI; and 2) patients agreed to ICP probe implantation and data collection after admission. Exclusion criteria were as follows: 1) patients had cerebral hernia or other trauma that seriously affected their survival; 2) patients had severe hypertension, heart disease, liver or kidney failure, respiratory failure, or other diseases affecting outcome; or 3) patients had intracranial arteriovenous malformations, severe coagulation dysfunction, or other diseases that can induce secondary intracranial hemorrhage. The patients were divided into two groups based on their GOS scores at 6 months after discharge. The unfavorable outcome group had GOS scores of 1 to 3, while the favorable outcome group had GOS scores of 4 or 5.

ICP, DICP, CPP, PRx, and RAP analysis

After admission, ICP probes (Johnson & Johnson, New Brunswick, NJ, USA) were implanted in all patients using appropriate surgical procedures. ICP-related data were collected using the Neumatic system (Shanghai Haoju Medical Technology Co. Ltd., Shanghai, China) and transmitted to a server for storage in real time. The measurement intervals for all data were 3s (Figure 1). The ICP probes ware removed after 3 days, and the continuous acquisition data were stored in a microcomputer. The average ICP, DICP, CPP, PRx, and RAP values were analyzed, and any differences between the favorable and unfavorable outcome groups were compared.

For the average ICP, PRx, and RAP values, 1-hour intervals were considered for the time points, and the corresponding averages for ICP, PRx, and RAP were then calculated. The CPP was calculated as follows: CPP = mean arterial pressure – ICP. For the DICP values, a graphical representation of the continuously collected ICP data was generated. The DICP was taken as the area under the curve and above the threshold. During TBI treatment, the ICP threshold was set at 22 mmHg, based on the US Guidelines for the Management of Severe Traumatic Brain Injury (4th edition),[7] and was used as secondary grade evidence.[8] Hence, this study mainly focused on DICP with a

Figure 1. ICP-related data displayed by real-time monitoring in the Neumatic system.
CPP, cerebral perfusion pressure; BP, blood pressure; ICP, intracranial pressure; RAP, regression of the correlation coefficient between amplitude and pressure; PRX, pressure reactivity index.

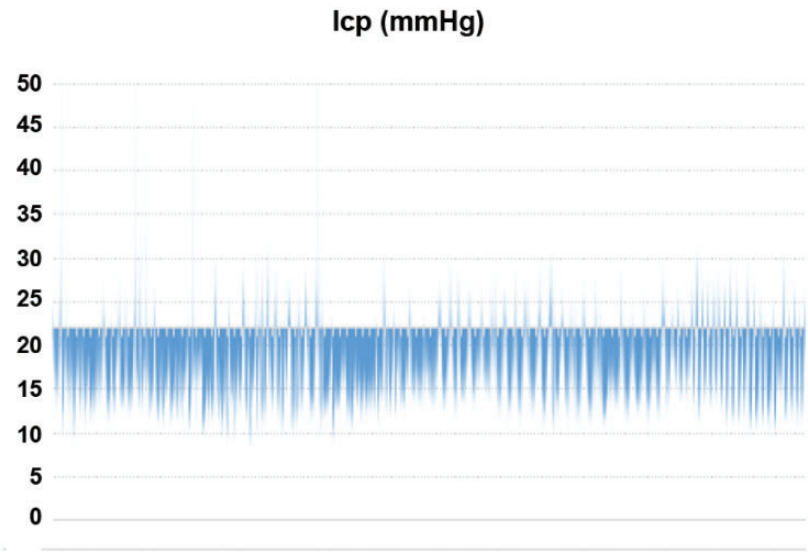

Figure 2. The area under the curve above the threshold (ICP = 22 mmHg).
ICP, intracranial pressure.

threshold of 22 mmHg (hereafter referred to as DICP22) (Figure 2).

Statistical analysis

SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Data that conformed to a normal distribution were represented as the mean ± standard deviation, and the Student's t-test was used for the analysis. Data that did not conform to a normal distribution were represented as the median (interquartile range), and the Mann–Whitney U test was used to compare between the two groups. Categorical date were represented as percentages or cases, and the χ^2 test was used for analysis. $P < 0.05$ was considered statistically significant.

Ethics

The study protocol was approved by the Ethics Committee of Lishui People's Hospital. All participants provided written informed consent.

