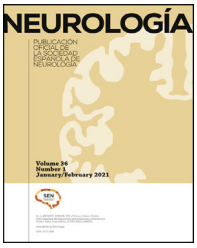
Neurología 38 (2023) 357—363

NEUROLOGÍA

www.elsevier.es/neurologia



REVIEW ARTICLE

Current status and outlook for the management of intracranial hypertension after traumatic brain injury: decompressive craniectomy, therapeutic hypothermia, and barbiturates

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Received 17 February 2020; accepted 4 August 2020
Available online 7 April 2023

KEYWORDS
Traumatic brain injury;
Refractory intracranial hypertension;
Decompressive craniectomy;
Therapeutic hypothermia;
Barbiturates

Abstract
Introduction: Increased intracranial pressure (ICP) has been associated with poor neurological outcomes and increased mortality in patients with severe traumatic brain injury (TBI). Traditionally, ICP-lowering therapies are administered using an escalating approach, with more aggressive options reserved for patients showing no response to first-tier interventions, or with refractory intracranial hypertension.
Development: The therapeutic value and the appropriate timing for the use of rescue treatments for intracranial hypertension have been a subject of constant debate in literature. In this review, we discuss the main management options for refractory intracranial hypertension after severe TBI in adults. We intend to conduct an in-depth revision of the most representative randomised controlled trials on the different rescue treatments, including decompressive craniectomy, therapeutic hypothermia, and barbiturates. We also discuss future perspectives for these management options.
Conclusions: The available evidence appears to show that mortality can be reduced when rescue interventions are used as last-tier therapy; however, this benefit comes at the cost of severe disability. The decision of whether to perform these interventions should always be patient-centred and made on an individual basis. The development and integration of different physiological variables through multimodality monitoring is of the utmost importance to provide more robust prognostic information to patients facing these challenging decisions.

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https://doi.org/10.1016/j.nrleng.2020.08.024

PALABRAS CLAVE
Traumatismo craneoencefálico (TCE);
Hipertensión intracraneal refractaria;
Craniectomía decompresiva;
Hipotermia terapéutica;
Barbitúricos

Estado actual y perspectivas futuras en el manejo de la hipertensión intracraneal posterior a traumatismo craneoencefálico: craniectomía descompresiva, hipotermia terapéutica y barbitúricos

Resumen
Introducción: El aumento de la presión intracraneal (PIC) se ha asociado a un pronóstico neurológico desfavorable y a un incremento en la mortalidad en pacientes con traumatismo craneoencefálico (TCE) grave. Tradicionalmente, las terapias para disminuir la PIC se administran utilizando un enfoque progresivo, reservando el uso de opciones más agresivas para los casos sin respuesta a intervenciones de primer nivel, o de hipertensión intracraneal (HTIC) refractaria.
Desarrollo: El valor terapéutico de las intervenciones de rescate para la HTIC, así como el momento adecuado para su uso ha sido debatido constantemente en la literatura. En esta revisión, discutiremos las principales opciones de tratamiento para la HTIC refractaria posterior a un TCE grave en adultos. Tenemos la intención de llevar a cabo una revisión a profundidad de los ensayos controlados aleatorios (ECA) más representativos sobre las diferentes intervenciones terapéuticas de rescate, incluyendo; la craniectomía decompresiva (CD), hipotermia terapéutica (HT) y barbitúricos. Además, discutiremos las perspectivas futuras de estas opciones tratamiento.
Conclusiones: La evidencia parece mostrar que se puede reducir la mortalidad al utilizar estas intervenciones de rescate como terapia de último nivel, sin embargo, este beneficio viene acompañado de una discapacidad severa. La decisión de realizar o no estas intervenciones debe ser individualizada y centrada en el paciente. El desarrollo e integración de diferentes variables fisiológicas a través del monitoreo multimodal (MMM) es de suma importancia para poder proporcionar información pronostica más sólida a los pacientes que enfrentan este tipo de decisiones.

