VILNIAUS UNIVERSITETAS
MEDICINOS FAKULTETAS

Baigiamasis darbas

SYSTEMATIC LITERATURE REVIEW OF OPTIMAL CEREBRAL PERFUSION PRESSURE-TARGETED TREATMENT IMPACT ON OUTCOMES AFTER SEVERE TRAUMATIC BRAIN INJURY

Raimondas Juškys

Klinikinės Medicinos Institutas

Neurologijos ir Neurochirurgijos Klinika

Darbo vadovas	**Dr. Aidanas Preikšaitis**
Konsultantas	**Prof. Dr. Jolanta Dadonienė**
Katedros arba Klinikos vadovas	**Prof. Dr. Dalius Jatužis**

2022-05-20

raimondas.juskys@mf.stud.vu.lt

ABSTRACT

Traumatic brain injury is closely associated with deterioration in cerebral autoregulation function. Maintaining cerebral perfusion pressure closer to the patient-specific "optimal" cerebral perfusion pressure (a derivative of arterial blood pressure and intracranial pressure monitoring data) was postulated to improve neurological outcome after brain trauma. This systematic review evaluates the link between optimal cerebral perfusion pressure deviations and outcomes in the traumatic brain injury population. In April 2021 we searched for eligible studies in MEDLINE, Cochrane Library Central Register of Controlled trials, ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform, and Web of Science databases. Studies addressing optimal cerebral perfusion pressure deviations effect on outcomes (i.e. neurological recovery and mortality rates) after traumatic brain injury were included. A net total of 18 studies met eligibility criteria for qualitative analysis. Although the collected data supports an idea that wider deviations from optimal cerebral perfusion pressure might lead to worse outcomes, the lack of quality of evidence and high level of risk of bias in the underlying studies were the main limiting factors preventing the establishment of decisive conclusions. The topic should be studied further in a controlled and well-designed fashion in order to lay an evidence-based foundation regarding the optimal cerebral perfusion pressure and clinical outcomes association.

Keywords: traumatic brain injury, optimal cerebral perfusion pressure, mortality, outcomes, systematic review

SANTRAUKA

Vienas iš galvos smegenų traumos patofiziologinių mechanizmų yra smegenų kraujotakos autoreguliacijos sutrikimas. Literatūroje aprašoma, jog smegenų perfuzinio slėgio palaikymas arčiau individualizuoto „optimalaus" smegenų perfuzinio slėgio (įvertis gaunamas iš arterinio kraujo spaudimo ir intrakranijinio slėgio matavimų) sietinas su geresne neurologine pacientų išeitimi. Šios sisteminės literatūros apžvalgos tikslas yra įvertinti nukrypimų nuo optimalaus smegenų perfuzinio slėgio bei išeičių ryšį galvos smegenų traumą patyrusių žmonių populiacijoje. 2021 metų balandį atlikta tinkamų studijų paieška MEDLINE, Cochrane Library Central Register of Controlled trials, ClinicalTrials.gov, World Health Organization Internation Clinical Trials Registry Platform ir Web of Science duomenų bazėse. Į tyrimą įtrauktos studijos, vertinančios nukrypimų nuo optimalaus smegenų perfuzinio slėgio įtaką pacientų išeitims (neurologinei funkcijai bei mirtingumui). Iš viso į kokybinę analizę įtraukta 18 studijų. Nors ir pacientams su didesniais smegenų perfuzinio slėgio svyravimais nuo optimalaus pasireiškė prastesnės išeitys, įtrauktų studijų įrodymų kokybė ir šališkumo rizika buvo pagrindiniai limituojantys veiksniai neleidžiantys prieiti prie tvirtų išvadų. Norint geriau suprasti optimalaus smegenų perfuzinio slėgio nuokrypių ir išeičių ryšį reikėtų daugiau gerai suplanuotų, kokybiškų, aukštu įrodymų lygiu pasižyminčių bei žemą šališkumo riziką išlaikančių tyrimų.

Raktažodžiai: galvos smegenų trauma, optimalus smegenų perfuzinis slėgis, mirštamumas, išeitys, sisteminė literatūros apžvalga

INTRODUCTION

Traumatic brain injury (TBI) is a sensitive public health problem which, directly or not, affects all societies across the globe. Current annual incidence of TBI is estimated to vary between 50 and 60 million cases worldwide, primarily affecting young adults and the elderly. Looking specifically into the developed countries, 1.1% of Americans and 0.5% of Europeans are experiencing a TBI each year. Fortunately, around 90% of those TBIs are classified as mild (1). In case of severe TBI, the case-fatality rate can reach up to the 40%, and those who survive are likely to exhibit a spectrum of permanent disability in physical, psychological, and social domains (2). TBI is a very complex and heterogenous clinical entity that can be grossly separated into the primary and secondary components. Although the primary injury is self-explanatory as it results from various physical forces exerting mechanical strain on a fragile cerebral tissue, secondary brain injury is characterized by a sophisticated cascade of intertwined molecular processes that begin within seconds following the primary insult. A vector of these biochemical events leads to a significant neurological injury in a form of cerebral ischemia and intracranial hypertension (3). Therefore, the central focus of severe TBI management is based on prevention of secondary brain injury by maintaining continuous cerebral blood supply and normal intracranial pressure (ICP).

The outcomes of patients with severe TBI depends on many variables and their complex interactions. Combination of primary traumatic insult severity, individual patient characteristics, prehospital and emergency department care, neurocritical management of secondary brain injury, and incidence of extracerebral complications all collectively shape a long-term result. Although the primary traumatic event is irreversible, secondary injury can be effectively mitigated by implementing various therapeutic strategies aimed at prevention of cerebral ischemia and alleviation of intracranial hypertension. In order to optimize and standardize the care of brain-injured, Brain Trauma Foundation (BTF) established a guidelines on severe TBI management (4). This has eased the decision-making process for the clinicians, but the main challenge in severe TBI remains the complexity and heterogeneity of the entire process of secondary brain injury. Consequently, there is no “one-fit-all” approach, and each individual patient requires a tailored, case-adjusted care plan in order to achieve the optimal result.

One of the therapeutic options focuses on optimization of cerebrovascular autoregulation (CA) and prevention of secondary ischemic injury. The ultimate goal of CA is to maintain adequate cerebral blood flow (CBF) in a context of transient fluctuations in cerebral perfusion pressure (CPP). This effectively protects the brain from both, ischemic and hyperemic insults. Defective CA is seen in up to 87% of patients following severe TBI, with both severity and duration of impaired cerebrovascular reactivity being associated with worse neurological outcomes among brain-injured (5–9). Similarly, a treatment based on cerebrovascular reactivity optimization and CPP individualization has shown to produce promising results, but currently available literature is dispersed and the latest evidence has not been synthesized (10–13). The goal of our study is to systematically appreciate currently published literature in order to depict how deviations of CPP from individualized CPP values impacts outcomes in TBI population.

Normal cerebrovascular autoregulation

Brain tissue is very sensitive to hypoxic and ischemic insults, requiring a constant supply of oxygen and glucose in order to maintain a normal neural functioning. CA represents a physiological mechanism that is purposed to maintain a constant CBF despite momentary fluctuations in CPP, generally by adjusting cerebrovascular resistance of intracranial vessels. Physiologically, this process is controlled by a combination of myogenic, metabolic, and neurogenic factors (5).

Myogenic reflexes simply represent an intrinsic ability of vascular smooth muscle to change in length by responding to transmural pressure variations. Vessels constrict or dilate in response to increased or decreased intravascular pressure, respectively. Myogenic response works within a CPP range of 50 to 150 mmHg. Normally, a decrease in CPP will lead to a reflex vasodilatation with a consequent increase in CBF and cerebral blood volume (CBV). Anyway, there is a limit to the maximal vasodilatory capacity (up to 65% of the baseline diameter). Further decrease in perfusion pressure will eventually reach a critical closure pressure, or a threshold, after which an arterial collapse ensues, ceasing the cerebral blood supply completely (14). Similarly, episodes of hypertension are followed by cerebral vasoconstriction in order to prevent the hyperemia. In case the autoregulatory limit is exceeded, a further increase in CPP can potentially lead to hyperemic injury or hemorrhage. Both, partial pressure of carbon dioxide ($PaCO_2$) and partial pressure of oxygen (PaO_2) in arterial blood have a profound effect on the global cerebrovascular resistance, albeit the impact of PaO_2 is less notable. Normal value of $PaCO_2$ is in a range of 35-45 mmHg, and it is estimated that for a 1 mmHg change in $PaCO_2$, a proportional, up to a 4% change in CBF follows. There is a positive correlation between $PaCO_2$ and CBF, as any case of hypercapnia will precipitate a vasodilatory response, increasing CBF and CBV. Similarly, hyperventilation will lead to a decrease in $PaCO_2$, causing vasoconstriction and decrease in CBF and CBV. This hyperventilation-induced hypocapnia can be used as a measure to reduce ICP, but diminished perfusion places the patient at increased risk of ischemic injury (15). On the other hand, changes in PaO_2 have less profound effect on CBF, and only in cases of marked hypoxemia (e.g. <50 mmHg), the vasodilatory response is observed (5).

Finally, neurogenic mechanisms influence on CA is simply reflected by sympathetic nervous system activity. The regulatory effect is mainly exerted on midsized vessels, owing to their dense innervation by sympathetic fibers. Rise in sympathetic tone ends up in vasoconstrictive effect, shifting the myogenic autoregulatory plateau towards higher pressures, whereas decrease in sympathetic output produces the opposite result. Most likely, intact neurogenic mechanism plays a significant role while responding to abrupt arterial blood pressure changes in order to mitigate the possibility of ischemic or hyperemic injury (16).

Cerebrovascular autoregulation in severe TBI

CPP is the main net force driving blood into the brain and is expressed as a difference between mean arterial blood pressure (MABP) and ICP. As ischemia is one of the most significant types of secondary brain injury, maintaining appropriate CPP is a goal of priority in the field of neurocritical care. A classical study using arterial occlusion model in awake monkeys revealed that an ischemic damage starts at a CBF threshold of 18ml/100g/min, and if not reversed early, inevitably leads to the infarction (17).

Interestingly, the threshold of ischemic injury decreases to a level of 20ml/100g/min following traumatic insult, reflecting the increased vulnerability of neural tissue to the CBF impairments among brain-injured (18). In addition to this, the cerebrovascular regulatory mechanisms are disturbed in up to 87% of severe TBI patients and can even occur if CPP and CBF measurements are within normal values (5). When CA is malfunctioning, a drop in CPP will be followed by a passive vasoconstriction, instead of active vasodilation, leading to a decreased CBF. This in fact decreases CBV and ICP, but leaves the brain exposed to a significant risk of cerebral hypoperfusion, especially if intracranial hypertension is concurrently present (19). In other words, cerebral blood supply becomes directly reliant on systemic blood pressure to move nutrients and oxygen through flaccid, non-reactive cerebrovascular system. Although lower CPP diminishes the blood volume in the brain and therefore ICP, ischemia triggers secondary brain injury cascade that leads to a diffuse cerebral edema. This results in an exponential rise of ICP once intracranial compensatory mechanisms are exhausted, further reducing CPP and establishing a deadly, self-propagating cycle (20). If this was not enough, elevated ICP on itself has a negative effect on vasomotor reactivity, additionally contributing to the TBI-induced dysregulation (21).

Combination of increased susceptibility to ischemic insults and defective CA leaves severe TBI patients highly vulnerable to hypotensive episodes, especially within first few hours following primary injury, when hemodynamic instability is most probable. Traditionally, it was shown that hypotension on admission, defined as systolic blood pressure (SBP) <90 mmHg, doubled the rate of mortality among severe TBI patients (22). Anyway, the recent retrospective study of 15,733 moderate-to-severe TBI patients concluded that the optimal threshold might be higher, and better outcomes could be achieved if SBP is maintained at ≥100 mmHg for patients 50 to 69 years old or at ≥110 mmHg for those who are 15 to 49 or ≥70 years of age (23). The same blood pressure goals are recommended by BTF guidelines (4). Anyway, the utility of absolute blood pressure values is limited to the prehospital and emergency room management, as advanced neurocritical centers should pursue a more individualized, case-tailored approach by adjusting treatment based on the information acquired from multimodal patient monitoring. Various parameters obtained from invasive ICP and CPP monitoring could be used to direct the treatment in a personalized manner, as patient-optimized thresholds represents an attractive therapeutic goal.

Monitoring and assessment of cerebrovascular autoregulation

Monitoring of ICP and CPP in severe TBI patients yields a real-time information about currently ongoing secondary injury processes, provides prognostic value, and allows to make timely therapeutic decisions with possibility to adjust the strategy over the course of treatment. In addition, parameters derived from continuous multimodal neuromonitoring can be used to assess CA functionality and even determine the optimal CPP, or a value at which cerebrovascular reactivity works best for the particular patient of interest, establishing an individualized treatment goal to maintain CPP as close to the optimal value as possible.

Invasive ICP monitoring and intracranial hypertension treatment is the cornerstone of severe TBI management. BTF guidelines advocates the placement of ICP monitoring system for all patients with severe TBI, and initiate the treatment if ICP persistently exceeds 22 mmHg (4). Additionally, ICP

monitoring offers an additional insight into waveform morphology and amplitude, allowing to evaluate pressure-volume compensatory reserve. The gold standard for ICP tracing is an intraventricular catheter – it accurately reflects global ICP values, is cheap, allows recalibration *in situ* and has a therapeutic advantage of cerebrospinal fluid drainage as one of the methods for ICP control. Anyway, intraparenchymal pressure transducers should not be seen as inferior to the intraventricular device. They fairly accurately represent the local ICP, carries lower hemorrhage or infection risk, and are easier to insert, especially in cases when diffuse cerebral swelling complicates external ventricular drain introduction. Other options include epidural, subdural, and subarachnoid catheters, but those are not as commonly used due to less reliable measurements provided (20).

Although the association between the intracranial hypertension and a poor outcome in severe TBI patients is well established, the evidence supporting ICP monitoring importance remains controversial (24). Several large observational studies concluded that utilization of invasive ICP monitoring improves short-term mortality rates, advocating for ICP-guided care of brain-injured (25–27). On the other hand, a multicenter randomized clinical trial (RCT) involving 324 severe TBI patients compared outcomes between two protocols: the first group utilized ICP monitoring to guide the treatment, whereas the second group management was solely based on clinical examination and serial imaging findings. The results were surprising: authors found that the ICP-guided management protocol with a goal to maintain ICP ≤20 mmHg was not superior to neurochecks and surveillance imaging in terms of 6-month mortality and functional outcomes (28). This raised the question whether the ICP monitoring is necessary in first place to direct the treatment of severe TBI. To address the question, an international panel of leaders in the field of neurocritical care issued a consensus statement, concluding that the study did not assess the efficacy of ICP-guided care, and this should not change the common practice and adherence to the guidelines. In addition, the experts emphasized that further research is warranted in order to determine patient-specific ICP thresholds and develop new paradigms of treatment based on data obtained from invasive monitoring (29). Despite the fact that ICP monitoring provides an invaluable information about intracranial pressure dynamics throughout the monitoring period, the absolute ICP thresholds set in range of 20-25 mmHg are based on low quality data and ignores the inter-patient variability of predominating secondary brain injury type (4). Therefore, the management based solely on ICP does not allow to adapt the treatment on case-to-case basis, and there is a need for a more sophisticated multimodal monitoring.

Nevertheless, simultaneous invasive monitoring of ICP and arterial blood pressure (ABP) allow to extract a continuous, real-time measurements of CPP. This parameter reflects the pressure gradient driving the blood into the brain and could be used as a surrogate marker for the delivery of oxygen and nutrients. BTF guidelines recommend the employment of CPP monitoring, with a goal to maintain CPP in a range of 60 to 70 mmHg while avoiding aggressive attempts to preserve CPP >70 mmHg with a liberal use of fluids and vasopressors, as such practice might increase the incidence of systemic complications (4,30). Interestingly, a retrospective cohort of 459 severe TBI patients focused on identification of CPP threshold values that are associated with best outcomes. Authors concluded that the optimal CPP threshold is 70 mmHg, but subgroup analysis revealed that patients with impaired autoregulatory status who had mean CPP <70 mmHg had a statistically significantly higher rates of mortality and unfavorable outcomes (31).

