Intracranial pressure management in patients with traumatic brain injury: an update

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Purpose of review
Intracranial pressure (ICP) monitoring and treatment is central in the management of traumatic brain injury. Despite 4 decades of clinical use, several aspects remain controversial, including the indications for ICP and treatment options.

Recent findings
Two major trials tested surgical decompression and mild hypothermia as treatments for high ICP. Both were rigorous, randomized, multicenter studies, with different designs. Decompression was tested for ICP refractory to conventional treatment, whereas hypothermia was offered as an alternative to conventional medical therapy. Decompression reduced mortality, but at the expense of more disability. The hypothermia trial was stopped because of a worse outcome in the treated arm. Indications for ICP monitoring have been reviewed and new international guidelines issued. New contributions published in 2016 have dealt with computerized analysis for predicting ICP crises; noninvasive or innovative methods for measuring ICP; reassessment of standard therapeutic interventions, such as hypertonic solutions and the level of intensity of ICP therapy.

Summary
Aggressive strategies for ICP control, like surgical decompression or hypothermia, carefully tested, have controversial effects on outcome. Several articles have made worthwhile contributions to important clinical issues, but with no real breakthroughs.

Keywords
decompression, hypothermia, intracranial pressure, outcome, traumatic brain injury

INTRODUCTION

Intracranial pressure (ICP) monitoring and therapy are based more on consolidated clinical experience than solid scientific evidence. In recent years, the value of ICP monitoring has been questioned, and the efficacy of some therapeutic interventions has been tested in randomized trials. This review looks at two major investigations: on surgical decompression and moderate hypothermia. In the meantime, guidelines for traumatic brain injury (TBI) management have been updated. We also selected from the recent literature (restricting the search to articles dealing with adults and published in English in the last 18 months) several contributions dealing with four main topics:

(1) indications for ICP monitoring
(2) computerized analysis for predicting ICP crises
(3) noninvasive or innovative methods for measuring ICP
(4) reassessment of standard therapeutic interventions, such as hypertonic solutions, and the level of intensity of ICP therapy.

SURGICAL DECOMPRESSION

The RESCUEicp trial [1▪▪] randomized 408 TBI patients with ICP higher than 25 mmHg for 1–12 h despite medical therapy to two arms: conventional treatment, including barbiturates, or surgical decompression. Patients were severe on admission (half had a Glasgow Coma Scale motor score of 1–2, and 29% presented pupillary abnormalities), and the two groups were well balanced. Follow-up at 6 and 12 months was done using a mail questionnaire or a telephone interview. Decompression markedly

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KEY POINTS

- Surgical decompression for intracranial hypertension refractory to conventional therapy decreased mortality after TBI in a large randomized trial (RESCUEicp); the effect on favorable outcome remains controversial, raising question about the acceptable quality of life in the most severe patients.
- Hypothermia, as first-line therapy for elevated ICP, showed a deleterious effect on long-term outcome after TBI in a multicentric trial: side effects and complications could offset the potential benefits of this therapy.
- Management of severe TBI patients using information from ICP monitoring is recommended in the BTF guidelines recently updated: the quality of evidence remains limited and based on observational studies.
- Noninvasive methods for ICP monitoring with no risk of brain damage or infection are under investigation, but they cannot yet be considered a valid alternative to intracranial probes.

reduced mortality (22% more survivors in the treated group) but more patients remained in a vegetative state or with severe disability. The findings of this study differ from those of the DECRA trial [2], which could not demonstrate any outcome improvement due to decompression and a very similar mortality in the two groups.

The two trials had different inclusion criteria and design: DECRA enrolled only patients with diffuse injury, and cases were randomized after a cumulative time of 15 min with ICP more than 20 mmHg. RESCUEicp included patients with a wide spectrum of brain damage and was designed with a pragmatic definition of ICP refractory to conventional therapies, for 1–12 h. Different criteria may explain why mortality in the DECRA conventional group was 18%, compared with 49% in the corresponding arm of RESCUEicp. Because of the more pragmatic design on RESCUEicp, its results may be more generalizable.