Introduction

Intracranial hypertension (IH) following traumatic brain injury (TBI) is associated with higher mortality rates and poorer neurological outcomes.[1–3] The main aims of intracranial pressure (ICP) monitoring and management are to enable timely detection of secondary brain lesions and to optimise therapeutic interventions.[4] ICP and cerebral perfusion pressure are important factors involved in the development of secondary brain lesions, and have been linked to the brain ischaemia observed after the primary injury; therefore, they have a considerable impact on neurological outcomes.[5–7]

The most recent Brain Trauma Foundation (BTF) guidelines recommend reducing ICP after TBI if levels are greater than 22 mm Hg.[8] Treatments to decrease ICP are generally administered progressively, with more aggressive options generally being reserved for refractory cases that do not respond to first-tier treatments.[9] This tiered treatment generally follows an empirical approach, and includes such strategies as sedation and analgesia, hyperosmolar agents, cerebrospinal fluid drainage, induced hypocapnia, barbiturates, temperature modulation, and decompressive surgery.[10]

The literature includes little information on the frequency with which ICP is refractory to first-tier treatments and a higher-tier treatment must be used.[11,12] A recent study reported that the need for more aggressive treatment to manage ICP was associated with less favourable neurological outcomes and higher mortality rates; however, these measures are only needed in a minority of cases.[12]

The value of the classical thresholds for ICP management has been debated in recent years. The BEST-TRIP clinical trial,[13] conducted in South America, found no differences in neurological outcomes between treatment focusing on ICP and treatment based only on imaging studies and neurological examination. The authors concluded that treatment focused on keeping ICP at or below 20 mm Hg is not superior to treatment based on imaging and clinical examination.[13] However, current consensus regarding that conclusion is that the trial did not truly test the value of monitoring ICP; rather, it compared the efficacy of 2 methods of managing IH.[14] The main repercussion of the BEST-TRIP trial has been an increase in research efforts to establish the clinical profile of patients with severe TBI and identify which patient profiles may benefit from ICP monitoring, supporting the argument that more comprehensive, individualised approaches should be taken in future research.[15,16]

The potential therapeutic value of more aggressive interventions for IH, as well as the optimum time when they should be administered, have been a subject of constant debate. This review addresses the main therapeutic options for refractory IH following severe TBI, focusing on the current role and future perspectives of decompressive craniectomy (DC), therapeutic hypothermia (TH), and barbiturates.

Decompressive craniectomy

A considerable body of evidence supports the role of DC as an effective treatment to control ICP.[17–23] DC can be categorised into 2 types, primary and secondary. Primary DC is a prophylactic intervention to prevent potential damage caused by brain oedema.[20] Secondary DC is usually a last-resort treatment option used in cases refractory to medical

treatment; however, although to a lesser extent, it has also been performed early in individuals with less sustained IH.[20]

Two recent randomised clinical trials, the DECRA[21] and RESCUEicp trials,[22] assessed the role of DC in the treatment of IH following severe TBI. Their contrasting results have led to a debate about the optimum time to perform DC and the long-term effects of the treatment in the context of TBI.

In the DECRA trial,[21] reported in 2011, adults with TBI and IH refractory to first-tier treatments were randomly allocated to undergo bifrontal DC or receive standard medical treatment.[21] Compared to medical treatment, surgical decompression was associated with lower mean ICP and shorter stays at the intensive care unit. Mortality rates were similar in both groups, although unfavourable neurological outcomes were more frequent in the surgery group than in the standard care group.[21]

This study has been criticised for several reasons.[23] Firstly, the criteria used (ICP > 20 mm Hg for >15 minutes during a one-hour period, despite optimised first-tier treatment) have been considered insufficient to indicate surgical management. Secondly, the study excluded patients with intracranial masses. Finally, several authors consider the surgical technique selected (bifrontal DC) to be inappropriate.[11,23] Despite these issues, the results of the DECRA trial are highly relevant, providing compelling evidence that early indication of ''neuroprotective'' bifrontal DC is not superior to standard medical treatment for severe TBI.[24]

The results of the RESCUEicp trial were published more recently. In this trial, patients were randomly allocated to undergo DC (in this case, hemicraniectomy or bifrontal craniectomy) or standardised medical treatment. Inclusion criteria were ICP greater than 25 mm Hg of 1-12 hours' duration, and lack of response to first- and second-tier interventions.[22]

As in the DECRA trial, DC was associated with a reduction in ICP, compared to standard treatment. However, the RESCUEicp trial did find significantly lower mortality rates in the DC group, although this benefit was associated with higher rates of severe disability.[22] Only 36% of DC survivors presented favourable long-term neurological outcomes.[22]

The limitations of the RESCUEicp trial include the fact that it does not analyse data according to the type of surgery performed. Furthermore, a relatively high percentage of patients (37%) from the standard treatment group underwent DC due to the failure of medical treatment to control ICP.[11,22]

The differences in the results reported in these 2 trials may be attributed to differences in the study hypotheses, inclusion/exclusion criteria, and treatment protocols. RESCUEicp analysed the use of DC as a last-tier or rescue therapy, whereas DECRA assessed earlier indication of this intervention. Compared to the DECRA trial, inclusion in the RESCUEicp trial required higher ICP levels and resistance to more aggressive treatments.[25]