The results of the study question the reliability of the currently suggested threshold range of optimal CPP, as patients with impaired autoregulatory capacity might not be suitable for such approach. On the other hand, a prospective study involving 131 severe TBI adults came up with an opposite conclusion. Researchers compared two protocols in terms of 6-month outcomes: ICP-oriented therapy (maintaining ICP <20 mmHg and CPP as close to 60 mmHg) versus CPP-based approach (aiming to keep CPP >70 mmHg and ICP <25-30 mmHg). Patients with intact cerebrovascular reactivity did better in CPP-oriented group, as opposed to non-autoregulating patients, where CPP maintained at >70 mmHg led to a markedly worse results as compared to the CPP kept close to 60 mmHg (32). Although both studies provide the contradicting conclusions, authors agree that adherence to fixed CPP threshold might not be optimal for every patient and establishing the universal value is not realistic as there is no one-fit-all approach in medicine. Therefore, efforts to individualize the critical care of severely brain-injured, while taking into account the state of CA, seem rational and attempt worthy.

The mechanism of CA should not be seen as a static process which is either present or absent. Rather, it is better to envision it in a spectrum of dysregulation, starting from completely intact cerebrovascular reactivity, moving through a worsening degree of impairments, and finally ending in a total absence of vasomotor regulation. This continuum of abnormal autoregulatory responses also has a significant temporospatial variability, meaning it can fluctuate in its severity based on time of the day and throughout the injured brain itself (5,33). Therefore, continuous monitoring of CA status allows to evaluate the dynamic aspect of the regulatory capacity in a real-time, providing the possibility to adjust the treatment accordingly throughout the monitoring period. Generally, the assessment of autoregulation is based on minute-to-minute CBF (or CBV) changes in response to systemic blood pressure fluctuations. Although the direct evaluation of CBF is possible, the indirect route represents a more practical approach, as it is possible to estimate the state of vasomotor reactivity while analyzing the data acquired from invasive multimodal monitoring, which is an established standard of care in the first place (34). For example, ICP can be used as a surrogate marker of CBV in patients with a poor intracranial compliance. Combination of invasive, continuous ICP and ABP monitoring allows not only to extract momentary CPP values, but also provides a glance at CA functionality if collected data is utilized appropriately (35).

One of the most commonly used parameters to reflect a cerebral autoregulation status is a pressure reactivity index (PRx). This metric is calculated as a moving correlation coefficient between spontaneous slow waves of MABP and ICP, both extracted from continuous multimodal neuromonitoring data (36). Normally, a rise in ABP is followed by an increase in cerebrovascular resistance and thus, reduction in CBV and ICP. Anyway, non-autoregulating patients respond pressure-passively, and transient spikes in ABP are followed by concomitant hyperemia and rise in ICP. Therefore, negative PRx tracings (in a range of -1 to 0) suggest a normal vasomotor reactivity, whereas positive PRx values (in a range of 0 to +1) reflect an aberrant response and are in linear relationship with severity of autoregulatory derangement (21). Alternative surrogate marker of cerebrovascular reactivity is a mean flow index (Mx), which represents the effect of spontaneous CPP changes on cerebral blood flow velocity in middle cerebral artery as measured by transcranial Doppler. In general, both methods are reliable and reflect the same process, but PRx could be seen as more suitable for long-term monitoring given the ease of use and consistent data acquisition. In a

contrast, Mx use is mainly limited by the lack of reliable probe holders for continuous, prolonged Doppler velocimetry calculations (21,35).

The prognostic importance of PRx, as a derivative parameter reflecting autoregulatory status, is illustrated by various clinical studies. A retrospective study involving 459 severe TBI patients investigated the prognostic value of PRx: individuals with a mean PRx value above 0.25 throughout the monitoring period had a significantly higher mortality rates, whereas average PRx below 0.05 was associated with a favorable outcome (31). Similar results were found in a prospective cohort of 28 patients, where the critical PRx threshold of 0.24 was associated with a fatal outcome (7). The prognostic value of PRx remains significant even when the outcomes are adjusted for baseline admission characteristics and ICP, as demonstrated by a recent prospective multi-center cohort of 193 moderate-to-severe TBI patients (6). These studies provide the evidence that the state of CA is indeed closely related with the long-term outlook. However, there is a marked variance in a real-time PRx values throughout the monitoring period, and the averaged PRx neglects the potential impact of prolonged temporary episodes of critically impaired CA (when index is close to +1). This issue was addressed in a recent prospective study of 33 severely brain-injured adults. The authors concluded that even a single prolonged event of elevated PRx was associated with an adverse outcome at 6 months and showed stronger predictive value than the averaged PRx. The critical threshold separating non-survivors and survivors was a PRx above 0.7 for 40 minutes (9).

Optimal cerebral perfussion pressure calculation

Besides the prognostic value of PRx, the index can be used to establish an individualized, patient-specific treatment strategy. This concept is based on identification of optimal CPP (CPPopt) from invasive multimodal monitoring data and patient management at or near this optimal level, as multiple studies suggest that CPPopt-guided care is associated with better outcomes, albeit the evidence is mainly observational in nature (7,8,10–13,37). The CPPopt is quantified by plotting continuous PRx calculations against CPP values and identifying the CPP level at which PRx turns out minimal. The data is acquired from a moving 3-to-6 hour time window and a parabolic, U-shaped graph is constructed, with the lowest PRx value representing the CPPopt target (38). This parameter reflects the patient-specific CPP at which cerebrovascular reactivity is at its finest, and deviations above or below the optimal level (Δ CPPopt) worsen the clinical results (10–12). One of the pioneering studies exploring this concept enrolled 114 patients with severe TBI, and the difference between mean CPP values and CPPopt indeed significantly correlated with a 6-month outcome: patients with an averaged CPP close to CPPopt were more likely to make superior recovery (10). Another retrospective analysis of monitoring data from 299 severely brain-injured patients found that negative CPP deviations from the personalized CPPopt were associated with higher mortality rates, whereas positive drifts significantly increased the incidence of severe disability. Additionally, authors revealed that divergence from fixed CPP values of 60 to 70 mmHg, a range proposed by current BTF guidelines, had lower discriminatory value in terms of prognosis as compared to CPPopt-derived threshold, advocating for the importance of individualization (4,11). A recent clinical study of 52 severe TBI patients concluded that superior clinical outcomes are achieved when actual CPP is sustained at gentle hyperperfusion of <10 mmHg above CPPopt when the optimal threshold is within the range of 60 to

80 mmHg. However, patients fared better when CPP declinations are maintained within the interval of ±5 mmHg if calculated CPPopt is >80mmHg (12).

METHODS

Systematic review of the literature was conducted in compliance with the guidelines provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (39). The PRISMA statement checklist addressing all of the necessary conditions in the systematic review is provided in supplementary material, Appendix A. The protocol was registered on International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42022293992).

Eligibility criteria

The eligible study designs were Randomized Clinical Trials (RCTs), Quasi-experimental, Cohort, and Case-Control studies. Case reports were excluded from the analysis. Inclusion criteria was based on PICO methodology ontological components, with studies involving children and pregnant women being excluded (40):

-Population: adult after TBI with multimodal neuromonitoring and derived CPPopt

-Intervention: BTF guidelines-based management, CPP/ICP-guided, or CPPopt-guided treatments

-Comparison: no comparison group

-Outcomes: Mortality and Functional/Neurological outcomes (based on Glasgow Outcome Scale [GOS], GOS-Extended [GOS-E], Quality of Life interviews, Modified Rankin Scale).

Search strategy and data sources

Development of search strategy was based on principles described in Peer Review of Electronic Search Strategies (PRESS) 2015 guideline checklist (41). The following databases were searched on April 2021 for relevant studies: MEDLINE and Cochrane Library Central Register of Controlled trials (CENTRAL). Unpublished data was searched through the following trials registers: ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (ICTRP). A manual search of the reference lists of included studies and relevant previous reviews was also performed. In addition, the citation index of Web of Science was leveraged for further Cited Reference Search. No additional restrictions (e.g. year or language) were applied during the search process. The precise search strategy employed for each database is provided in a supplementary material, Appendix B.

Study selection

A single reviewer (R.J.) screened the titles and abstracts for the full-text review eligibility in the respective databases. Generally, individual studies were retrieved for the further assessment if outcome-related data was provided in the studies focusing on cerebral autoregulation and/or multimodal neuromonitoring in TBI population and were deemed potentially relevant for the research question. Duplicates detected in the separate databases were removed. Full paper review was conducted by a single reviewer (R.J.) and final studies were selected based on critical appraisal after applying our

inclusion/exclusion criteria. Eventual decision regarding inclusivity was made after second author (A.P.) reviewed the list of selected full-text records. Any disagreement was resolved by discussion until the consensus was reached.

Data extraction

A single reviewer (R.J.) extracted the following information from included full-text papers, where applicable: study design, year of publication, sample demographic and baseline characteristics (size, age, gender parity, TBI severity, notable subgrouping), methods of CPPopt estimation, statistical methods and results in terms of CPPopt data connection with the outcomes, measures of outcomes, and size of effect. Extracted data was stored in an excel spreadsheet. A second reviewer (A.P.) independently assessed the extracted data and provided appropriate amendments. Any disagreement between authors was sought by discussion. No further attempts to contact original authors were made regarding missing or potentially unreported data.

Risk of bias and quality of evidence assessment

A single reviewer (R.J.) assessed the risk of bias using Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool (42). Similarly, the quality of evidence was assessed employing Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria in an akin fashion (43). A second reviewer (A.P.) reviewed the risk of bias and evidence quality results for suitability. Disagreement between reviewers judgement was resolved by discussion.

Effect size estimation and data synthesis

The effect size for binary dichotomized outcomes was reported as a relative risk ratio (RR) with 95% confidence intervals (CI 95%) for hypothesis testing using 0.05 value as a significance level. Calculated RR and CI 95% results are reported with two digits after the decimal point. Outcome relationship with the categorical ordinal, continuous metric, and correlation data will be presented as intended originally by the authors. Data of each study was synthesised into a table based on outcome metrics and their corresponding results. Any missing data will be reported as so. Unfortunately, due to currently available literature diversity in terms of design, methodology, and reported outcomes, further quantitative meta-analytical methods were not pursued. Therefore, the results of our qualitative analysis are reported in a descriptive manner.

RESULTS

Study selection

A total of 1272 records were identified for screening after duplicates removal, of which 75 papers were elected for a full-text eligibility assessment. Majority of the studies excluded (n = 1197) at the screening stage were non-relevant for our research question based on concise title and abstract evaluation. A net total of 57 studies were excluded after full-text review, each of which are reported in Appendix C with a rationale of exclusion. Accordingly, 18 studies have met our eligibility criteria and were included in

the final qualitative analysis. Quantitative meta-analytic methods were not engaged due to the heterogeneity of the studies identified. Figure 1 delineates the study selection process in the form of flow diagram.

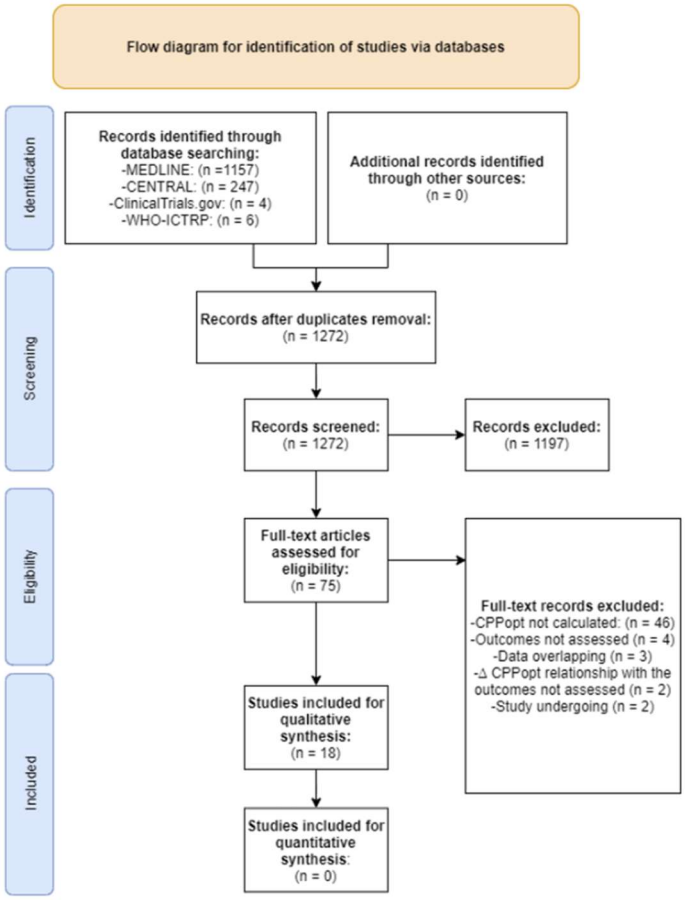

Figure 1: Flow diagram of the study selection process.

Study characteristics

All of the studies included for the final qualitative analysis were observational in nature, leveraging retrospective analysis of prospectively collected data for statistical interpretation. Unfortunately, none of the studies compared CPPopt-guided protocol with a standard of care. A comprehensive assessment of study characteristics is provided in table 1, sorted by the date of publication. A net total of 4140 patients with mild-to-severe TBI were included, althougth there was a significant overlap in datasets used in different studies (specifically from the same scientific groups) and precise number of unique cases remains unavailable. All of the studies originated from developed countries and included 7 main distinct entities: 8 studies were published by Addenbrooke's Hospital group from Cambridge, 3 studies from Republican Vilnius University Hospital investigators, 2 papers were drafted by Uppsala University hospital group, and each Hospital Sao Joao, Porto and Foothills Medical Centre, Calgary authors contributed with a single study (44–58). Moreover, 3 additional multicentric studies were identified - 2 from Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) cohort and 1 from Brain Monitoring with Information Technology Research group (BrainIT) database (59–61). The sample size ranged from 18 to 729 patients per study.

Majority of the studies provided the management protocol used during the neurocritical care phase of TBI patients. Despite the fact that protocols varied, all of the cohorts struck with ICP < 20 mmHg, but CPP treatment goals varied between 50-70 mmHg, providing some heterogeneity. 5 out of 18 studies did not describe the management tactics used (47,48,59–61). Remaining 3 studies adhered to CPPopt-guided protocol, although explicit explanation of the protocol parameters was not provided (46,49,56).

The most common method for CPPopt value estimation was based on generic PRx computations, where all but one of the papers included provided the data using a classical cerebrovascular reactivity estimation method described by Czosnyka et al. back in 1997 (53,62). Anyway, later studies attempted to improve on the original PRx method by introducing some adjustments in how computational formula works, primarily to enchance CPPopt curve yield and stability in time. 3 studies described a similar method of using ICP/MABP correlation data (named as low-frequency autoregulation index, LAx, and multiwindow-weighter PRx, mwPRx) generated at multiple time intervals and weighted over multiple time windows in order to generate final, individualized CPPopt recommendation (50,53,59). Uppsala group, who contributed with 2 studies, employed an alternative index called PRx55-15, which simply applies bandpass filter on ICP and ABP signals inputs for frequency oscillations with periods from 55 to 15 seconds (57,58). Two studies assessed the long PRx (L-PRx) equivalent, which is a classical PRx variant capturing ICP/ABP inputs as lower frequency and thus, resolution (47,61). Finally, the remaining 3 authors used 4 other indices: Andresen et al. investigated oxygen reactivity index (ORx), a Pearson correlation coefficient between partial brain tissue oxygenation (PbtO2) and CPP, Liu et al. provided data on transform-based wavelet PRx (wPRx), capturing the phase difference between ABP and ICP tracings through the complex wavelet tranform computations (51,52). Zeiler with colleagues compared CPPopt calculations also using two additional methods for CA assessment – Pulse amplitude index (PAx, derived via the correlation between MABP and pulse amplitude of ICP pulse waveforms) and RAC index (standing for correlation (R) between pulse amplitude (A) and cerebral perfusion pressure (P)) (60).

The tool used to assess the outcomes was GOS in 13 articles and GOS-E in the remaining 5 papers. Although majority of drafts provided the GOS score at 6 months, two studies deviated from that – one assessed the GOS-E until the last follow-up and another one provided GOS-E scores during the 6-to-12 months follow-up after the injury (54,60). One study also collected the GOS scores at the time of hospital discharge (48). 14 out of 18 studies included provided the data on mortality outcomes, whereas 15 studies included neurological outcome as well, and majority of studies assessed both outcome domains.