Results

Of the 29 patients included in this study, 16 had a favorable outcome and 13 had an unfavorable outcome (Table 1). There were no significant differences in sex, age, or GCS scores at admission between the favorable and unfavorable outcome groups. The average ICP, DICP22, PRx, and RAP in patients with favorable outcomes were significantly lower than in patients with unfavorable outcomes ($P = 0.002$, $P = 0.001$, $P < 0.01$, and $P < 0.01$, respectively). In addition, CPP in patients with unfavorable outcomes was significantly lower than in patients with favorable outcomes ($P < 0.01$).

The distribution of DICP22 data in patients with favorable outcomes was more concentrated compared with the data from patients with unfavorable outcomes. DICP22 values in patients with favorable outcomes were significantly lower than in patients with unfavorable outcomes (Figure 3). The range of DICP22 values was from 20.87 to 459.56 mmHg * h in the favorable outcome group, and from 55.21 to 789.58 mmHg * h

Table 1. General characteristics and comparison of ICP-related derivative parameters.

Groups	N	Sex (M/F)	Age (years)	GCS score at admission	Average ICP (mmHg)	DICP22 (mmHg*h)	PRx	RAP	CPP (mmHg)
Patients with unfavorable outcomes	13	8/5	58.85 ± 16.12	5.62 ± 1.33	29.02 ± 16.74	93.56 (242.22)	0.33 ± 0.12	0.38 ± 0.12	51.34 ± 11.10
Patients with favorable outcomes	16	10/6	57.31 ± 16.12	4.88 ± 1.54	11.22 ± 4.69	71.15 (126.57)	0.08 ± 1.00	0.12 ± 0.11	72.52 ± 7.87
Test value		$\chi^2 = 0.003$	t = 0.293	t = 1.389	t = 3.718	U = 32.000	t = 5.856	t = 5.831	t = 5.796
P		1.000	0.773	0.176	0.002	0.001	<0.001	<0.001	<0.001

Data are shown as the mean ± standard deviation or median (interquartile range).
ICP, intracranial pressure; DICP, ICP dose; PRx, pressure reactivity index; RAP, regression of the correlation coefficient between amplitude and pressure; CPP, cerebral perfusion pressure.

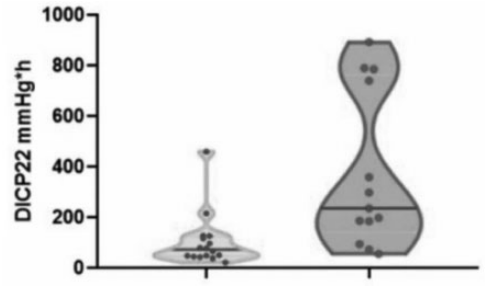

Figure 3. Comparison of detailed DICP22 data between the two groups.
DICP, intracranial pressure dose.

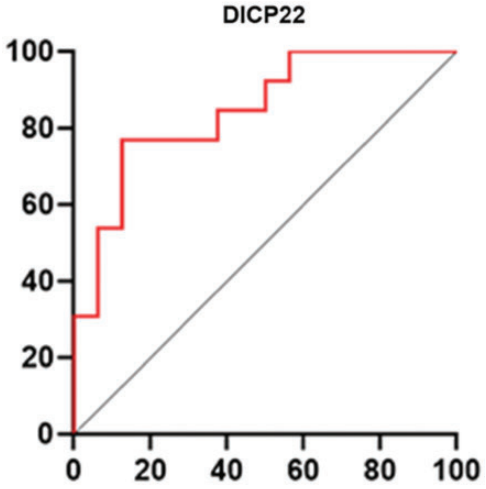

Figure 4. Results of the receiver operating characteristic curve for DICP22.
DICP, intracranial pressure dose.

in the unfavorable group. Receiver operating characteristic (ROC) curve analysis revealed that DICP22 had an area under the curve of 0.846 (95% Cl: 0.704–0.988, P = 0.0016). This was a statistically significant result, indicating that DICP22 was able to predict outcomes (Figure 4).