One significant issue with the RESCUEicp trial is the authors' definition of favourable neurological outcomes, which included ''upper severe disability.''[22] While the results appear to support the use of DC in the context of severe TBI, several important ethical questions have been raised.[26] Firstly, to justify this change in the traditional classification of results, researchers asked survivors with severe disability whether they regretted undergoing the procedure and whether, in retrospect, they would have agreed to participate had they known the final outcome in advance. These studies have shown a high level of ''retrospective consent'' and support considering ''upper severe disability'' as an acceptable outcome. However, an alternative interpretation is that these patients have adapted to living with significant disability, which they previously would have considered unacceptable[26—28]; moreover, there may be a class of patients who would consider a given level of disability to be unacceptable from the initial discussion.[28] The results of the DECRA and RESCUEicp trials highlight our ethical responsibility to patients who definitively express that they would consider it unacceptable to live with severe disability.[26]

In the light of the conclusions of these studies, we should follow a more holistic, evidence-based approach to the management of IH in severe TBI. Despite the available data, many important questions remain unanswered. While the evidence seems to show that DC as a last resort can reduce mortality rates, the procedure is associated with high costs in terms of patient independence.[29] Deciding whether or not to perform DC will always be a challenge, and the data reported by these 2 trials may be useful in generating a patient-centred discussion about realistic expectations and outcomes.[27]

The latest BTF guidelines do not recommend bifrontal DC in patients presenting severe TBI with diffuse lesions and ICP elevation above 20 mm Hg lasting more than 15 minutes in a one-hour period, showing resistance to first-tier treatment; however, these guidelines were issued prior to the publication of the RESCUEicp trial and have not yet been updated.[8]

Although both trials conclude that treatment focused on ICP management does not improve long-term outcomes, it is yet to be established whether there is a subset of patients who do stand to benefit from surgical decompression. It is for this reason that multimodal monitoring (MMM) can be useful.[26] Models including different physiological variables have shown greater predictive capacity than traditional ICP thresholds, and can be valuable for decision-making, providing specific, individualised information.[30—32]

Therapeutic hypothermia

TH has been considered an attractive treatment strategy for severe TBI, as it provides multiple theoretical benefits, including reduced ICP, increased cerebral perfusion pressure, reduced cerebral oxygen consumption, reduced concentrations of excitatory neurotransmitters and inflammatory mediators, and potentially maintenance of blood-brain barrier integrity.[33] Although animal studies into this intervention have shown promising results, these have not been replicated in subsequent clinical studies.[33—35]

Clinical trials of TH have taken 2 approaches: short-term and long-term TH. In 2001, the NABIS:H study[36] evaluated short-term TH as a possible neuroprotective strategy. TH was started in the first 6 hours after TBI, and was maintained for 48 hours. This trial found no differences between the hypothermia and normothermia groups; one important issue with the study is the significant difference in success rates

between the participating centres.[36,37] Subsequently, the NABIS:H-II trial[38] aimed to address issues with the first study, limiting participation to specialised centres with experience using TH. In this study, TH was started in the first 2.5 hours after TBI, and was maintained for 48 hours. The study was terminated early due to the lack of differences between the hypothermia and normothermia groups.[38] Furthermore, the TH group showed higher ICP levels than the normothermia group. It has been suggested that this may be explained by a rebound effect due to the short duration of TH.

A subgroup analysis found that TH may be useful in patients with intracerebral haematoma[38]; this hypothesis is under study in the HOPES trial, which is currently underway.

The NABIS:H and NABIS:H-II trials suggest that short-term TH does not improve neurological outcomes or provide neuroprotection in severe TBI. As a result, subsequent studies have focused on prolonging TH beyond 48 hours.[37]

In the Eurotherm3235 trial,[39] published in 2015, patients with IH refractory to first-tier interventions up to 10 days post-injury were randomly allocated to the TH or normothermia groups. Patients in both groups may receive second-tier (mannitol, hypertonic solutions, inotropic agents) or third-tier treatments (barbiturates or DC). ICP levels were similar in both groups, although fewer patients in the TH group required second-tier interventions, suggesting better ICP control with this treatment.[40] An interim analysis found that the TH group presented a greater number of patients with unfavourable neurological outcomes, as well as a higher mortality rate. As a result, the trial was terminated early. However, it is unclear whether this increase in the rate of unfavourable outcomes was related to TH or to the longer duration of treatment resistance itself. Critics of this study argued that it did not control for the use of second- and third-tier interventions in either group, and did not study the effectiveness of TH in patients with refractory IH.[33,41,42]