Table 1. Table of study characteristics

Author	Setting	Demographics	TBI severity	Management protocol	CPPopt method	Outcomes assessed
Steiner 2002 (44)	Cambridge, data from 1997 to 2000	-N = 114 -mean age (± SD) = 34 ± 16 -84.2% males	Mild-Severe	CPP > 70 mmHg; ICP < 20 mmHg	PRx	GOS at 6 mo.: -Mortality -Neurological outcome
Aries 2012 (45)	Cambridge, data from 2003 to 2009	-N = 299 -median age = 36 -75% males	Severe	CPP > 60 mmHg; ICP < 20 mmHg	PRx	GOS at 6 mo.: -Mortality -Neurological outcome

Depreitere 2014 (59)	2 data sets: 1) BrainIT database, data from 2003 to 2005; 2) Leuven (from 2010 to 2012)-Tubingen (2009) dataset	1) BrainIT database: -N = 180 -median age (IQR) = 33 (21-51) -80% males 2) Leuven-Tubingen: -N = 21 -median age (IQR) = 49 (31 - 66) -61.9% males	Moderate-Severe	Not described	PRx and LAx	GOS at 6 mo.: -Mortality
Dias 2015 (46)	Porto, data from 2011 to 2013	-N = 18 -mean age (± SD) = 42 ± 16 -89% males	Severe	CPPopt-guided where applicable, otherwise CPP goal between 50 and 70 mmHg, ICP < 20 mmHg	PRx	GOS at 6 mo.: -Neurological outcome
Lang 2015 (47)	Cambridge, data from 2003 to 2009	-N = 302 -median age (IQR) = 36 (26) -77% males	Not described	Not described	PRx and L-PRx	GOS at 6 mo.: -Mortality -Neurological outcome
Petkus 2016 (48)	Vilnius	-N = 28 -mean age = 37.6 -89% males	Severe	Not described	PRx	GOS at hospital discharge and at 6 mo.: -Mortality -Neurological outcome
Petkus 2017 (49)	Vilnius	-N = 52 -mean age (±SD) = 38.3 ± 15.3	Severe	CPPopt-guided treatment	PRx	GOS at 6 mo.: -Mortality -Neurological outcome
Liu[1] 2017 (50)	Cambridge, data from 2003 to 2015	-N = 526 -mean age (±SD) = 38.6 ± 16.5 -58.4% males	Moderate-severe	CPP > 60 mmHg; ICP < 20 mmHg	PRx and mwPRx	GOS at 6 mo.: -Mortality -Neurological outcome
Donnelly 2017 (53)	Cambridge, data from 1996 to 2016	-N = 729 -mean age (±SD) = 42 ± 17 -79% males	Severe	CPP > 50-60 mmHg, ICP < 20 mmHg	mwPRx	GOS at 6 mo.: -Mortality -Neurological outcome
Andresen 2017 (52)	Cambridge, data from 2006 to 2012	-N = 85 -median age (IQR) = 37 (25-58) -76% males	Not described	CPP > 70 mmHg; ICP < 20 mmHg	PRx and ORx	GOS at 6 mo.: -Mortality -Neurological outcome
Liu[2] 2017 (51)	Cambridge, data from 2003 to 2014	-N = 515 -mean age (±SD) = 38.4 ± 16 -75% males	Mild-Severe	CPP in a range of 60 to 70 mmHg, ICP < 20 mmHg	PRx and wPRx	GOS at 6 mo.: -Mortality -Neurological outcome
Kramer 2018 (54)	Calgary, data from 2012 to 2016	-N = 71 -median age (IQR) = 25 (20-40) -70% males	Severe	CPP > 60 mmHg; ICP < 20 mmHg	PRx	GOS-E up to the last contact: -Neurological outcome
Donnelly 2018 (55)	Cambridge, data from 2010 to 2015	-N = 231 -mean age = 42 -81% males	Severe	CPP in a range of 60 to 70 mmHg, ICP < 20 mmHg	PRx	GOS at 6 mo.: -Mortality
Zeiler 2018 (60)	CENTER-TBI cohort, data from 2015 to 2017	-N = 204 -mean age (±SD) = 46.6 ± 19.3 -79.9% males	Moderate-Severe	Not described	PRx, PAx, and RAC	GOS-E at 6 to 12 mo.: -Mortality -Neurological outcome
Petkus 2019 (56)	Vilnius	-N = 81 -mean age (±SD) = 40 ± 16 -80.2% males	Severe	CPPopt-guided treatment	PRx	GOS at 6 mo.: -Mortality
Svedung Wettervik 2019 (57)	Uppsala, data from 2008 to 2016	-N = 362 -mean age (±SD) = 47 ± 19 -79% males	Not described	CPP > 60 mmHg; ICP < 20 mmHg	PRx and PRx55-15	GOS-E at 6 mo.: -Neurological outcome

Riemann 2020 (61)	CENTER-TBI cohort, data from 2015 to 2017	-N = 224 -median age (IQR) = 51 (33-64) -78.6% males	Mild-Severe	Not described	PRx and L-PRx	GOS-E at 6 mo.: -Mortality -Neurological outcome
Svedung Wettervik 2021 (58)	Uppsala, data from 2008 to 2018	-N = 98 -mean age (±SD) = 43 ± 20 -76% males	Severe	CPP > 60 mmHg; ICP < 20 mmHg	PRx55-15	GOS-E at 6 mo.: -Neurological outcome

CPPopt – optimal cerebral perfusion pressure; GOS(-E) – Glasgow Outcome Scale (-Extended); SD – standard deviation; IQR – interquartile range; PRx – pressure reactivity index; LAx – low-frequency autoregulation index; L-PRx – Long PRx; mwPRx – multiwindow-weighted PRx; ORx – oxygen reactivity index; wPRx – wavelet PRx; PAx – pulse amplitude index; RAC – correlation (R) between pulse amplitude (A) and cerebral perfusion pressure (P); PRx55-15 – filtered slow waves from 15-55sec range PRx;

Outcomes

The results of individual studies on both mortality and neurological outcomes are reported in table 2. Generally, authors described CPPopt-outcome relationships in 3 forms, as either:

-(a) Δ CPPopt averaged for a whole monitoring period (13 studies);

-(b) a percentage of time spent within certain interval or above/below specific threshold (8 studies);

-(c) mean hourly dose of CPP < -5 mmHg below CPPopt (1 study);

The specific thresholds and intervals of Δ CPPopt used for statistical comparisons varied significantly between studies. Both papers published by Donnelly and colleagues tried to individualize CPPopt thresholds, defining them as either lower or upper limits of regulation (LLR and ULR, respectively), albeit definitions of these limits differed between the two studies (53,55).

All of the 14 studies addressing mortality reported the positive results regarding the predictive value of Δ CPPopt prognostic capacity (44,45,47–53,55,56,59–61). Generally, a positive averaged Δ CPPopt for a whole monitoring period (i.e. hyperperfusion in relation to the CPPopt) was associated with a superior survival in 6 studies (44,47,50–52,61). Similarly, 2 papers indicated that a smaller deviation from averaged Δ CPPopt was associated with lower mortality rates (59,61). 4 studies described the critical thresholds associated with mortality, which ranged between -6 and -4 mmHg of optimum on the averaged basis (45,48,49,56). The significance of averaged Δ CPPopt predictive value remained robust when adjusted for confounding variables (such as age, GCS score at presentation, pupillary reactivity, etc.) in 2 studies (59,61). On the similar note, the percentage of time spent in the hypoperfusive zone (defined as an interval between -15 to -5 mmHg of CPPopt, differing between individual studies) was statistically significantly higher among fatal cases in 3 studies (49,53,60). Both papers drafted by Donnelly et al., where dynamic LLR values were used, found that percentage of time spent below the individualized autoregulatory thresholds was identically associated with higher mortality rates (53,55). One study found that the percentage of time spent within ±5 mmHg of optimum was higher in those patients who survived (59). The statistical comparisons and effect sizes, where applicable, are provided within the summary of findings table (Table 2).

Besides the two studies done by Kramer and Riemann with colleagues, all of the remaining 13 studies found the positive results in terms of neurological outcome and Δ CPPopt relationship (44–

54,57,58,60,61). Better functional outcomes were found in those with averaged Δ CPPopt for a whole monitoring period being either positive or closer to CPPopt in 3 studies (44,45,51). Anyway, in 4 papers authors reported that mean positive Δ CPPopt (or in Aries et al. study > +5 mmHg) was associated with a higher rate of severe disability (45,47,50,52). Additionally, 3 studies performed the correlation analysis between Δ CPPopt and GOS categories, reporting a uniformly negative correlation between the two variables (44,48,49). Dias et al. reported that the critical threshold of median Δ CPPopt for a poor outcome throughout the whole monitoring period was -6.6 mmHg (46). On the contrarary, Kramer and colleagues failed to identify the association between averaged Δ CPPopt differences while comparing favourable and unfavourable outcome groups, whereas in Riemann et al. study authors did not find the difference in severe disability rates between hypoperfused (-5 mmHg) and hyperperfused (+5 mmHg) patient groups (54,61). Likewise, the higher percentage of time spent in both, hypoperfused (Δ CPPopt ranging from -15 to -5mmHg, 3 studies) and hyperperfused states (Δ CPPopt > +10 mmHg, 1 study) was associated with an unfavourable outcomes (49,53,60). In addition, Donnelly with colleagues used dynamic LLR and ULR as the thresholds, reporting same hypoperfusion-hyperperfusion and functional outcome relationship, with percentage of time with Δ CPPopt being below LLR emerging as the strongest predictor in a logistic regression model for poor outcome (53). Moreover, the percentage of time with Δ CPPopt being < -5 mmHg showed a negative correlation with GOS categories in one additional study (49). On the other side of the coin, Uppsala group found that the percentage of time spent within ± 10 mmHg of the CPPopt was related with a favourable neurological outlook, positively correlated with GOS-E categorical scores, and remained significant predictor of outcome after multivariate adjustments (57,58). Comparably, the results reported by Petkus et al. revealed that better functional outcomes were statistically significantly more frequent when percentage of time spent with Δ CPPopt within 0 and +10 mmHg was above 30%. In addition, the percentage of time spent within 0 and +10mmHg of optimum correlated positively with the GOS categories (49). Finally, mean hourly dose with Δ CPPopt being < -5 mmHg was associated with an unfavourable outcome in Zeiler's study, but averaged positive hourly Δ CPPopt values failed to reveal a statistical relationship with functional outcomes (60). The statistical evaluation with effect sizes, where applicable, are depicted within the summary of findings table (Table 2).

Table 2: Summary of findings table

Study	**Data provided for CPPopt-outcome relationship**	**Mortality and effect size**	**Neurological outcome and effect size**
Steiner 2002 (44)	Δ CPPopt averaged for a whole monitoring period	-Mortality RR (CI 95%) = 0.23 (0.05-0.89) if averaged Δ CPPopt was positive (> 0 mmHg)	-Good outcome (GOS 4-5) more likely if averaged Δ CPPopt was positive, RR (CI 95%) = 0.48 (0.25 – 0.89); -Δ CPPopt negatively correlated with GOS (r = -0.51, p < 0.01), also in subgroups where averaged Δ CPPopt was < 0 mmHg (r = 0.53, p < 0.01) and where averaged Δ CPPopt was > 0 mmHg (r = -0.4, p < 0.05)
Aries 2012 (45)	Δ CPPopt averaged for a whole monitoring period	-Mortality RR (CI 95%) = 0.27 (0.19 – 0.38) if median Δ CPPopt was > -5 mmHg	-GOS 4-5 more likely if median Δ CPPopt was within ± 5 CPPopt (No RR, no p values);

			-Severe disability (GOS 3) more likely if median Δ CPPopt was > + 5 mmHg from CPPopt (No RR, no p values)
Depreitere 2014 (59)	1) Δ CPPopt averaged for a whole monitoring period; 2) Percentage of time spent within Δ CPPopt of ± 5 mmHg	1) Averaged Δ CPPopt closer to optimum in survivors vs non-survivors (5.2 mmHg vs 6.9 mmHg, p = 0.01); 2) percentage of time spent within Δ CPPopt of ± 5 mmHg higher in survivors (25.6% vs 19.7%, p = 0.01); -Higher averaged Δ CPPopt remained independent negative predictor in multivariate analysis when adjusted for age, GCS, pupillary reactivity, and presence of extracranial injury.	-
Dias 2015 (46)	Δ CPPopt averaged for a whole monitoring period	-	-Median (IQR) Δ CPPopt in poor outcome group (GOS 1-2) was - 6.6 mmHg (5.3) vs - 1.0 mmHg (5.8) in good outcome group (p = 0.04)
Lang 2015 (47)	Δ CPPopt averaged for a whole monitoring period	-Mortality (GOS 1-2) associated with a mean negative Δ CPPopt (p < 0.01)	-Severe disability (GOS 3) associated with a mean positive Δ CPPopt (p < 0.01)
Petkus 2016 (48)	Δ CPPopt averaged for a whole monitoring period	-Averaged Δ CPPopt threshold for mortality was -4 mmHg at hospital discharge (p = 0.023) and -6 mmHg (p = 0.012) at 6 months.	Δ CPPopt negatively correlated with GOS at hospital discharge (r = -0.549, p < 0.01) and 6 months (r = -0.484, p < 0.01).
Petkus 2017 (49)	1) Δ CPPopt averaged for a whole monitoring period; 2) Percentage of time spent with Δ CPPopt: a) below -5 mmHg; b) within 0 and +10 mmHg	1) Averaged Δ CPPopt threshold for mortality was -5 mmHg (p < 0.01); 2.a) Percentage of time when Δ CPPopt was < -5 mmHg associated with mortality was above 45% (p = 0.031)	1) Averaged Δ CPPopt negatively correlated with GOS (r = -0.416, p < 0.01); 2.a) Percentage of time with Δ CPPopt < - 5 mmHg negatively correlated with GOS (r = -0.448, p < 0.01); percentage of time when Δ CPPopt was < -5 mmHg associated with unfavourable outcome (GOS 1-3) was above 27% (p = 0.012); 2.b) percentage of time with Δ CPPopt being within 0 and +10 mmHg correlated positively with GOS (r = 0.441, p < 0.01); percentage of time when Δ CPPopt was within 0 and +10 mmHg associated with unfavourable outcome was below 30% (p = 0.038)
Liu[1] 2017 (50)	Δ CPPopt averaged for a whole monitoring period	Mortality associated with a mean negative Δ CPPopt (p < 0.01)	Severe disability (GOS 3) associated with a mean positive Δ CPPopt (p value not provided)
Donnelly 2017 (53)	percentage of time spent with Δ CPPopt below and above: a) -10 mmHg; b) +10 mmHg; c) LLR and ULR thresholds*	a) percentage of time when Δ CPPopt was < -10 mmHg associated with mortality (AUROC [CI 95%] 0.66 [0.61-0.72], p < 0.01); c) percentage of time with CPP below LLR was significant predictor of mortality (AUROC [CI 95%] 0.73 [0.68-0.77], p < 0.01); -In binary logistic regression model (adjusted for age, GCS, and ICP), percentage of time below LLR was strongest predictor for mortality (AUROC 0.82, p < 0.01)	a) percentage of time when Δ CPPopt was < -10 mmHg associated with unfavourable outcome (GOS 1-3) (AUROC [CI 95%] 0.56 [0.51-0.61], p < 0.01); c) percentage of time with CPP below LLR was significant predictor of unfavourable outcome (AUROC [CI 95%] 0.6 [0.56-0.64], p < 0.01); percentage of time with CPP above ULR was significant predictor of unfavourable outcome (AUROC [CI 95%] 0.54 [0.50-0.58], p < 0.01); -In binary logistic regression model (adjusted for age, GCS, and ICP), percentage of time below LLR was strongest predictor for unfavourable outcome (AUROC 0.75, p < 0.01)
Andresen	Δ CPPopt averaged for a whole monitoring period	Mortality associated with a mean negative Δ CPPopt (p = 0.02)	Severe disability (GOS 3) associated with a mean positive Δ CPPopt calculated with ORx-5 (p = 0.03).