In RESCUEicp, decompression seems very effective in reducing mortality, but the question of quality of life in surviving patients remains open. The authors of RESCUEicp propose that in a subcategory of severe disability (patients needing home assistance but not continuously, unable to be independent in shopping or moving outside their homes), the outcome could be considered favorable, considering the severity of the initial brain damage. Only if this evaluation is accepted decompression can be considered to increase favorable outcomes compared with conventional treatment.

After decompression, when patients are more stable and ICP is no longer an issue, repair of the cranial defect is very useful. An article measuring outcomes and cerebral hemodynamics after cranioplasty documented clinical improvement in 43% of 54 patients [3].

HYPOTHERMIA

Hypothermia has been tested repeatedly in the last 20 years for improving outcome after TBI, with conflicting – often disappointing – results. A new multicenter trial (47 centers in 18 countries), which recruited 387 patients with ICP monitoring, was reported recently [4▪▪]. Cases were ventilated and sedated in the ICU; if ICP rose above 20 mmHg for at least 5 min, they were randomized to standard care (control group) or hypothermia (32–35 °C) and standard care. It is noteworthy that no conventional therapies against ICP rises, like mannitol, were used before randomization, with two consequences: hypothermia was employed as first-line treatment, even for cases who might have responded to simpler, less risky therapies.

Six months after injury outcome was evaluated with the Glasgow Outcome Scale. The outcome was significantly worse in the hypothermia arm than in the control group. This trial, which was stopped for safety concerns, demonstrated that hypothermia is a complex treatment with harmful side effects. If used as an alternative to milder therapies, it may worsen the outcome, probably because hypothermia-related complications offset the potential benefits (like ICP reduction) [5].

IS INTRACRANIAL PRESSURE MONITORING USEFUL? GUIDELINES, INDICATIONS, SIDE EFFECTS, AND POSSIBLE BENEFITS

High ICP is associated with worse outcome and particularly with increased mortality. This was confirmed by a recent analysis of prospectively collected minute-by-minute ICP data of 261 adults and 99 pediatric TBI patients from multiple European centers [6].

As ICP is dangerous, it seems rational to measure it, provided that cost and side effects are minimized. In developing countries, the costs of ICP monitoring may not be bearable, especially for intraparenchymal probes, which have the lowest incidence of infection compared with intraventricular/subdural catheters and give reliable and accurate pressure recordings. A recent article [7▪] describes the use of resterilized intraparenchymal strain gauge catheters. In 66 consecutive severe TBI patients, ICP was monitored using catheters resterilized with ethylene oxide. This was not associated with any

increases in the incidence of meningitis or fever (the surrogate marker for infection in this study). The accuracy of the reused device was not scientifically tested. This article raises a number of regulatory questions about accuracy and safety, but those concerns have to be weighed against the necessity (in difficult situations with financial restrains) of providing a level of monitoring and care that is standard in wealthy countries.

The Brain Trauma Foundation (BTF) guidelines for severe adult TBI have been updated, with endorsements by the American Association of Neurological Surgeons and the Congress of Neurological Surgeons [8▪]. Indications for ICP monitoring have changed from previous editions based on rigorous review of published evidence. The guidelines now indicate ICP monitoring 'with the recommendation that management of severe TBI patients using information from ICP monitoring may reduce in-hospital and 2-week postinjury mortality'. This recommendation leaves undefined who may benefit from ICP measurement. A pragmatic approach, based purely on clinical experience and consensus, tried to identify specific practical indications in comatose TBI patients, combining clinical and computed tomography (CT) scan findings [9].

A critical point is that the outcome depends on the interplay between severity and therapies (which may be guided by monitoring) and not directly on the monitoring modalities employed. Even the most valuable monitor is totally useless if effective therapy is not applied. Therefore, it is hard – even impossible – to prove a direct link between specific monitoring and outcome improvement. In fact, when this link was sought in a randomized trial, no differences in outcome were found [10]. A critical reappraisal of that study was then published, making it clear that the design of the investigation did not address the value of ICP monitoring itself [11] but rather the efficacy of two different therapeutic protocols.