Discussion

Severe TBI has a high mortality rate. The main pathological feature of severe TBI is an increase in ICP, which leads to a

decrease in CPP and cerebral blood flow. This is usually followed by secondary manifestations, including hypoxic necrosis and cerebral ischemia. Further increases in ICP may even lead to brain hernia, which severely endangers patients' lives. Thus, ICP is considered a major factor associated with patient outcomes.[9–11] Several studies have reported that ICP monitoring can help to improve clinical efficacy and prognosis in patients with severe TBI, and can also reduce mortality rates.[12,13] Saiegh et al.[14] performed a retrospective analysis of clinical data from all TBI patients in the state (36,929 patients) who were over the age of 18 years and had GCS < 9, from January 2000 to December 2017. Compared with the non-ICP-monitored patients, the in-hospital mortality rate of patients with ICP monitoring was reduced by 25%.[14] Although ICP monitoring technology has been gradually popularized nationwide in China, many hospitals still rely on average ICP values to guide treatments and assess outcomes. Many experts in China and abroad recognize that ICP data have the shortcomings of incomplete information and data lag. It is therefore insufficient to rely on ICP alone to guide treatment strategy, and ICP-related derivative data need to also be taken into consideration. Patients' treatment plans and outcomes should be comprehensively assessed with reference to all relevant parameters, including PRx, RAP, and DICP22 (PRx and RAP data can be obtained, while DICP22 data need to be calculated twice).

Severe TBI can lead to space-occupying effects, mainly through hematomas and edema, resulting in damage or even the loss of cerebrovascular function. This condition is further aggravated by secondary oxygen deficiency and metabolic disorder. Thus, ICP may indirectly reflect the conditions of patients with intracranial hematomas and indicate intracranial disease progression during the early stages of TBI. ICP increases markedly with the appearance of intracranial conditions, and can therefore help as a real-time guide for clinicians to better handle treatments and effectively improve outcomes. Several studies have reported that ICP values can be used to guide the scientific use of dehydration drugs, such as mannitol, to effectively reduce the incidence of complications such as kidney injuries.[15] In this previous study, the average ICP value in the patients with favorable outcomes was 21.58 mmHg, while the average ICP value in the patients with unfavorable outcomes was 52.14 mmHg. When ICP values are over 22 mmHg, a certain dose of dehydrating agent intervention should be given rapidly. After dehydration treatment, ICP decreased slightly or even increased in some patients, suggesting that new intracranial hemorrhage may occur.[15] A computed tomography scan should be reexamined immediately to confirm whether new cerebral contusion has occurred, and interventions should be given. However, although timely intervention can reduce patient mortality, it cannot completely improve patient outcome. In the present study, the average ICP value of patients with favorable outcomes was significantly lower than that of patients with unfavorable outcomes. Patient outcomes vary with an increase in ICP. However, several researchers believe that DICP can be used to judge patient outcomes, and is superior to and more effective than ICP alone.[6,16] ICP only reflects the amplitude of ICP, but not the specific timespan of ICP increase in patients. A short-term high ICP in patients can also lead to an average ICP increase, and the outcome of such patients may be better than in patients with long-term high ICP.

DICP reflects the amount of time in which the ICP exceeds the threshold; that is, when the DICP is higher, it means that the ICP has exceeded the threshold for a

longer time, and the outcome is worse. Accordingly, our results demonstrated that the DICP22 in patients with favorable outcomes was significantly lower than in patients with unfavorable outcomes. The ROC curve reflects the reliability of these indicators. Our results demonstrated that DICP22 had a large area under the ROC curve, of 0.846. We therefore concluded that the DICP22 was a significant indicator of treatment and outcome for severe TBI. However, further studies are required to confirm whether or not DICP22 is a more reliable indicator than ICP. DICP is area data, and although it contains more information than ICP values, it does not accurately show the relationship between the extent by which the threshold is exceeded and the amount of time that the threshold is exceeded. Some patients had extremely high ICPs over a short period of time, and ICP was markedly decreased by symptomatic treatment, but still exceeded the threshold. However, these patients were able to access favorable outcomes. The DICP22 in these cases may be similar, or even higher, than the DICP22 values of patients who have a slightly elevated ICP for a long period of time. The outcome of these patients may be unfavorable. Therefore, in the present study, a small number of patients with favorable outcomes had relatively high DICP22 values. Together, these results suggest that more parameters need to be combined for analysis, such as PRx and RAP, which can more accurately reflect the autonomous regulation of cerebral blood.