2017 (52)			
Liu[2] 2017 (51)	Δ CPPopt averaged for a whole monitoring period	Mortality RR (CI 95%) = 0.50 (0.35-0.73) if averaged Δ CPPopt was positive (> 0 mmHg)	-Favourable outcome associated with a smaller Δ CPPopt (no p value provided).
Kramer 2018 (54)	1) Δ CPPopt averaged for a whole monitoring period; 2) percentage of time spent with a positive or negative Δ CPPopt	-	1) Δ CPPopt averaged for whole monitoring time did not differ between favourable (GOS-E 4 - 8) and unfavourable outcome groups (p = 0.47). Degree of deviation from CPPopt did not differ between two outcome groups (p value not provided); 2) percentage of time with negative Δ CPPopt tended to increase with monitoring time in unfavourable outcome group (p = 0.04);
Donnelly 2018 (55)	Percentage of time spent with CPP below LLR**	percentage of time spent with a CPP below LLR was associated with mortality (AUROC [CI 95%] = 0.76 [0.68-0.84], no p value provided)	-
Zeiler 2018 (60)	1) percentage of time spent with Δ CPPopt below and above 5, 10 and 15 mmHg thresholds; 2) mean hourly dose of CPP < -5 mmHg below CPPopt	1) percentage of time with Δ CPPopt < -5, -10, and -15 mmHg associated with mortality (p < 0.015 at statistically weakest treshold); no relationship with positive Δ CPPopt values and mortality outcomes	1) percentage of time with Δ CPPopt < -5, -10, and -15 mmHg associated with unfavourable outcome (GOS-E 5-8) (p < 0.035 at statistically weakest threshold); 2) mean hourly dose with Δ CPPopt < -5 mmHg associated with unfavourable outcome (p = 0.01, only significant with RAC-based CPPopt); no relationship with positive hourly Δ CPPopt values and functional outcomes
Petkus 2019 (56)	Δ CPPopt averaged for a whole monitoring period	Δ CPPopt thresholds below -5 mmHg and below -4 mmHg associated with fatal outcome in younger (age < 45 years) and in elevated ICP groups (>22 mmHg) (p = 0.014 and p < 0.01, respectively); Averaged Δ CPPopt significantly different between fatal and non-fatal groups in younger (age < 45 years) and in elevated ICP (>22 mmHg) patient groups (p < 0.01 in both cases, no averages provided);	-
Svedung Wettervik 2019 (57)	Used 3 time periods (day 1, days 2 to 5, and days 6 to 10), calculated for each period: percentage of time spent with Δ CPPopt < -10 mmHg, within ±10 mmHg, and > +10 mmHg of optimum	-	-Day 1: no significance; -Days 2-5: percentage of time with Δ CPPopt > +10 mmHg was significantly higher and percentage of time with Δ CPPopt within ±10 mmHg was significantly lower in unfavourable outcome (GOS-E 1-4) groups (22% vs 18% and 53% vs 57%, respectively, p < 0.01 in both comparisons); -Days 6-10: percentage of time with Δ CPPopt within ±10 mmHg was significantly lower in unfavourable outcome group (53% vs 56%, p = 0.038). -In binary logistic regression model (adjusted for age, GCS-M, pupillary abnormality and PRx), percentage of time spent with Δ CPPopt > 10 mmHg remained independent predictor of unfavourable outcome

Riemann 2020 (61)	Δ CPPopt averaged for a whole monitoring period, also subgrouped into hypoperfused (mean Δ CPPopt < -5 mmHg) and hyperperfused (mean Δ CPPopt > +5 mmHg) groups	-Averaged Δ CPPopt was significantly higher in patients with fatal outcome (3.7 mmHg vs 1.9 mmHg, $p < 0.01$); -Mortality rates were significantly higher in hypoperfused vs hyperperfused groups (RR [CI 95%] = 0.11 [0.02-0.82], $p < 0.01$); -Δ CPPopt remained a significant predictor of mortality when adjusted for age, GCS-M, pupillary abnormality, ICP and CPP metrics in a multivariate logistic regression model.	-Severe disability (exact GOS-E groups not specified) rates between hypoperfused and hyperperfused patients did not show statistically significant difference ($p = 0.064$)
Svedung Wettervik 2021 (58)	Used 3 time periods (day 1, days 2 to 5, and days 6 to 10), calculated for each period: percentage of time spent with Δ CPPopt < -10 mmHg, within ±10 mmHg, and > +10 mmHg of optimum	-	-Day 1: no significance; -Days 2-5: percentage of time with Δ CPPopt within ±10 mmHg was significantly higher in favourable outcome (GOS-E 5-8) group (60% vs 54%, $p < 0.05$); percentage of time with Δ CPPopt within ±10 mmHg correlated with GOS-E score ($r = 0.29$, $p < 0.01$); -Days 6-10: no significance; percentage of time spent within ±10 mmHg during days 2-5 remained a significant predictor of favourable outcome when adjusted for age, GCS-M and pupillary responses in multivariate logistic regression model.

Δ CPPopt – difference between cerebral perfusion pressure and optimal cerebral perfusion pressure; GOS(-E) – Glasgow Outcome Scale (-Extended); IQR – interquartile range; RR = relative risk; CI 95% = 95% confidence interval; AUROC – Area under the receiver operating characteristics; Orx-5 – oxygen reactivity index using 5 minute window; RAC – correlation (R) between pulse amplitude (A) and cerebral perfusion pressure (P); ICP – intracranial pressure; GCS-M – Glasgow Coma Scale, Motor response score; PRx – pressure reactivity index; LLR – lower limit of regulation; ULR – upper limit of regulation *Donnelly 2017 LLR and ULR were based on PRx = 0.3 threshold. **Donnelly 2018 LLR was defined as a threshold when Δ CPPopt was negative and PRx was > 0.15.

Risk of bias assessment

The summary of risk of bias assessments by ROBINS-I tool is presented in figure 2. Of note, all of the data gathered was observational in nature, highlighting an inherently greater risk of bias in the underlying studies. Besides 2 studies regarded as at moderate overall risk of bias, all of the included studies were deemed as being at either serious or critical levels of overall risk of bias (53,58). A confounding domain was one of the most common origins of bias among included studies. Only 5 out of 18 studies were judged at low risk of bias due to confounding as authors addressed pre-intervention variables in a multivariate analysis manner (53,57–59,61). The data regarding deviations from intended interventions was inherently sparse, hence the risk of bias in this domain could not be assessed in 6 studies (47–49,51,55,56,59). The most significant source of bias arose from selective reporting, where 11 out of 18 studies were considered as either at serious or critical degrees of bias in the domain, mainly because lack of congruence between outcome measurements specified in methodology and analyses reported in the results (44–47,50–52,54–57).

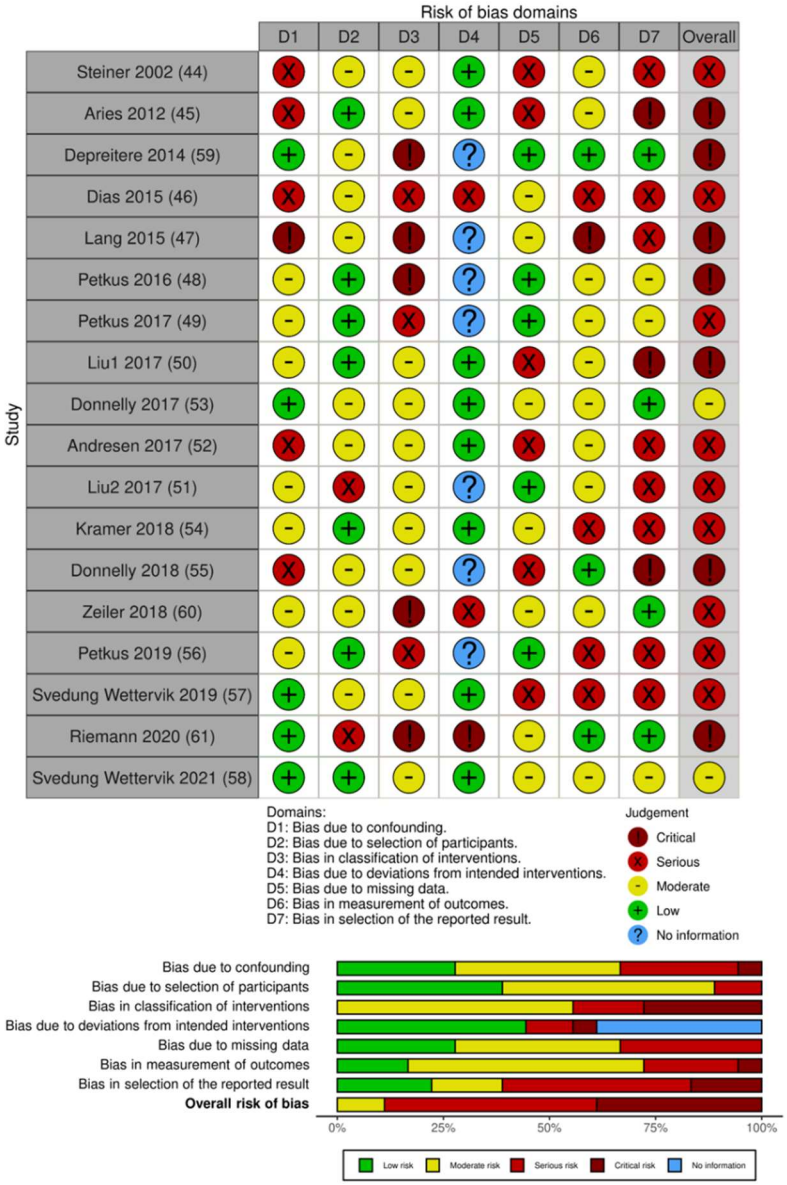

Figure 2: Risk of bias assessment by ROBINS-I tool.

Quality of Evidence

The degree of certainty in the body of evidence for mortality and functional outcomes is provided in tables 3 and 4, respectively. For both outcome domains, the final grade of evidence quality assigned was "very low", primary due to observational nature of the studies included, failure to account for confounding pre-interventional variables, and indirectness in comparisons of samples, outcomes and interventions. Therefore, a robust conclusion on the direct linkage between CPPopt-based treatment approach and mortality/neurological outcomes could not be made.

Table 3: Body of evidence for mortality by GRADE scoring system.

Mortality		
GRADE criteria	**Rating**	**Comment**
A-priori ranking	Low	Observational studies
"Upgrades": 1) Effect size 2) Dose-response relationship 3) Confounding	 1) No 2) No 3) No	Not enough data to upgrade certainty
"Downgrades": 1) Risk of bias 2) Inconsistency 3) Indirectness 4) Imprecision 5) Publication bias	 1) Serious (-1) 2) No 3) Serious (-1) 4) Not assessable 5) Undetected	 1) Confounders poorly controlled, reported results bias. 2) Results and conclusions are consistent among studies 3) Indirect comparison of samples, outcomes and interventions 4) Data not provided, no CI 95% data available in majority of studies 5) Not enough data to confirm
Final grade for quality of evidence	Very low	

Table 4: Body of evidence for neurological outcome by GRADE scoring system.

Neurological outcome		
Grade criteria	**Rating**	**Comment**
A-priori ranking	Low	Observational studies
"Upgrades": 1) Effect size 2) Dose-response relationship 3) Confounding	 1) No 2) No 3) No	Not enough data to upgrade certainty
"Downgrades": 1) Risk of bias 2) Inconsistency 3) Indirectness 4) Imprecision 5) Publication bias	 1) Serious (-1) 2) No 3) Serious (-1) 4) Not assessable 5) Undetected	 1) Confounders poorly controlled, reported results bias. 2) Results and conclusions are consistent among studies 3) Indirect comparison of samples, outcomes and interventions 4) Data not provided, no CI 95% data available in majority of studies 5) Not enough data to confirm
Final grade for quality of evidence	Very low	

DISCUSSION

Majority of the studies included in the qualitative analysis indicates, at least on the observational basis, that maintenance of CPP in close proximity to the individualized CPPopt values might indeed provide the therapeutic benefits for patients suffering from TBI. Notably, two studies did not reach such

conclusions concerning the neurological function outcomes (54,61). Kramer with colleagues failed to identify any statistical difference in mean Δ CPPopt averaged for a whole monitoring period between favourable and unfavourable outcome groups ($p = 0.47$). Similarly, they did not find that deviations of actual CPP from the CPPopt would be related to the disability level (p value not provided). Of note, authors did not assess the Δ CPPopt impact on mortality (54). Riemann et al., the group which analysed multicentric CENTER-TBI data, did not found the difference in severe disability rates between hypoperfused (mean Δ CPPopt averaged for a whole monitoring time < -5 mmHg) and hyperperfused (mean Δ CPPopt > +5 mmHg) patients ($p = 0.064$). Anyway, the same data analysis revealed that averaged Δ CPPopt was significantly higher in fatal cases (3.7 mmHg vs 1.9 mmHg in non-fatal, $p < 0.01$), and individuals who were kept hyperperfused had significantly higher probability of survivorship as compared to underperfused patients (RR [CI 95%] = 0.11 [0.02-0.82], $p < 0.01$). These findings remained significant even after adjusting for age, GCS-M score, pupillary abnormalities and ICP/CPP co-variates (61). Generally, the literature robustly suggests that maintenance of CPP as close as possible the optimum might be of benefit in terms of survival. Similar observations were made regarding positive Δ CPPopt values, although it was shown in multiple studies that hyperperfusion might elevate the risk of severe disability (45,47,50,52). The data is even more supportive towards the harms associated with hypoperfusive situations, where vast majority of studies included showed that both, negative Δ CPPopt and the degree of undershooting are associated with both reduced survival and worse neurological outcomes (44,46–53,56,59–61).

Our review should complement a similar, previously published systematic review on the topic written by Needham with colleagues back in 2017 (63). Authors identified 8 main studies in the field, although in addition to the mortality and neurological outcome domains investigators also considered physiological measures as a separate outcome metric. Anyway, our review should improve the knowledge on the topic due to wider selection criteria (we did not limit ourselves to the severity of TBI) and the sole volume of included studies as recent years has been fruitful with a lot of new publications emerging.

Of note, there are numerous important limitations in the studies underlying our qualitative analysis. First of all, every included study analyzed prospectively collected multimodal monitoring data in a retrospective manner, potentially increasing the risk of post hoc interpretations, data dredging, and ultimately the probability of type I errors in the results. Given the small circle of the research groups involved, there likely was a significant overlap in databases between different published studies by the same group of people. Authors from Cambridge, who essentially pioneered the CA-guided treatment concept and accounted for 8 out of 18 studies included, held an intellectual property of the techonology and thus have a financial interest in the success of the method, the element which could potentially contribute to reporting bias. Similarly, there was a considerable inconsistency in statistical methods used between studies, outcomes dichotomization methods, and CA assessment indices used for CPPopt calculations. Additional drawbacks in the underlying studies are reflected by generally high risk of bias in the underlying research and very low quality of generated evidence (figure 2, tables 3 and 4).

Although the review was conducted according to currently accepted and standartized guidelines, there are several considerable flaws in the review process of the current study (39). First of all, a single

author performed the the title/abstract screening, evaluation and full-text inclusion process, with the expert in the field validating findings in each step. A single reviewer approach is prone to individual biases and could potentially miss other important studies. Two independent reviewers responsible for the whole inclusion process would have been a superior methodological approach. Furthermore, a person responsible for the selection of the studies did not have prior experience with systematic review process, risk of bias evaluation, and quality of evidence assessment. Secondly, the results were described in a qualitative manner, remaining open to writer bias. Quantitative meta-analytic approach would objectively appreciate the evidence addressing the research question, but such methodology is not applicable due to significant heterogeneity of the eligible studies.

Individualization of the management strategy based on autoregulatory data is undeniably a promising concept that could improve the outlook for those suffering from TBI. Unfortunately, as based on the gathered evidence, there is not enough data available to issue any recommendations regarding the possible implementation of CPPopt-guided treatment strategies in routine clinical practice, and CPP goals provided in currently established BTF guidelines remain the standard of care (4). The main limiting factor stems from the observational nature of the studies addressing the question, high risk of biases, and very low quality of evidence of the underlying research done up-to-date in the field. In order to advance the concept further, a well-designed RCT comparing CPPopt-directed strategy versus standard fixed CPP values should be conducted. At the moment there is an ongoing phase II RCT taking place. The study was designed to evaluate the feasibility, safety, and physiological effects of CPPopt-targeted management protocol in a properly controlled environment (64). Similarly, we managed to identify an additional RCT protocol in ICTRP database addressing the issue, but further details were not available (65).

CONCLUSIONS

The evidence gathered from identified studies suggests that targeting optimal cerebral perfusion pressure during traumatic brain injury management might be of benefit for the patients as it potentially reduces the burden of secondary brain injury and improves survival with neurological outcomes. Anyway, given the low quality and high risk of bias in the underlying studies, the causal relationship between deviations from optimal cerebral perfusion pressure and inferior clinical outlook could not be made. Currently, the concept of optimal cerebral perfusion pressure-guided management remains experimental, and in order to translate the concept into clinical practice, a thoughtfully planned RCT comparing optimal cerebral perfusion pressure-focused strategy versus the current standard of care is required.