Despite this background, the search for a possible 'demonstration' of ICP benefit is continuing. A systematic review and meta-analysis of 18 articles (including more than 13 000 cases) dealing with the relationships between ICP and several clinical parameters has been published [12]. This pooled analysis found no positive effect of ICP monitoring on hospital mortality, but possible 'benefits' in reducing the rates of electrolyte disturbances, renal failure, and a not clearly defined 'favorable' prognosis. A subsequent meta-analysis on the same topic [13] analyzed two randomized controlled trials and 16 observational trials, involving more than 25 000 patients. The main finding was significantly lower mortality in the ICP-monitored group. An additional observation seems a remarkable difference over time, that is before or after publication of the 2007 BTF guidelines for TBI: a better outcome with ICP monitoring could be identified only after those guidelines appeared.

The inherent limitations of the meta-analyses, despite the size of the samples, call for careful consideration; it is striking, for instance that two analyses have been based on a partially different selection of articles, reaching different conclusions. We believe that these exercises do not permit any firm conclusion, but may, at best, identify associations.

A retrospective analysis of 497 severe TBI patients in India based on the propensity score method (adjusting for covariates in comparing monitored patients with matching cases not monitored) indicated a modest reduction (8%) in mortality in patients who underwent ICP monitoring [14]. A similar retrospective analysis of 287 TBI patients without mass lesions in whom ICP was monitored was attempted in China [15]. After propensity score matching with 195 cases not monitored, ICP monitoring seemed significantly associated with lower 6-month mortality but not with favorable outcome.

Reduced mortality and a more favorable outcome seemed associated with ICP monitoring in a series of 80 patients aged more than 64 years in another study [16]. However, in view of the design of this study, which was purely observational, there can be no demonstration that ICP monitoring, rather than differences in other outcome predictors, caused the estimated benefit.

All these analyses, in conclusion, suggest at best an association between variables, including ICP monitoring and outcome. Because of methodological flaws, the proposed associations all seem extremely weak.

COMPUTERIZED ANALYSIS FOR PREDICTING INTRACRANIAL PRESSURE CRISES

The possibility of extracting more information, and possibly detecting warning signals of further deterioration, from ICP recordings is clinically very attractive. Two recent articles have addressed this desirable goal. Myers *et al.* [17] looked retrospectively at 817 TBI patients, using an algorithm aimed at predicting ICP crises in the next 30 min. Not unexpectedly, the main predictor of these crises was a previous high ICP. This is interesting, but very obvious for clinicians who know from experience that a patient with previous episodes of high ICP is at risk of further crises. The computerized analysis presented in the article may, at best, confirm this

clinical impression, rather than providing a new tool for identifying patients at risk.

As part of the BRAIN–IT effort, a model for better prediction of increases in ICP was developed years ago. Further validation of the model in new patients has been recently published [18]. Statistically (discrimination and calibration), the model performed well, though its clinical value remains unclear. Ideally, a model should warn of spontaneous ICP fluctuations due to changes over time of intracranial volumes and compliance. Prediction of these changes themselves would be extremely useful. In clinical reality, however, very often ICP rises because of nursing (suctions, movements, cleaning, etc.), and is controlled, or at least blunted, by therapies. If these events are not taken into consideration, it is unlikely that a computerized system will 'predict' nursing and other interventions, or 'understand' the therapy applied. A precondition for a clinically reasonable model is that events causing ICP rises or attenuating ICP fluctuations should be clearly identified and separate from spontaneous, dangerous ICP crises. This information is not provided in the studies reviewed.

NONINVASIVE AND INNOVATIVE METHODS FOR ESTIMATING INTRACRANIAL PRESSURE

Different techniques have been developed in the last 3 decades to estimate ICP noninvasively [19]; these have the obvious advantage of minimizing the risks of brain injury and infection. Transcranial Doppler ultrasonography (TCD) is a well tolerated bedside technique to detect cerebral blood flow velocity in the large cerebral arteries. Analyses of the flow velocity waveform have been implemented to estimate ICP and autoregulation. Cardim *et al.* [20] examined different TCD parameters for calculating ICP in 40 TBI patients. Beside statistical observations (three out of four analytical methods found a significant relationship between ICP and TCD), the results did not indicate any usable, noninvasive technique for ICP monitoring.