A previous study has reported that PRx is a more reliable predictor of death than the ICP threshold.[17] The values of PRx range from –1 to 1. A negative value indicates that the trend of arterial blood pressure is opposite to that of the ICP. When arterial blood pressure decreases, the cerebrovasculature autoregulates the expansion of intracranial vessels, resulting in increased ICP; thus, this cerebrovascular autoregulatory function is beneficial. PRx is mainly used to dynamically evaluate the autonomous regulatory ability of cerebral blood,[18] and PRx values can also indicate disease severity. However, no consensus PRx threshold value has yet been agreed to. Several researchers have recommended 0.25 as an appropriate threshold for the treatment of TBI. In contrast, RAP values reflect cerebrovascular compliance, mainly by reflecting the cerebrospinal compensatory reserve capacity. A RAP value approaching 1 indicates a failure of cerebrospinal compensatory reserve capacity and a lack of cerebrovascular compliance. Conversely, a RAP value approaching 0 means that the ICP will not change markedly as a result of changes in cranial volume, thus indicating good cerebrovascular compliance and a large intracranial compensation space.[17,19]In the present study, both the PRx and the RAP values of patients with favorable outcomes were significantly lower than those of patients with unfavorable outcomes.

We should therefore judge patients' cerebrovascular autonomic regulatory function by combining PRx and RAP values when the DICP22 results cannot accurately judge disease severity or patient outcome. In the current study, the DICP22 of one patient with a favorable outcome was 21.58 mmHg * h. This value was markedly higher than the DICP22 values of most other patients in this group, and even higher than the DICP22 values of some patients with unfavorable outcomes. However, we cannot exclude this value as an accidental phenomenon, because this patient's average PRx and RAP values indicate relatively normal cerebrovascular compliance and autonomous regulation of cerebral blood. It is therefore reasonable to believe that this patient can obtain a favorable outcome. Because of the limitations of the research samples in the present

investigation, as well as of the current ICP monitoring technology, these results need confirming in future in-depth studies.

CPP can be derived by calculating the difference between mean arterial pressure and ICP, and reflects cerebral blood flow. Hence, CPP values indirectly reflect the nutritional status of the brain tissue as well as the response of cerebrovascular autoregulation to blood pressure fluctuations. Many researchers therefore believe that CPP is a more convincing indicator of cerebral blood flow than ICP. The US Guidelines for the Management of Severe Traumatic Brain Injury (4th edition) also suggests that CPP monitoring can reduce 2-week patient mortality, and is a Level IIB recommendation.[20,21]When CPP is maintained within a certain range, the body can tolerate an increase in ICP. At present, for the treatment of TBI, the target value for CPP is 60 to 70 mmHg. When CPP is less than 50 mmHg, automatic cerebrovascular regulation is lost, resulting in a rapid decrease of cerebral blood flow, as well as secondary brain injury caused by cerebral ischemia and hypoxia. This results in disease progression and unfavorable outcomes.[22] In the present study, the CPP of patients with favorable outcomes was significantly higher than that of patients with unfavorable outcomes. The patient mentioned in the previous paragraph, with the relatively high DICP22 value, had an average CPP of 68.15 mmHg, which means that their cerebral blood flow was good. Thus, although this patient's DICP22 data predicted an unfavorable outcome, the data from all of the other indexes indicated a favorable outcome. There is therefore no reason to regard the high DICP22 as an accidental event. This patient should be allowed to have a slightly high ICP, and their treatment should continue to be standardized to achieve a favorable outcome. Therefore, although most patient outcomes can be judged from a single indicator (e.g., ICP or CPP), we should combine multiple indicators to analyze patient outcomes and guide treatments to improve outcomes, especially when different indicators indicate changes in opposite directions.

In summary, ICP monitoring can be used to guide the treatment of severe TBI. Disease progression can be detected in a timely manner based on changes in related parameters, and effective treatment measures to minimize or even avoid secondary brain injuries can thus be determined to improve outcomes. The ICP-related derivative parameters ICP, DICP22, PRx, and RAP were lower in patients with favorable outcomes, while CPP was higher in patients with favorable outcomes. In addition, combined with ROC curve analysis, a DICP threshold of 22 mmHg had a high accuracy in judging patient outcomes. For the guidance and judgment of patients' disease severity and outcomes, the use of a single parameter is not always accurate; to obtain more accurate results we need to use multiple parameters.

Author contributions

Yuchun Pan and Yuanfeng Xue carried out the studies, collected the data, and drafted the manuscript. Zhiwen Ren and Jian Xu performed the statistical analysis and participated in its design. Penglai Zhao and Junhong Ding participated in the acquisition, analysis, or interpretation of the data and drafted the manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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