REFERENCES:

1. Maas AIR, Menon DK, Adelson PD, Andelic N, Bell MJ, Belli A, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. Lancet Neurol. 2017 Dec 1;16(12):987–1048.
2. Rosenfeld JV, Maas AI, Bragge P, Morganti-Kossmann MC, Manley GT, Gruen RL. Early management of severe traumatic brain injury. The Lancet. 2012 Sep 22;380(9847):1088–98.
3. Prins M, Greco T, Alexander D, Giza CC. The pathophysiology of traumatic brain injury at a glance. Dis Model Mech. 2013 Nov;6(6):1307–15.

4. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GWJ, Bell MJ, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. Neurosurgery. 2017 Jan 1;80(1):6–15.
5. Rangel-Castilla L, Gasco J, Nauta HJW, Okonkwo DO, Robertson CS. Cerebral pressure autoregulation in traumatic brain injury. Neurosurg Focus. 2008 Oct;25(4):E7.
6. Zeiler FA, Ercole A, Beqiri E, Cabeleira M, Thelin EP, Stocchetti N, et al. Association between Cerebrovascular Reactivity Monitoring and Mortality Is Preserved When Adjusting for Baseline Admission Characteristics in Adult Traumatic Brain Injury: A CENTER-TBI Study. J Neurotrauma. 2020 May 15;37(10):1233–41.
7. Petkus V, Krakauskaitė S, Preikšaitis A, Ročka S, Chomskis R, Ragauskas A. Association between the outcome of traumatic brain injury patients and cerebrovascular autoregulation, cerebral perfusion pressure, age, and injury grades. Medicina (Mex). 2016 Jan 1;52(1):46–53.
8. Güiza F, Meyfroidt G, Piper I, Citerio G, Chambers I, Enblad P, et al. Cerebral Perfusion Pressure Insults and Associations with Outcome in Adult Traumatic Brain Injury. J Neurotrauma. 2017 Aug 15;34(16):2425–31.
9. Preiksaitis A, Krakauskaite S, Petkus V, Rocka S, Chomskis R, Dagi TF, et al. Association of Severe Traumatic Brain Injury Patient Outcomes With Duration of Cerebrovascular Autoregulation Impairment Events. Neurosurgery. 2016 Jul;79(1):75–82.
10. Steiner LA, Czosnyka M, Piechnik SK, Smielewski P, Chatfield D, Menon DK, et al. Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. Crit Care Med. 2002 Apr;30(4):733–8.
11. Aries MJH, Czosnyka M, Budohoski KP, Steiner LA, Lavinio A, Kolias AG, et al. Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury. Crit Care Med. 2012 Aug;40(8):2456–63.
12. Petkus V, Preiksaitis A, Krakauskaite S, Zubaviciute E, Rocka S, Rastenyte D, et al. Benefit on optimal cerebral perfusion pressure targeted treatment for traumatic brain injury patients. J Crit Care. 2017;41:49–55.
13. Petkus V, Preiksaitis A, Chaleckas E, Chomskis R, Zubaviciute E, Vosylius S, et al. Optimal Cerebral Perfusion Pressure: Targeted Treatment for Severe Traumatic Brain Injury. J Neurotrauma. 2020 15;37(2):389–96.
14. Cardim D, Schmidt B, Robba C, Donnelly J, Puppo C, Czosnyka M, et al. Transcranial Doppler Monitoring of Intracranial Pressure Plateau Waves. Neurocrit Care. 2017;26(3):330–8.
15. Meng L, Gelb AW. Regulation of cerebral autoregulation by carbon dioxide. Anesthesiology. 2015 Jan;122(1):196–205.
16. Gross PM, Heistad DD, Strait MR, Marcus ML, Brody MJ. Cerebral vascular responses to physiological stimulation of sympathetic pathways in cats. Circ Res. 1979 Feb;44(2):288–94.
17. Jones TH, Morawetz RB, Crowell RM, Marcoux FW, FitzGibbon SJ, DeGirolami U, et al. Thresholds of focal cerebral ischemia in awake monkeys. J Neurosurg. 1981 Jun 1;54(6):773–82.
18. Schröder ML, Muizelaar JP, Kuta AJ, Choi SC. Thresholds for Cerebral Ischemia after Severe Head Injury: Relationship with Late CT Findings and Outcome. J Neurotrauma. 1996 Jan 1;13(1):17–23.
19. Schmidt B, Reinhard M, Lezaic V, McLeod DD, Weinhold M, Mattes H, et al. Autoregulation monitoring and outcome prediction in neurocritical care patients: Does one index fit all? J Clin Monit Comput. 2016;30:367–75.
20. Stocchetti N, Maas AIR. Traumatic intracranial hypertension. N Engl J Med. 2014 May 29;370(22):2121–30.
21. Budohoski KP, Czosnyka M, de Riva N, Smielewski P, Pickard JD, Menon DK, et al. The Relationship Between Cerebral Blood Flow Autoregulation and Cerebrovascular Pressure Reactivity After Traumatic Brain Injury. Neurosurgery. 2012 Sep 1;71(3):652–61.
22. Chesnut RM, Marshall LF, Klauber MR, Blunt BA, Baldwin N, Eisenberg HM, et al. The role of secondary brain injury in determining outcome from severe head injury. J Trauma. 1993 Feb;34(2):216–22.
23. Berry C, Ley EJ, Bukur M, Malinoski D, Margulies DR, Mirocha J, et al. Redefining hypotension in traumatic brain injury. Injury. 2012 Nov;43(11):1833–7.
24. Vik A, Nag T, Fredriksli OA, Skandsen T, Moen KG, Schirmer-Mikalsen K, et al. Relationship of "dose" of intracranial hypertension to outcome in severe traumatic brain injury: Clinical article. J Neurosurg. 2008 Oct 1;109(4):678–84.
25. Gerber LM, Chiu YL, Carney N, Härtl R, Ghajar J. Marked reduction in mortality in patients with severe traumatic brain injury. J Neurosurg. 2013 Dec;119(6):1583–90.
26. Farahvar A, Gerber LM, Chiu YL, Carney N, Härtl R, Ghajar J. Increased mortality in patients with severe traumatic brain injury treated without intracranial pressure monitoring. J Neurosurg. 2012 Oct;117(4):729–34.
27. Alali AS, Fowler RA, Mainprize TG, Scales DC, Kiss A, de Mestral C, et al. Intracranial pressure monitoring in severe traumatic brain injury: results from the American College of Surgeons Trauma Quality Improvement Program. J Neurotrauma. 2013 Oct 15;30(20):1737–46.
28. Chesnut RM, 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. 2012 Dec 27;367(26):2471–81.
29. M C, P B, CiterioGiuseppe, ClassenJan, James C, M C, et al. A Consensus-Based Interpretation of the Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure Trial. J Neurotrauma [Internet]. 2015 Nov 10 [cited 2020 Sep 20]; Available from: https://www.liebertpub.com/doi/abs/10.1089/neu.2015.3976
30. Contant CF, Valadka AB, Gopinath SP, Hannay HJ, Robertson CS. Adult respiratory distress syndrome: a complication of induced hypertension after severe head injury. J Neurosurg. 2001 Oct 1;95(4):560–8.
31. Sorrentino E, Diedler J, Kasprowicz M, Budohoski KP, Haubrich C, Smielewski P, et al. Critical thresholds for cerebrovascular reactivity after traumatic brain injury. Neurocrit Care. 2012 Apr;16(2):258–66.
32. Howells T, Elf K, Jones PA, Ronne-Engström E, Piper I, Nilsson P, et al. Pressure reactivity as a guide in the treatment of cerebral perfusion pressure in patients with brain trauma. J Neurosurg. 2005 Feb;102(2):311–7.
33. Marion DW, Darby J, Yonas H. Acute regional cerebral blood flow changes caused by severe head injuries. J Neurosurg. 1991 Mar 1;74(3):407–14.
34. Rosenthal G, Sanchez-Mejia RO, Phan N, Hemphill JC, Martin C, Manley GT. Incorporating a parenchymal thermal diffusion cerebral blood flow probe in bedside assessment of cerebral autoregulation and vasoreactivity in patients with severe traumatic brain injury. J Neurosurg. 2011 Jan;114(1):62–70.
35. Czosnyka M, Miller C. Monitoring of Cerebral Autoregulation. Neurocrit Care. 2014 Dec 1;21(2):95–102.
36. Czosnyka M, Smielewski P, Kirkpatrick P, Laing RJ, Menon D, Pickard JD. Continuous Assessment of the Cerebral Vasomotor Reactivity in Head Injury. Neurosurgery. 1997 Jul 1;41(1):11–9.
37. Needham E, McFadyen C, Newcombe V, Synnot AJ, Czosnyka M, Menon D. Cerebral Perfusion Pressure Targets Individualized to Pressure-Reactivity Index in Moderate to Severe Traumatic Brain Injury: A Systematic Review. J Neurotrauma. 2016 Jun 1;34(5):963–70.
38. Lazaridis C, Smielewski P, Steiner LA, Brady KM, Hutchinson P, Pickard JD, et al. Optimal cerebral perfusion pressure: are we ready for it? Neurol Res. 2013 Mar;35(2):138–48.
39. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71.
40. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 [Internet]. Cochrane; 2022. Available from: Available from www.training.cochrane.org/handbook.
41. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol. 2016 Jul 1;75:40–6.

42. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016 Oct 12;355:i4919.
43. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004 Jun 19;328(7454):1490–1490.
44. Steiner LA, Czosnyka M, Piechnik SK, Smielewski P, Chatfield D, Menon DK, et al. Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. Crit Care Med. 2002 Apr;30(4):733–8.
45. Aries MJH, Czosnyka M, Budohoski KP, Steiner LA, Lavinio A, Kolias AG, et al. Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury. Crit Care Med. 2012 Aug;40(8):2456–63.
46. Dias C, Silva MJ, 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 Aug;23(1):92–102.
47. Lang EW, Kasprowicz M, Smielewski P, Santos E, Pickard J, Czosnyka M. Short pressure reactivity index versus long pressure reactivity index in the management of traumatic brain injury. J Neurosurg. 2015 Mar;122(3):588–94.
48. Petkus V, Krakauskaitė S, Preikšaitis A, Ročka S, Chomskis R, Ragauskas A. Association between the outcome of traumatic brain injury patients and cerebrovascular autoregulation, cerebral perfusion pressure, age, and injury grades. Med Kaunas Lith. 2016;52(1):46–53.
49. Petkus V, Preiksaitis A, Krakauskaite S, Zubaviciute E, Rocka S, Rastenyte D, et al. Benefit on optimal cerebral perfusion pressure targeted treatment for traumatic brain injury patients. J Crit Care. 2017 Oct;41:49–55.
50. Liu X, Maurits NM, Aries MJH, Czosnyka M, Ercole A, Donnelly J, et al. Monitoring of Optimal Cerebral Perfusion Pressure in Traumatic Brain Injured Patients Using a Multi-Window Weighting Algorithm. J Neurotrauma. 2017 Nov 15;34(22):3081–8.
51. Liu X, Donnelly J, Czosnyka M, Aries MJH, Brady K, Cardim D, et al. Cerebrovascular pressure reactivity monitoring using wavelet analysis in traumatic brain injury patients: A retrospective study. PLoS Med. 2017 Jul;14(7):e1002348.
52. Andresen M, Donnelly J, Aries M, Juhler M, Menon D, Hutchinson P, et al. Further Controversies About Brain Tissue Oxygenation Pressure-Reactivity After Traumatic Brain Injury. Neurocrit Care. 2018 Apr;28(2):162–8.
53. Donnelly J, Czosnyka M, Adams H, Robba C, Steiner LA, Cardim D, et al. Individualizing Thresholds of Cerebral Perfusion Pressure Using Estimated Limits of Autoregulation. Crit Care Med. 2017 Sep;45(9):1464–71.
54. Kramer AH, Couillard PL, Zygun DA, Aries MJ, Gallagher CN. Continuous Assessment of "Optimal" Cerebral Perfusion Pressure in Traumatic Brain Injury: A Cohort Study of Feasibility, Reliability, and Relation to Outcome. Neurocrit Care. 2019 Feb;30(1):51–61.
55. Donnelly J, Czosnyka M, Adams H, Robba C, Steiner LA, Cardim D, et al. Pressure Reactivity-Based Optimal Cerebral Perfusion Pressure in a Traumatic Brain Injury Cohort. Acta Neurochir Suppl. 2018;126:209–12.
56. Petkus V, Preiksaitis A, Chaleckas E, Chomskis R, Zubaviciute E, Vosylius S, et al. Optimal Cerebral Perfusion Pressure: Targeted Treatment for Severe Traumatic Brain Injury. J Neurotrauma. 2020 Jan 15;37(2):389–96.
57. Svedung Wettervik T, Howells T, Enblad P, Lewén A. Temporal Neurophysiological Dynamics in Traumatic Brain Injury: Role of Pressure Reactivity and Optimal Cerebral Perfusion Pressure for Predicting Outcome. J Neurotrauma. 2019 Jun;36(11):1818–27.
58. Svedung Wettervik T, Howells T, Hillered L, Rostami E, Lewén A, Enblad P. Autoregulatory or Fixed Cerebral Perfusion Pressure Targets in Traumatic Brain Injury: Determining Which Is Better in an Energy Metabolic Perspective. J Neurotrauma. 2021 Jul 15;38(14):1969–78.
59. Depreitere B, Güiza F, Van den Berghe G, Schuhmann MU, Maier G, Piper I, et al. Pressure autoregulation monitoring and cerebral perfusion pressure target recommendation in patients with severe traumatic brain injury based on minute-by-minute monitoring data. J Neurosurg. 2014 Jun;120(6):1451–7.
60. Zeiler FA, Ercole A, Cabeleira M, Carbonara M, Stocchetti N, Menon DK, et al. Comparison of Performance of Different Optimal Cerebral Perfusion Pressure Parameters for Outcome Prediction in Adult Traumatic Brain Injury: A Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) Study. J Neurotrauma. 2019 May 15;36(10):1505–17.
61. Riemann L, Beqiri E, Smielewski P, Czosnyka M, Stocchetti N, Sakowitz O, et al. Low-resolution pressure reactivity index and its derived optimal cerebral perfusion pressure in adult traumatic brain injury: a CENTER-TBI study. Crit Care. 2020 May 26;24:266.
62. Czosnyka M, Smielewski P, Kirkpatrick P, Laing RJ, Menon D, Pickard JD. Continuous assessment of the cerebral vasomotor reactivity in head injury. Neurosurgery. 1997 Jul;41(1):11–7; discussion 17-19.
63. Needham E, McFadyen C, Newcombe V, Synnot AJ, Czosnyka M, Menon D. Cerebral Perfusion Pressure Targets Individualized to Pressure-Reactivity Index in Moderate to Severe Traumatic Brain Injury: A Systematic Review. J Neurotrauma. 2017 Mar 1;34(5):963–70.
64. Beqiri E, Smielewski P, Robba C, Czosnyka M, Cabeleira MT, Tas J, et al. Feasibility of individualised severe traumatic brain injury management using an automated assessment of optimal cerebral perfusion pressure: the COGiTATE phase II study protocol. BMJ Open. 2019 Sep 20;9(9):e030727.
65. ICTRP Search Portal [Internet]. [cited 2022 Mar 22]. Available from: https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR2000032607
66. Crippa IA, Creteur J, Smielewski P, Taccone FS, Czosnyka M. Delay of cerebral autoregulation in traumatic brain injury patients. Clin Neurol Neurosurg. 2021 Mar 1;202:106478.
67. Åkerlund CA, Donnelly J, Zeiler FA, Helbok R, Holst A, Cabeleira M, et al. Impact of duration and magnitude of raised intracranial pressure on outcome after severe traumatic brain injury: A CENTER-TBI high-resolution group study. PLOS ONE. 2020 Dec 14;15(12):e0243427.
68. Pan Y, Xue Y, Zhao P, Ding J, Ren Z, Xu J. Significance of ICP-related parameters for the treatment and outcome of severe traumatic brain injury. J Int Med Res. 2020 Aug 1;48(8):0300060520941291.
69. Howells T, Smielewski P, Donnelly J, Czosnyka M, Hutchinson PJA, Menon DK, et al. Optimal Cerebral Perfusion Pressure in Centers With Different Treatment Protocols. Crit Care Med. 2018 Mar;46(3):e235.
70. Güiza F, Meyfroidt G, Piper I, Citerio G, Chambers I, Enblad P, et al. Cerebral Perfusion Pressure Insults and Associations with Outcome in Adult Traumatic Brain Injury. J Neurotrauma. 2017 Aug 15;34(16):2425–31.
71. Lang EW, Kasprowicz M, Smielewski P, Santos E, Pickard J, Czosnyka M. Outcome, Pressure Reactivity and Optimal Cerebral Perfusion Pressure Calculation in Traumatic Brain Injury: A Comparison of Two Variants. In: Ang BT, editor. Intracranial Pressure and Brain Monitoring XV [Internet]. Cham: Springer International Publishing; 2016 [cited 2022 Mar 20]. p. 221–3. (Acta Neurochirurgica Supplement). Available from: https://doi.org/10.1007/978-3-319-22533-3_44
72. Zweifel C, Lavinio A, Steiner LA, Radolovich D, Smielewski P, Timofeev I, et al. Continuous monitoring of cerebrovascular pressure reactivity in patients with head injury. Neurosurg Focus. 2008 Oct 1;25(4):E2.
73. Wettervik TS, Engquist H, Howells T, Lenell S, Rostami E, Hillered L, et al. Arterial Oxygenation in Traumatic Brain Injury—Relation to Cerebral Energy Metabolism, Autoregulation, and Clinical Outcome. J Intensive Care Med. 2021 Sep 1;36(9):1075–83.
74. Svedung Wettervik TM, Engquist H, Lenell S, Howells T, Hillered L, Rostami E, et al. Systemic Hyperthermia in Traumatic Brain Injury—Relation to Intracranial Pressure Dynamics, Cerebral Energy Metabolism, and Clinical Outcome. J Neurosurg Anesthesiol. 2021 Oct;33(4):329–36.
75. Zeiler FA, Beqiri E, Cabeleira M, Hutchinson PJ, Stocchetti N, Menon DK, et al. Brain Tissue Oxygen and Cerebrovascular Reactivity in Traumatic Brain Injury: A Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury Exploratory Analysis of Insult Burden. J Neurotrauma. 2020 Sep;37(17):1854–63.