The optic nerve sheath contains cerebrospinal fluid (CSF) and communicates with intracranial CSF spaces. Being extensible, changes in ICP and CSF pressure may influence its volume and diameter. The optic nerve sheath diameter (ONSD) behind the ocular globe can be examined by ultrasound, magnetic resonance imaging, and CT and has promising correlations with ICP. The diameter may, however, change in proportion to other anatomical structures, being larger in patients with larger ocular bulbs. A recent study [21] introduced a new parameter, the ONSD-to-eyeball diameter ratio, rather than simply the nerve sheath diameter, as an indicator of ICP. The findings seem preliminary, so further validation is needed.

A swollen brain seems synonymous with high ICP, because reduction of CSF spaces, especially in the basal cisterns, is very often associated with intracranial hypertension and then with worse outcome. This relationship, however, may be influenced by other factors besides ICP. Changes induced by ICP may vary depending on the actual CSF spaces under normal conditions: for instance, young patients have smaller CSF spaces than elderly, atrophic cases. A global, quantitative ICP estimate has been attempted using an algorithm that semiautomatically segments the brain parenchyma from the CSF. In 45 CT scans from 20 TBI patients, the ratio of CSF to parenchymal volume was calculated and then plotted against the actual ICP. The results seem promising, with some cases showing a clear relation between pathologically reduced CSF spaces and high ICP. However, the distinction was not constant, so this must be viewed as a preliminary exploration [22].

To minimize infection, another approach is on the horizon. Kang *et al.* [23▪] recently described an innovative device for ICP and brain temperature monitoring. It is a bioresorbable and biocompatible silicon sensor that performs to a level of accuracy similar to commercial probes. Data collection is wireless, excluding the system from any direct external connection, and therefore limiting possible side effects to the insertion phase. These features could reduce the risk of infection and displacement related to percutaneous wires and make ICP monitoring safer for TBI patients. The sensor has been tested on rats, but further development can reasonably be expected in humans.

INTRACRANIAL PRESSURE THERAPY: OSMOTIC THERAPY AND THERAPY INTENSITY LEVEL

Osmotic agents such as mannitol or hypertonic solutions (HTS) have been used for decades to lower ICP. A Canadian group [24] retrospectively reviewed 124 TBI patients in two centers where continuous infusion of 3% HTS was used. HTS effectively lowered ICP but was associated with hypernatremia.

Any given ICP value, for instance 25 mmHg, has a quite different meaning if recorded without therapy or during maximal treatment. The amount of therapy used to control ICP must therefore be quantified for accurate interpretation. This observation led to the 'therapy intensity level' (TIL) concept. A novel approach to assess TIL has been developed as part of the Interagency Common Data Elements [25] scheme. This TIL has been validated in an observational trial [26].

CONCLUSION

Despite conflicting evidence, ICP monitoring is still a cornerstone in treating TBI, helping to reduce mortality. New observational studies and meta-analyses support this, even though monitoring itself does not influence the outcome.

To improve the ICP cost–benefit ratio in everyday practice studies on reducing costs and side effects have been published; the quest for noninvasive approaches to ICP measurement still has a long way to go.

Two major RCTs have been published, showing debatable advantages (decompressive craniectomy) or harmful effects (therapeutic hypothermia).

Management of intracranial hypertension will continue to rely on solid clinical experience, with prudent use of aggressive therapies, because extreme treatments carry extreme side effects.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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In this trial involving 52 centers, 408 patients were randomized to decompressive craniectomy or medical therapy for refractory intracranial hypertension, defined as intracranial pressure (ICP) greater than 25 mmHg for 1–12 h despite conventional treatment. Decompressed patients had lower 6-month mortality than controls, but higher rates of vegetative states and severe disability. This finding was different from a previous study [2] that found no difference between surgical and medical groups. Probably, this was due to different inclusion criteria in the two trials, with more severe cases in the latter and more liberal use of decompression in the former. In most severe cases, decompression may increase favorable outcomes compared with conventional treatment, but at the expense of more patients surviving with severe disability. Therefore, careful selection of candidates is essential.

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This randomized controlled trial involving 47 centers evaluated hypothermia as a first-stage treatment for ICP higher than 20 mmHg lasting more than 5 min. It enrolled 387 patients ventilated and sedated in the ICU. No conventional therapies against ICP rises, such as mannitol, were used before randomization. The trial was stopped for health safety reasons. Therapeutic hypothermia as first-stage treatment for increased ICP should be avoided, but its role as extreme therapy has not been adequately addressed.

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