76. Bajpai BK, Preiksaitis A, Vosylius S, Rocka S. Association Between the Cerebral Autoregulation Index (Pressure Reactivity), Patient's Clinical Outcome, and Quality of ABP(t) and ICP(t) Signals for CA Monitoring. Med Kaunas Lith. 2020 Mar 20;56(3):E143.
77. Riemann L, Beqiri E, Younsi A, Czosnyka M, Smielewski P. Predictive and Discriminative Power of Pressure Reactivity Indices in Traumatic Brain Injury. Neurosurgery. 2020 Oct;87(4):655–63.
78. Bennis FC, Teeuwen B, Zeiler FA, Elting JW, van der Naalt J, Bonizzi P, et al. Improving Prediction of Favourable Outcome After 6 Months in Patients with Severe Traumatic Brain Injury Using Physiological Cerebral Parameters in a Multivariable Logistic Regression Model. Neurocrit Care. 2020 Oct 1;33(2):542–51.
79. Zeiler FA, Aries M, Cabeleira M, van Essen TA, Stocchetti N, Menon DK, et al. Statistical Cerebrovascular Reactivity Signal Properties after Secondary Decompressive Craniectomy in Traumatic Brain Injury: A CENTER-TBI Pilot Analysis. J Neurotrauma. 2020 Jun;37(11):1306–14.
80. Svedung Wettervik T, Howells T, Lewén A, Enblad P. Blood Pressure Variability and Optimal Cerebral Perfusion Pressure—New Therapeutic Targets in Traumatic Brain Injury. Neurosurgery. 2020 Mar;86(3):E300.
81. Zeiler FA, Ercole A, Beqiri E, Cabeleira M, Thelin EP, Stocchetti N, et al. Association between Cerebrovascular Reactivity Monitoring and Mortality Is Preserved When Adjusting for Baseline Admission Characteristics in Adult Traumatic Brain Injury: A CENTER-TBI Study. J Neurotrauma. 2020 May 15;37(10):1233–41.
82. Donnelly J, Smielewski P, Adams H, Zeiler FA, Cardim D, Liu X, et al. Observations on the Cerebral Effects of Refractory Intracranial Hypertension After Severe Traumatic Brain Injury. Neurocrit Care. 2020 Apr 1;32(2):437–47.
83. Zeiler FA, Ercole A, Beqiri E, Cabeleira M, Aries M, Zoerle T, et al. Cerebrovascular reactivity is not associated with therapeutic intensity in adult traumatic brain injury: a CENTER-TBI analysis. Acta Neurochir (Wien). 2019 Sep 1;161(9):1955–64.
84. Zeiler FA, Ercole A, Cabeleira M, Beqiri E, Zoerle T, Carbonara M, et al. Patient-specific ICP Epidemiologic Thresholds in Adult Traumatic Brain Injury: A CENTER-TBI Validation Study. J Neurosurg Anesthesiol. 2021 Jan;33(1):28–38.
85. Zeiler FA, Ercole A, Cabeleira M, Zoerle T, Stocchetti N, Menon DK, et al. Univariate comparison of performance of different cerebrovascular reactivity indices for outcome association in adult TBI: a CENTER-TBI study. Acta Neurochir (Wien). 2019 Jun 1;161(6):1217–27.
86. Kim H, Lee HJ, Kim YT, Son Y, Smielewski P, Czosnyka M, et al. Novel index for predicting mortality during the first 24 hours after traumatic brain injury. J Neurosurg. 2018 Dec 21;131(6):1887–95.
87. Donnelly J, Czosnyka M, Adams H, Cardim D, Kolias AG, Zeiler FA, et al. Twenty-Five Years of Intracranial Pressure Monitoring After Severe Traumatic Brain Injury: A Retrospective, Single-Center Analysis. Neurosurgery. 2019 Jul 1;85(1):E75–82.
88. Nourallah B, Zeiler FA, Calviello L, Smielewski P, Czosnyka M, Menon DK. Critical thresholds for intracranial pressure vary over time in non-craniectomised traumatic brain injury patients. Acta Neurochir (Wien). 2018 Jul 1;160(7):1315–24.
89. Moreira M, Fernandes D, Pereira E, Monteiro E, Pascoa R, Dias C. Is There a Relationship Between Optimal Cerebral Perfusion Pressure-Guided Management and PaO2/FiO2 Ratio After Severe Traumatic Brain Injury? In: Heldt T, editor. Intracranial Pressure & Neuromonitoring XVI. Cham: Springer International Publishing; 2018. p. 59–62. (Acta Neurochirurgica Supplement).
90. Zeiler FA, Donnelly J, Smielewski P, Menon DK, Hutchinson PJ, Czosnyka M. Critical Thresholds of Intracranial Pressure-Derived Continuous Cerebrovascular Reactivity Indices for Outcome Prediction in Noncraniectomized Patients with Traumatic Brain Injury. J Neurotrauma. 2018 May 15;35(10):1107–15.
91. Eun J, Huh J, Yang SY, Huh HY, Ahn JK, Cho KW, et al. Determining the Lower Limit of Cerebral Perfusion Pressure in Patients Undergoing Decompressive Craniectomy Following Traumatic Brain Injury. World Neurosurg. 2018 Mar 1;111:e32–9.
92. So JS, Yun JH. The Combined Use of Cardiac Output and Intracranial Pressure Monitoring to Maintain Optimal Cerebral Perfusion Pressure and Minimize Complications for Severe Traumatic Brain Injury. Korean J Neurotrauma. 2017 Oct 1;13(2):96–102.
93. Adams H, Donnelly J, Czosnyka M, Kolias AG, Helmy A, Menon DK, et al. Temporal profile of intracranial pressure and cerebrovascular reactivity in severe traumatic brain injury and association with fatal outcome: An observational study. PLOS Med. 2017 Jul 25;14(7):e1002353.
94. Cabella B, Donnelly J, Cardim D, Liu X, Cabeleira M, Smielewski P, et al. An Association Between ICP-Derived Data and Outcome in TBI Patients: The Role of Sample Size. Neurocrit Care. 2017 Aug 1;27(1):103–7.
95. Aries MJH, Wesselink R, Elting JWJ, Donnelly J, Czosnyka M, Ercole A, et al. Enhanced Visualization of Optimal Cerebral Perfusion Pressure Over Time to Support Clinical Decision Making*. Crit Care Med. 2016 Oct;44(10):e996.
96. Depreitere B, Güiza F, Van den Berghe G, Schuhmann MU, Maier G, Piper I, et al. Can Optimal Cerebral Perfusion Pressure in Patients with Severe Traumatic Brain Injury Be Calculated Based on Minute-by-Minute Data Monitoring? In: Ang BT, editor. Intracranial Pressure and Brain Monitoring XV [Internet]. Cham: Springer International Publishing; 2016 [cited 2022 Mar 20]. p. 245–8. (Acta Neurochirurgica Supplement). Available from: https://doi.org/10.1007/978-3-319-22533-3_49
97. Lazaridis C, Smielewski P, Menon DK, Hutchinson P, Pickard JD, Czosnyka M. Patient-Specific Thresholds and Doses of Intracranial Hypertension in Severe Traumatic Brain Injury. In: Ang BT, editor. Intracranial Pressure and Brain Monitoring XV [Internet]. Cham: Springer International Publishing; 2016 [cited 2022 Mar 20]. p. 117–20. (Acta Neurochirurgica Supplement). Available from: https://doi.org/10.1007/978-3-319-22533-3_23
98. Sykora M, Czosnyka M, Liu X, Donnelly J, Nasr N, Diedler J, et al. Autonomic Impairment in Severe Traumatic Brain Injury: A Multimodal Neuromonitoring Study. Crit Care Med. 2016 Jun;44(6):1173–81.
99. Gao L, Smielewski P, Czosnyka M, Ercole A. Cerebrovascular Signal Complexity Six Hours after Intensive Care Unit Admission Correlates with Outcome after Severe Traumatic Brain Injury. J Neurotrauma. 2016 Nov 15;33(22):2011–8.
100. Preiksaitis A, Krakauskaite S, Petkus V, Rocka S, Chomskis R, Dagi TF, et al. Association of Severe Traumatic Brain Injury Patient Outcomes With Duration of Cerebrovascular Autoregulation Impairment Events. Neurosurgery. 2016 Jul;79(1):75–82.
101. Schmidt B, Reinhard M, Lezaic V, McLeod DD, Weinhold M, Mattes H, et al. Autoregulation monitoring and outcome prediction in neurocritical care patients: Does one index fit all? J Clin Monit Comput. 2016 Jun 1;30(3):367–75.
102. Tackla R, Hinzman JM, Foreman B, Magner M, Andaluz N, Hartings JA. Assessment of Cerebrovascular Autoregulation Using Regional Cerebral Blood Flow in Surgically Managed Brain Trauma Patients. Neurocrit Care. 2015 Dec 1;23(3):339–46.
103. Liu X, Czosnyka M, Donnelly J, Budohoski KP, Varsos GV, Nasr N, et al. Comparison of Frequency and Time Domain Methods of Assessment of Cerebral Autoregulation in Traumatic Brain Injury. J Cereb Blood Flow Metab. 2015 Feb 1;35(2):248–56.
104. Griesdale DEG, Örtenwall V, Norena M, Wong H, Sekhon MS, Kolmodin L, et al. Adherence to guidelines for management of cerebral perfusion pressure and outcome in patients who have severe traumatic brain injury. J Crit Care. 2015 Feb 1;30(1):111–5.
105. Karamanos E, Teixeira PG, Sivrikoz E, Varga S, Chouliaras K, Okoye O, et al. Intracranial pressure versus cerebral perfusion pressure as a marker of outcomes in severe head injury: a prospective evaluation. Am J Surg. 2014 Sep 1;208(3):363–71.
106. Johnson U, Lewén A, Ronne-Engström E, Howells T, Enblad P. Should the Neurointensive Care Management of Traumatic Brain Injury Patients be Individualized According to Autoregulation Status and Injury Subtype? Neurocrit Care. 2014 Oct 1;21(2):259–65.
107. Narotam PK, Morrison JF, Schmidt MD, Nathoo N. Physiological Complexity of Acute Traumatic Brain Injury in Patients Treated with a Brain Oxygen Protocol: Utility of Symbolic Regression in Predictive Modeling of a Dynamical System. J Neurotrauma. 2014 Apr;31(7):630–41.
108. Dizdarevic K, Hamdan A, Omerhodzic I, Kominlija-Smajic E. Modified Lund concept versus cerebral perfusion pressure-targeted therapy: A randomised controlled study in patients with secondary brain ischaemia. Clin Neurol Neurosurg. 2012 Feb 1;114(2):142–8.

109. Stein DM, Hu PF, Brenner M, Sheth KN, Liu KH, Xiong W, et al. Brief Episodes of Intracranial Hypertension and Cerebral Hypoperfusion Are Associated With Poor Functional Outcome After Severe Traumatic Brain Injury. J Trauma Acute Care Surg. 2011 Aug;71(2):364–74.
110. Jaeger M, Dengl M, Meixensberger J, Schuhmann MU. Effects of cerebrovascular pressure reactivity-guided optimization of cerebral perfusion pressure on brain tissue oxygenation after traumatic brain injury*. Crit Care Med. 2010 May;38(5):1343–7.
111. Radolovich DK, Czosnyka M, Timofeev I, Lavinio A, Hutchinson P, Gupta A, et al. Reactivity of Brain Tissue Oxygen to Change in Cerebral Perfusion Pressure in Head Injured Patients. Neurocrit Care. 2009 Jan 30;10(3):274.
112. Lin JW, Tsai JT, Lin CM, Lee LM, Hung KS, Huang SJ, et al. Evaluation of optimal cerebral perfusion pressure in severe traumatic brain injury. In: Chiu WT, Chiang YH, Kao MC, Hung CC, Lin SZ, Chen HJ, et al., editors. Reconstructive Neurosurgery. Vienna: Springer; 2008. p. 131–6. (Acta Neurochirurgica Supplementum).
113. Huang SJ, Hong WC, Han YY, Chen YS, Wen CS, Tsan YS, et al. Clinical outcome of severe head injury in different protocol-driven therapies. J Clin Neurosci. 2007 May 1;14(5):449–54.
114. Ang BT, Wong J, Lee KK, Wang E, Ng I. Temporal changes in cerebral tissue oxygenation with cerebrovascular pressure reactivity in severe traumatic brain injury. J Neurol Neurosurg Psychiatry. 2007 Mar 1;78(3):298–302.
115. Balestreri M, Czosnyka M, Steiner LA, Hiler M, Schmidt EA, Matta B, et al. Association between outcome, cerebral pressure reactivity and slow ICP waves following head injury. In: Poon WS, Chan MTV, Goh KYC, Lam JMK, Ng SCP, Marmarou A, et al., editors. Intracranial Pressure and Brain Monitoring XII. Vienna: Springer; 2005. p. 25–8. (Acta Neurochirurgica Supplementum).
116. Cremer OL, van Dijk GW, Amelink GJ, de Smet AMGA, Moons KGM, Kalkman CJ. Cerebral Hemodynamic Responses to Blood Pressure Manipulation in Severely Head-Injured Patients in the Presence or Absence of Intracranial Hypertension. Anesth Analg. 2004 Oct;99(4):1211–7.
117. Feng H, Huang G, Gao L, Tan H, Liao X. Effect of intracranial pressure and cerebral perfusion pressure on outcome prediction of severe traumatic brain injury. Chin J Traumatol Zhonghua Chuang Shang Za Zhi. 2000 Nov 15;3(4):226–30.
118. Kirkness CJ, Mitchell PH, Burr RL, Newell DW. Cerebral Autoregulation and Outcome in Acute Brain Injury. Biol Res Nurs. 2001 Jan 1;2(3):175–85.
119. Johnson U, Nilsson P, Ronne-Engström E, Howells T, Enblad P. Favorable Outcome in Traumatic Brain Injury Patients With Impaired Cerebral Pressure Autoregulation When Treated at Low Cerebral Perfusion Pressure Levels. Neurosurgery. 2011 Mar 1;68(3):714–22.
120. Kirkness CJ, Burr RL, Cain KC, Newell DW, Mitchell PH. Relationship of cerebral perfusion pressure levels to outcome in traumatic brain injury. In: Poon WS, Chan MTV, Goh KYC, Lam JMK, Ng SCP, Marmarou A, et al., editors. Intracranial Pressure and Brain Monitoring XII. Vienna: Springer; 2005. p. 13–6. (Acta Neurochirurgica Supplementum).

Supplementary Material

Appendix A. PRISMA 2020 checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	8
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	8
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix B
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	8-9
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	9
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	9
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	9
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	9
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	9
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	n.y.
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	n.y.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	n.y.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	n.y.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	n.y.
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	n.y.
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	9
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	9
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	9-10
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Appendix C
Study characteristics	17	Cite each included study and present its characteristics.	11-13
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	17-18
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	14-17
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	n.y.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	n.y.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	n.y.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	n.y.
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	17-18
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	18-19
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	19-20
	23b	Discuss any limitations of the evidence included in the review.	20
	23c	Discuss any limitations of the review processes used.	20-21
	23d	Discuss implications of the results for practice, policy, and future research.	21
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	8
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	8
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	n.y.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	n.y.
Competing interests	26	Declare any competing interests of review authors.	n.y.
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	n.y.

Appendix B. Complete search strategies used.

Database	Date	Search strategy	Results
MEDLINE (PubMed)	April 2021	("traumatic brain injury"[Title/Abstract] OR "head trauma"[Title/Abstract] OR "head injury"[Title/Abstract] OR "traumatic brain insult"[Title/Abstract] OR "cranial trauma"[Title/Abstract] OR "craniocerebral trauma"[Title/Abstract]) AND ("cerebral perfusion pressure"[Title/Abstract] OR "optimal cerebral perfusion pressure"[Title/Abstract] OR "CPP"[Title/Abstract] OR "cerebrovascular reactivity"[Title/Abstract] OR "cerebrovascular autoregulation"[Title/Abstract] OR "cerebral autoregulation"[Title/Abstract] OR "pressure reactivity"[Title/Abstract] OR "pressure reactivity index"[Title/Abstract] OR "pressure autoregulation"[Title/Abstract] OR "neuromonitoring"[Title/Abstract] OR "invasive monitoring"[Title/Abstract]) NOT ("pediatric"[Title/Abstract] OR "paediatric"[Title/Abstract] OR "child*"[Title/Abstract]) NOT ("review"[Publication Type]) NOT ("animal*"[Title/Abstract])	1157
CENTRAL (Cochrane library)	April 2021	((traumatic brain injury OR head trauma OR head injury OR traumatic brain insult OR cranial trauma OR craniocerebral trauma) AND (cerebral perfusion pressure OR optimal cerebral perfusion pressure OR CPP OR cerebrovascular reactivity OR cerebrovascular autoregulation OR cerebral autoregulation OR pressure reactivity OR pressure reactivity index OR pressure autoregulation OR neuromonitoring OR invasive monitoring) NOT (Pediatric OR paediatric OR child OR animal OR rodent))	247
ClinicalTrials.gov	April 2021	Clinicaltrials.gov: Traumatic brain injury AND optimal cerebral perfusion pressure	4
WHO ICTRP	April 2021	Title: traumatic brain injury OR head trauma OR head injury OR traumatic brain insult OR cranial trauma OR	6

		craniocerebral trauma cerebral perfusion pressure OR optimal cerebral perfusion pressure OR CPP OR cerebrovascular reactivity OR cerebrovascular autoregulation OR cerebral autoregulation OR pressure reactivity OR pressure reactivity index OR pressure autoregulation OR neuromonitoring OR invasive monitoring (AND) Condition: traumatic brain injury (AND) Intervention: cerebral perfusion pressure OR CPP OR cerebrovascular reactivity OR cerebrovascular autoregulation OR cerebral autoregulation OR pressure reactivity OR pressure reactivity index OR pressure autoregulation OR neuromonitoring OR invasive monitoring	

Appendix C: Excluded studies with the reasons of exclusion after full text review

Study	**Publication date**	**Reason of exclusion**
Crippa (66)	2021	CPPopt not provided
Åkerlund (67)	2020	CPPopt not provided
Pan (68)	2020	CPPopt not provided
Howells (69)	2018	No outcomes assessed
Güiza (70)	2017	CPPopt not provided
Lang (71)	2016	Data included in Lang 2016 full-text
Zweifel (72)	2008	Data included in Steiner 2002 full-text
Wettervik (73)	2020	CPPopt not provided
Wettervik (74)	2021	CPPopt not provided
Zeiler (75)	2020	CPPopt not provided
Bajpai (76)	2020	CPPopt not provided
Riemann (77)	2020	CPPopt not provided
Bennis (78)	2020	CPPopt not provided

Zeiler (79)	2020	CPPopt not provided
Wettervik (80)	2020	No outcomes assessed
Zeiler (81)	2020	CPPopt not provided
Beqiri (64)	2019	Study undergoing
Donnelly (82)	2020	CPPopt not provided
Zeiler (83)	2019	CPPopt not provided
Zeiler (84)	2021	CPPopt not provided
Zeiler (85)	2019	CPPopt not provided
Kim (86)	2018	Δ CPPopt not correlated with the outcomes
Donnelly (87)	2019	CPPopt not provided
Nourallah (88)	2018	CPPopt not provided
Moreira (89)	2018	Δ CPPopt not correlated with the outcomes
Zeiler (90)	2018	CPPopt not provided
Eun (91)	2018	CPPopt not provided
So (92)	2017	CPPopt not provided
Adams (93)	2017	CPPopt not provided
Cabella (94)	2017	CPPopt not provided
Aries (95)	2016	CPPopt not provided
Depreitere (96)	2016	Data included in Depreitere 2014 full-text
Lazaridis (97)	2016	CPPopt not provided
Sykora (98)	2016	CPPopt not provided
Gao (99)	2016	CPPopt not provided
Preiksaitis (100)	2016	CPPopt not provided
Schmidt (101)	2016	CPPopt not provided
Tackla (102)	2015	CPPopt not provided
Liu (103)	2015	CPPopt not provided

Griesdale (104)	2015	CPPopt not provided
Karamanos (105)	2014	CPPopt not provided
Johnson (106)	2014	CPPopt not provided
Narotam (107)	2014	CPPopt not provided
Dizdarevic (108)	2012	CPPopt not provided
Stein (109)	2011	CPPopt not provided
Jaeger (110)	2010	No outcomes assessed
Radolovich (111)	2009	No outcomes assessed
Lin (112)	2008	CPPopt not provided
Huang (113)	2007	CPPopt not provided
Ang (114)	2007	CPPopt not provided
Balestreri (115)	2005	CPPopt not provided
Cremer (116)	2004	CPPopt not provided
Feng (117)	2000	CPPopt not provided
Kirkness (118)	2001	CPPopt not provided
Johnson (119)	2011	CPPopt not provided
Kirkness (120)	2005	CPPopt not provided
Hengli (65)	2021	Study undergoing

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2022 March 7; 0(0): 0-0

DOI: 10.12998/wjcc.v0.i0.0000

ISSN 2307-8960 (online)

CASE REPORT

Plexiform neurofibroma of the cauda equina with follow-up of 10 years: A case report

Zilvinas Chomanskis, Raimondas Juskys, Saulius Cepkus, Justyna Dulko, Vaiva Hendrixson, Osvaldas Ruksenas, Saulius Rocka

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ma X, Munakomi S

Received: August 2, 2021
Peer-review started: August 2, 2021
First decision: September 28, 2021
Revised: October 9, 2021
Accepted: March 7, 2022
Article in press: March 7, 2022
Published online: March 7, 2022

Zilvinas Chomanskis, Saulius Rocka, Department of Neurology and Neurosurgery, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius 03104, Lithuania

Raimondas Juskys, Anatomy, Histology and Anthropology Department, Vilnius University, Faculty of Medicine, Vilnius 03104, Lithuania

Saulius Cepkus, Department of Neurosurgery, Republican Vilnius University Hospital, Vilnius 04130, Lithuania

Justyna Dulko, Faculty of Medicine, Vilnius University, Vilnius 03104, Lithuania

Vaiva Hendrixson, Institute of Biomedicine, Faculty of Medicine, Vilnius University, Vilnius 03104, Lithuania

Osvaldas Ruksenas, Institute of Biosciences, Life Sciences Centre, Vilnius University, Vilnius 10257, Lithuania

Corresponding author: Raimondas Juskys, MD, Assistant, Anatomy, Histology and Anthropology Department, Vilnius University, Faculty of Medicine, Ciurlionio str. 21, Vilnius 03104, Lithuania. raimondas.juskys@mf.vu.lt

Abstract

BACKGROUND

Plexiform neurofibromas are extremely rarely found in the region of cauda equina and can pose a significant challenge in the diagnostic and management sense. To our knowledge, only 7 cases of cauda equina neurofibromatosis (CENF) have been reported up-to-date.

CASE SUMMARY

We describe a case of a 55-year-old man with a 10 years history of progressive lower extremities weakness and bladder dysfunction. Before presenting, patient was misdiagnosed with idiopathic polyneuropathy. Lumbar spine MRI revealed a tortuous tumorous masses in the cauda equina region, extending through the Th12-L4 vertebrae. The patient underwent Th12-L3 Laminectomy with duraplasty. During the operation, the most enlarged electroneurographically silent nerve root was resected, anticipating inadequate decompression if nerve root was spared. The patient's neurological condition improved post-operatively, but urinary retention became the major complaint. We provide a follow-up period

Cureus

Open Access Original Article

DOI: 10.7759/cureus.21979

Anatomical Variations of Superior Sagittal Sinus and Tributary Bridging Veins: A Cadaveric Study

Raimondas Juskys [1], Saulius Rocka [1], Andrej Suchomlinov [2]

1. Faculty of Medicine, Vilnius University, Vilnius, LTU 2. Department of Anatomy, Histology, and Anthropology, Faculty of Medicine, Vilnius University, Vilnius, LTU

Corresponding author: Raimondas Juskys, raimondas.juskys@mf.vu.lt

Review began 01/28/2022
Review ended 02/03/2022
Published 02/07/2022

Abstract

Background and objective

Injuries to the parasagittal cerebrovenous structures may lead to devastating complications. Being aware of the inherent anatomical heterogeneity in the region might lower the rate of undesirable outcomes. In this study, our goal was to characterize the superior sagittal sinus (SSS) positioning in relation to the midline and depict tributary bridging veins (BVs) distribution over the lateral surface of the cerebral hemispheres.

Methods

We performed anatomical dissections of the brain in 10 cadaveric specimens (five females and five males; median age: 52 years, range: 44-74 years). Measurements (in mm) of the SSS width and deviation of its lateral margin from the midline were obtained along the entire length of the structure at six craniometric points [at mid-distance between Nasion and Bregma (½ N-B); at Bregma (B); in the middle of the Bregma-Lambda segment (½ B-L); at Lambda (L); halfway between Lambda and Inion (½ L-I); and at Inion (I)]. The count, diameter, and lateral insertion points of the draining BVs were also documented in three segments [Nasion-Bregma (N-B), Bregma-Lambda (B-L), and Lambda-Inion (L-I)].

Results

The width of the SSS increased progressively along the direction of the blood flow ($p<0.01$). There was an SSS lateral deviation bias to the right, but the comparison failed to reach the significance level ($p=0.12$). The maximal lateralization of the SSS in the pre-Lambdal interval was 13.1 mm on the right side and 11.7 mm on the left side. These values increased up to 19.8 mm and 15.1 mm in the torcular area on the right and left sides, respectively. A total of 191 BVs were identified (a mean of 19.1 ± 2.5 per individual). The L-I segment showed a lower number of BVs as compared to its N-B and B-L counterparts (mean: 0.9 ± 0.6 vs. 8 ± 1.8 and 10.2 ± 2, respectively, $p<0.01$). Along the entire span of the SSS, the average diameter of the BVs was larger on the right side (mean: 1.4 ± 0.9 mm vs. 1.1 ± 0.8 mm on the left, $p<0.01$). The average lateralization of BVs dural entry points was lower on the left side in the B-L segment (mean: 5.6 ± 6.4 mm vs. 8.8 ± 6.7 mm on the right, $p<0.01$). There was a statistically significant trend of decreasing BVs lateralization with each consecutive SSS segment (mean: 10.9 ± 7.4 mm in the N-B segment, 7.3 ± 6.7 mm in B-L, and 1.6 ± 1.2 mm in L-I, $p<0.01$). The maximal lateral deviation of BVs insertion points was 33.6 mm in N-B, 30 mm in B-L, and 4.1 mm in L-I portions of the SSS.

Conclusions

In most cases, the SSS deviated laterally from the midline, up to 13 mm in the pre-Lambdal segment and up to 20 mm in the torcular area. Right-sided BVs were of larger average diameters. The lateral insertion points of BVs decreased along the rostrocaudal span of the SSS.

Categories: Neurology, Neurosurgery, Anatomy
Keywords: brain anatomy, parasagittal region, cadaveric dissection, bridging veins, superior sagittal sinus

Introduction

A good understanding of the neurosurgical anatomy is a crucial prerequisite for optimizing outcomes and limiting the frequency of intra- and postoperative complications. The superior sagittal sinus (SSS) is a caudally-expanding dural structure collecting venous blood from the medial parts of the fronto-parieto-occipital cortex and the basal surface of the frontal lobe. Generally, superficial cortical veins, also known as bridging veins (BVs), are responsible for the vast majority of the volumetric contribution to the SSS [1].

Although permanent neurological sequelae after venous drainage obliteration are less common in comparison to the arterial system, (in)advert interruption of cortical venous outflow nonetheless might lead to potentially preventable complications such as bleeding, cerebral edema, infarction, and ultimately severe neurological outcomes. Similarly, besides the hazards associated with the BVs termination, injury to the SSS

How to cite this article
Juskys R, Rocka S, Suchomlinov A (February 07, 2022) Anatomical Variations of Superior Sagittal Sinus and Tributary Bridging Veins: A Cadaveric Study. Cureus 14(2): e21979. DOI 10.7759/cureus.21979

Cureus

Open Access Case Report

DOI: 10.7759/cureus.8019

Glioblastoma Following Traumatic Brain Injury: Case Report and Literature Review

Raimondas Juškys [1], Žilvinas Chomanskis [2]

1. Department of Anatomy, Histology and Anthropology, Faculty of Medicine, Vilnius University, Vilnius, LTU 2. Department of Neurology and Neurosurgery, Faculty of Medicine, Vilnius University, Vilnius, LTU

Corresponding author: Raimondas Juškys, raimondas.juskys@mf.vu.lt

Abstract

The association between traumatic brain injury and brain cancer is a matter of debate. The available literature is sparse and yields conflicting results. Even though there is a pathophysiological rationale for post-traumatic intracranial cancerogenesis, the direct link still has not been proven. Here we present a case of a patient who developed glioblastoma multiforme four years following the traumatic intracerebral hemorrhage. In addition, we provide a brief review of the relevant literature.

Categories: Neurology, Neurosurgery, Oncology
Keywords: traumatic brain injury, intracerebral hemorrhage, glioblastoma, case report

Introduction

The causal role between traumatic brain injury (TBI) and development of malignant brain tumor remains a matter of debate. There is a limited amount of literature exploring this topic. Theoretical and experimental data support such association, but currently available epidemiological studies yield conflicting results. Here we present a case of a male patient who developed glioblastoma (GBM) at the same location as did the former traumatic intracerebral hemorrhage (ICH) occurred four years ago. In addition, we have briefly reviewed available literature with an emphasis on relevant epidemiological studies and potential pathophysiological mechanisms that explain the link between trauma and gliomagenesis.

Case Presentation

Our patient was a 47-year-old male who suffered a moderate TBI as a result of an accident of falling down the stairs in 2014. He was brought to the emergency department at a local university hospital with a Glasgow Coma Scale (GCS) score of 12. An initial neurological examination revealed a moderate aphasia, right-sided hemiparesis, and a positive Babinski sign on the right. Urgent head CT showed a left-sided frontotemporal ICH with a midline shift of 9 mm (Figures *1A*, *1B*). The patient underwent an emergency pterional craniotomy and hematoma evacuation. There was no evidence of tumor during the intraoperative period. Next day, postoperative CT scan showed a diminished midline shift to 4 mm and the remnants of hematoma (Figures *1C*, *1D*). The postoperative period was uneventful. The patient gradually improved and was discharged for further rehabilitation after 12 days with a GCS score of 15, mild motor aphasia, and slight right-sided hemiparesis. The patient showed up for the follow-up after two years in 2016. The clinical condition was satisfactory, no focal neurological signs were observed, and the patient complained only of easy fatigability and mild intermittent head pains in the region of craniotomy. No need for an additional neuroimaging was indicated at that moment as the patient did not show any signs of neurological deficits.

Received 04/22/2020
Review began 04/26/2020
Review ended 05/01/2020
Published 05/07/2020

How to cite this article
Juškys R, Chomanskis Ž (May 07, 2020) Glioblastoma Following Traumatic Brain Injury: Case Report and Literature Review. Cureus 12(5): e8019. DOI 10.7759/cureus.8019

Journal of Forensic Radiology and Imaging 19 (2019) 100342

Contents lists available at ScienceDirect

Journal of Forensic Radiology and Imaging

journal homepage: www.elsevier.com/locate/jofri

The trepanned skull from Comiso (Ragusa): Trauma, surgery, and care in Modern Age Sicily

Dario Piombino-Mascali[a,*], Raimondas Juškys[a], Marcello Longo[b], Robert Loynes[c]

[a] Faculty of Medicine, Vilnius University, Vilnius, Lithuania
[b] Neuroradiology Unit, Messina University Hospital, Messina, Italy
[c] KNH Centre for Biomedical Egyptology, The University of Manchester, Manchester, United Kingdom

ARTICLE INFO

Keywords:
Skull
Trepanation
Paleopathology
Paleoradiology
Sicily

ABSTRACT

Trepanation, or the removal of a bony piece from the cranial vault, has been widely investigated by both paleopathologists and medical historians. The aim of this report is to employ a paleoradiological approach to complement a macroscopic inspection of the lesions present in a historic case of trepanation from Sicily, to obtain a better understanding of the consequences of the trauma the subject sustained during life, as well as create a permanent, digital record of this unique osteo-archaeological finding for future research.

1. Introduction

The evidence for trepanation dates back at least to the late Neolithic era and is considered to be the oldest known surgical procedure practiced [1]. Trepanation involves the removal of one or more pieces of bone from the cranial vault avoiding injury to underlying structures, namely the meninges, brain, and blood vessels [2,3]. Archaeological data suggest four basic techniques were employed to achieve trepanation: scraping, grooving, drilling, and cutting [4]. The purpose of such interventions ranged from evil spirit expulsion, migraine and/or epilepsy treatment, to the surgical management of cranial injury [4,5]. Here we present the case of a trepanned skull recovered from the Capuchin Church of Comiso, which belonged to a middle-aged individual and shows evidence of healing, suggesting that the subject survived the surgery and beyond. The aim of this paper is to employ paleoradiology to 1) complement a macroscopic inspection of the paleopathological lesions present on this specimen; 2) obtain a better understanding of the consequences of the trauma and 3) create a permanent, digital record of this unique osteo-archaeological finding for future investigations.

2. Materials and methods

The Capuchin Church of Comiso, a religious building that was completed in the early 17th century, possesses (as an annexed structure) a mortuary chapel containing an assemblage of 46 mummified bodies located inside wall niches [6]. Some of the mummies are labelled with the individual's name and date of death, ranging from the mid-18th century to the mid-19th century. The mummies without a label may be even earlier. All of the bodies wear religious clothes, except for one, dressed in civilian clothes. Examination of the subjects reveals that the mummies are natural, and their preservation due to a process of draining cadavers typical of Sicily and the south of Italy [7,8]. The presence of a large number of skulls, within wall niches, suggests that this bone element was preserved as a symbol of social identity. Following autopsy of the mummies, carried out by a team with the University of Pisa in 1987, a reportedly adult male skull with evidence of trepanation was taken and stored in the university's museum of pathological anatomy until early 2016, when it was transferred back to its original location (Figs. 1 and 2). This skull lacks the mandible but shows areas covered by soft tissue. An accession number of the finding (101) is seen at the back of the skull. Upon inspection, the skull shows cribra orbitalia, periodontitis in the form of pitting of the alveolar processes, and calculus on the remaining tooth: the first left molar. Skull trepanation, along with a number of additional lesions, was also observed as initially described by Germanà and Fornaciari [9]. Prior to final entombment in the original crypt, the skull was CT-scanned in Messina University Hospital in 2016, using a Siemens Somatom Definition AS machine with a slice thickness of 0.6 mm. Computed tomography has in fact been reported as a technique for mummy investigation since 1979, and it is of relevance due to its non-invasiveness, the possibility of post-processing the data, as well as the creation of three-dimensional reconstructions [10]. As a result of these

* Corresponding author at: Department of Anatomy, Histology and Anthropology, Institute of Biomedical Sciences, MK Čiurlionis Street 21, LT-03101, Vilnius, Lithuania.
E-mail address: dario.piombino@mf.vu.lt (D. Piombino-Mascali).

https://doi.org/10.1016/j.jofri.2019.100342
Received 21 May 2019; Received in revised form 23 August 2019; Accepted 29 September 2019
Available online 30 September 2019

ACTA MEDICA LITUANICA. 2020. Vol. 27. No. 1. P. 17–24

High-grade well-differentiated neuroendocrine tumour of the cecum diagnosed following incisional hernia repair: a case report

Raimondas Juškys[1*],

Eligijus Poškus[2, 3],

Augustas Beiša[2, 3],

Liutauras Gumbys[4],

Donatas Jocius[4],

Raimundas Meškauskas[5],

Kęstutis Strupas[2, 3]

[1] *Department of Anatomy, Histology and Anthropology, Faculty of Medicine, Vilnius University, Vilnius, Lithuania*

[2] *Centre of Abdominal Surgery, Clinic of Gastroenterology, Nephrourology and Surgery, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania*

[3] *Centre of Abdominal Surgery, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania*

[4] *Centre of Radiology and Nuclear Medicine, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania*

[5] *National Centre of Pathology, Affiliate of Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania*

High-grade well-differentiated neuroendocrine tumour tumours (NETs) of gastrointestinal tract are rare; they can arise in any part of the digestive system and usually present in advanced stages. Low incidence and wide heterogeneity in the biological behaviour of such lesions pose a diagnostic and therapeutic challenge. Loco-regional NETs should be resected whenever feasible, potentially with a curative intent. Management of a metastatic disease is often more complex, primarily aimed at the alleviation of symptoms, prevention of further complications, and prolongation of survival. Current literature describing the optimal treatment plan for such patients is sparse and further studies are necessary to enhance our understanding of the disease. Here we present a case of high-grade well-differentiated cecal NET with an associated carcinoid syndrome that was diagnosed following the incisional hernia repair.

Keywords: case report, neuroendocrine tumour tumour, cecum, incisional hernia, carcinoid syndrome

* Correspondence to: Raimondas Juškys, Faculty of Medicine, Vilnius University, M. K. Čiurlionio St. 21, Vilnius 03101, Lithuania. Email: raimondas.juskys@mf.vu.lt

ACTA MEDICA LITUANICA. 2018. Vol. 25. No. 2. P. 53–60

Effectiveness of treatment of occipital neuralgia using the nerve block technique: a prospective analysis of 44 patients

Raimondas Juškys[1*],

Gytis Šustickas[2,3]

[1] *Faculty of Medicine, Vilnius University, Vilnius, Lithuania*

[2] *Department of Neurosurgery, State Vilnius University Hospital, Vilnius, Lithuania*

[3] *Faculty of Medicine, Utena University of Applied Sciences, Utena, Lithuania*

Background. There is a great deal of tools for treatment of occipital neuralgia but currently we are lacking a complete consensus among practitioners regarding the optimal approach to this debilitating condition. Occipital nerve block (ONB) is known as one of the management options but there is lack of scientific literature exploring its effectiveness.

Materials and methods. The prospective study was undertaken between March 2014 and February 2018 at the State Vilnius University Hospital. Forty-four patients aged from 28 to 84 years (age mean = 56.30 ± 14.71) of which 79.55% were female ($n = 35$) were diagnosed with occipital neuralgia (ON) and treated with a local anaesthetic and corticosteroids combination injection into the greater or greater plus lesser occipital nerve ($n = 29$ and $n = 15$, respectively) and followed up after 6 months. Analysis of the outcomes of those patients was done by comparing the Visual Analog Scale (VAS) and Barrow Neurological Institute Pain Intensity Score (BNIPIS) prior to treatment, 24 hours after the block, and at a follow-up 6 months later. Analgesic medication consumption before and after 6 months was recorded. A comparison of procedure efficacy in lidocaine and bupivacaine groups was made. Evaluation of block potency for acute and chronic pain categories was conducted as well. The success criteria were defined as patient satisfaction with own condition for at least 6 months, not requiring another block in order to stay comfortable.

Results. Of 44 patients, 42 (95.45%) who underwent the occipital nerve block procedure showed satisfactory results for at least 6 months. Mean headache VAS scores decreased from 7.23 ± 0.93 (pre-treatment) to 1.95 ± 1.59 (24 hours after, $p < 0.0001$) and increased to 2.21 ± 1.73 at the follow-up after 6 months, showing no statistically significant difference between post-interventional and six-month VAS scores ($p = 0.07$). In all patients the necessity of medication to control pain decreased to 16.67% ($n = 7$) during the the check-up after 6 months. There was no statistically significant difference in the effectiveness of ONB with regard to the local anaesthetic used or the pain group targeted. Similar results were obtained comparing patients who underwent more than one ONB.

Conclusions. Occipital nerve block with a local anaesthetic and corticosteroids provides a safe, simple, and effective treatment method for the patient with medically-refractory occipital neuralgia.

Keywords: occipital neuralgia, greater occipital nerve, lesser occipital nerve, occipital nerve block, headache

* Correspondence to: Raimondas Juškys, Faculty of Medicine, Vilnius University, M. K. Čiurlionio St. 21, Vilnius 03101, Lithuania. Email: raimondas.juskys@gmail.com

Vilnius University Press

Contents lists available at Vilnius University Press

Lietuvos chirurgija
2019, vol. 18(2), pp. 62–71

ISSN 1392–0995 eISSN 1648–9942
DOI: https://doi.org/10.15388/LietChirur.2019.18.7

Pathophysiology of severe traumatic brain injury and management of intracranial hypertension

Raimondas Juškys

Vilniaus universiteto Medicinos fakultetas, M. K. Čiurlionio g. 21/27, LT-03101 Vilnius, Lietuva
Faculty of Medicine, Vilnius University, M. K. Čiurlionio Str. 21/27, LT-03101 Vilnius, Lithuania
E-mail: raimondas.juskys@gmail.com

Vaiva Hendrixson

Biomedicinos mokslų institutas, Vilniaus universiteto Medicinos fakultetas, M. K. Čiurlionio g. 21/27, LT-03101 Vilnius, Lietuva
Institute of Biomedicine, Faculty of Medicine, Vilnius University, M. K. Čiurlionio Str. 21/27, LT-03101 Vilnius, Lithuania

Abstract. It is well recognized that severe traumatic brain injury causes major health and socioeconomic burdens for patients their families and society itself. Over the past decade, understanding of secondary brain injury processes has increased tremendously, permitting implementation of new neurocritical methods of care that substantially contribute to improved outcomes of such patients. The main objective of current treatment protocols is to optimize different physiological measurements that prevent secondary insults and reinforce the ability of the brain to heal. The aim of this literature review is to uncover the pathophysiological mechanisms of severe traumatic brain injury and their interrelationship, including cerebral metabolic crisis, disturbances of blood flow to the brain and development of edema, putting emphasis on intracranial hypertension and its current management options.

Key words: traumatic brain injury, head injury, head trauma, critical care, intracranial hypertension.

Sunkios galvos smegenų traumos patofiziologija ir intrakranijinės hipertenzijos gydymas

Santrauka. Gerai žinoma, jog sunki galvos smegenų trauma yra didelė našta pacientams, jų artimiesiems ir, apskritai, visuomenei. Per paskutinį dešimtmetį mūsų suvokimas apie antrinio smegenų pažeidimo procesus smarkiai išaugo. Tai leido sukurti naujų neurokritinių ligonių gydymo metodų, kurie svariai prisidėjo prie geresnių išeičių po sunkių galvos smegenų traumų. Pagrindinis gydymo tikslas – optimizuoti skirtingus fiziologinius parametrus, kurie sumažintų antrinį smegenų pakenkimą ir palengvintų smegenų galimybę gyti pačioms.

Pristatomos apžvalgos tikslas – atskleisti sunkios galvos smegenų traumos patofiziologinius mechanizmus ir jų sąveiką, įskaitant smegenų metabolinę krizę, kraujotakos sutrikimus ir edemos vystymąsi, daugiau dėmesio skiriant intrakranijinei hipertenzijai ir jos gydymo galimybėms.

Reikšminiai žodžiai: galvos smegenų trauma, smegenų pažeidimas, intensyvus gydymas, intrakranijinė hipertenzija.

Introduction

Traumatic brain injury (TBI) could be simply defined as an alteration in brain function due to external forces and is considered as one of the leading cause of death and disability worldwide, especially among young adults and the elderly. Current estimates imply that annual incidence of TBI is 50–60 million worldwide, and specifically for Europe and USA, 0.5% of Europeans and 1.1% of Americans are experiencing a TBI each year [1]. Fortunately, about 85% of those injuries are classified as mild. In case of severe TBI, there is a 40% mortality rate regardless of age [2]. TBI is commonly classified according to Glasgow Coma Scale (GCS) scores as mild (GCS 13–15), moderate (GCS 9–12), or severe (GCS 3–8). This scale, however, only helps to

Received 2019/01/10. **Accepted** 2019/02/27.

Current Applications of Deep Brain Stimulation for Treatment of Neurological and Psychiatric Disorders

R. Juškys*
R. Mameniškienė**

**Faculty of Medicine, Vilnius University, Vilnius, Lithuania*

***Department of Neurology and Neurosurgery, Center for Neurology, Vilnius University, Vilnius, Lithuania*

Summary. Deep Brain Stimulation (DBS) seems to be an effective and minimally invasive surgical treatment for a variety of neurological and psychiatric disorders. In comparison to early surgical lesioning procedures, DBS has a considerably lower adverse effect rate and is usually reversible, making this procedure very attractive. Despite the clinical success of DBS, the exact therapeutic mechanism remains under active debate. Current clinical trials focus on identification of alternative targets, establishing new indications and capturing electrical biomarkers during DBS in order to improve individual stimulation parameters. In this article we provide a comprehensive review of DBS focusing on movement, psychiatric and ictal disorders, including the historical evolution of the technique, applications and outcomes with an overview of the most pertinent literature, current views on mechanisms of stimulation and description of hardware and programming techniques. Finally, we conclude with a discussion of potential future applications of neurostimulation and currently active topics of research.

Keywords: deep brain stimulation, Parkinson disease, tremor, dystonia, depression, Tourette syndrome, obsessive-compulsive disorder, epilepsy, treatment.

Neurologijos seminarai 2017; 21(74): 201–207

INTRODUCTION

Deep brain stimulation (DBS) is a surgical procedure that involves unilateral or bilateral implantation of electrodes in a specific area of the brain. Electrodes are connected to wires which deliver a very fine electrical current to those regions in the brain from the generator placed inferiorly to the clavicle, under the skin. After recovery of the procedure, generators are activated and electrical parameters including pulse widths, current amplitudes and patterns of stimulation are tuned individually for each patient, hence desired clinical effect can be achieved. DBS in fact is an evolution of functional stereotactic neurosurgery techniques, initially used to produce selective lesions of specific deep brain structures. Formerly, intra-operative electrical stimulation of these targets was systematically used for the exploration and the localization of the deep cerebral nuclei and for target confirmation, but these observations led to suggestion that electrical stimulation method could not only be used for diagnostic purposes but also as a therapeutic method itself [1]. DBS is applied to a wide range of neurological and psychiatric disorders, including Parkinson's disease, essential tremor, dystonia, obsessive-compulsive disorder, treatment-resistant depression, Tourette syndrome, and epilepsy [2, 3]. The exact physiological mechanism of DBS remains unknown. Current theories include inhibition, excitation or disruption theory but to this day it is known that stimulation of certain groups of neurons in the brain stops pathological pattern of neuronal activity [4]. DBS is contraindicated for patients who have inability to operate the device or if test stimulation was unsuccessful. There is a potential for neuropsychiatric side-effects including depression, cognitive dysfunction, apathy, hallucinations or euphoria, but usually it is a consequence of poorly calibrated stimulation pattern or wrong site of implantation [5]. Additional limitations of DBS therapy that need to be considered prior to the surgery include risk for intracranial hemorrhage (in approximately 3% of all cases), electrode misplacement (in up to 2%), electrode migration (up to 1.7%) and electrode lead infection (1 to 8%) [3]. Nonetheless, principal feature of DBS attractiveness is that in case of undesired side effects it can be reversed at any time during the period of application, bringing patient back to pre-operational condition.

Address:
Raimondas Juškys
Faculty of Medicine, Vilnius University
M. K. Čiurlionio str. 21, LT-03101 Vilnius
E-mail: raimondas.juskys@gmail.com