Another study published in 2015, the B-HYPO study,[43] also assigned patients to TH or normothermia following severe TBI. In this trial, TH was applied for at least 72 hours. The study was terminated early due to slow recruitment, and no significant differences in neurological outcomes or mortality rates were observed between the 2 groups; the authors concluded that long-term TH does not improve mortality rates after severe TBI.[43]

Finally, the POLAR study,[44] published in 2018, aimed to determine whether early, sustained, prophylactic TH (duration, 3—7 days) improves long-term neurological outcomes. The authors concluded that this treatment does not improve neurological outcomes at 6 months, compared to normothermia. Similarly, the LTH-1 trial, which is currently underway, aims to determine whether TH applied for 5-14 days is associated with better 6-month outcomes. The central hypothesis of that study is that longer exposure to TH may attenuate cytotoxic oedema and intracellular neurotoxic cascades.[35,45]

The most recent BTF guidelines, published in 2017, do not recommend early (within 2.5 h), short-term (48 h post-injury) prophylactic TH to improve neurological outcomes in patients with TBI,[8] although they do not give an opinion on the use of TH to treat refractory IH. These guidelines were published prior to completion of the POLAR and LTH-1 studies and have not yet been updated.

There are significant methodological differences between these studies, and their conclusions do not necessarily present a unified argument against using TH. However, efforts to find evidence in favour of early TH have clearly been unsuccessful.[40] Currently, TH should not be used for prophylaxis or in patients with IH responsive to first- or second-tier interventions, except within the context of a clinical trial.[40] According to the current evidence, the use of TH should be restricted to cases in which few alternatives remain, as a last resort or rescue therapy. This is currently the only potential indication for TH, pending the results of the clinical trial underway.[40]

Barbiturates

Several mechanisms have been proposed to explain the therapeutic effects of barbiturates in the context of severe TBI. Barbiturates depress cerebral oxygen consumption, reducing cerebral blood flow and causing a proportional decrease in ICP.[46] In addition to the reduction in ICP, studies have also reported a reduction in excitatory amino acids, which may decrease excitotoxicity in TBI,[47] and an increase in brain tissue partial pressure of oxygen ($PbtO_2$) associated with pentobarbital use.[48—50]

Four randomised clinical trials have assessed the use of barbiturates to control ICP following severe TBI in adults. In 1984, Schwartz et al.[51] reported a multicentre study comparing the effectiveness of pentobarbital and mannitol in reducing ICP, including a total of 59 patients with severe TBI and IH. Pentobarbital was administered as soon as possible after onset of IH. The authors found pentobarbital to be less effective than mannitol for lowering ICP, and reported no significant intergroup differences in mortality at one year.[51]

Ward et al.[52] conducted a similar study, evaluating the possible neuroprotective effect of early barbiturate therapy. Fifty-three patients with TBI and presenting evidence of intracranial haematoma, with indication of surgical decompression or whose best motor response was abnormal posture, were randomly allocated to the pentobarbital or the control groups. IH was managed with hyperventilation, cerebrospinal fluid drainage, and mannitol in all patients. Patients in the experimental group also received pentobarbital, which was administered as early as possible regardless of ICP values. No significant differences between groups were observed in ICP control, IH duration, or treatment response, or in mortality at one year; furthermore, the barbiturate group presented higher rates of hypotension and sepsis. Although the prophylactic use of pentobarbital in severe TBI cannot be recommended, it may be necessary as a last resort after failure of other measures to reduce ICP.[52]

A study by Eisenberg et al.[53] exclusively evaluated the effectiveness of barbiturates in the treatment of IH refractory to first-tier interventions. Seventy-three patients with severe TBI and refractory IH were randomly allocated to receive conventional treatment (control group) or conventional treatment plus pentobarbital (barbiturate group). The results showed that pentobarbital was beneficial for control-

ling ICP, although only 12% of the patients potentially eligible for inclusion met the ICP threshold established for randomisation; therefore, the authors conclude that pentobarbital may be effective after failure of the remaining treatments, although it would only be indicated for a specific subset of patients.[53]

In 2008, Pérez-Bárcena et al.[54] compared the effects of pentobarbital and thiopental in reducing ICP. Forty-four patients with severe TBI and IH were randomly assigned to receive pentobarbital or thiopental after failure of first-tier measures. ICP was adequately controlled in 28% and 50% of cases, respectively. The authors concluded that thiopental appears to be more effective than pentobarbital for controlling refractory IH, but urge caution in interpreting their results due to the differences observed between groups in imaging findings at baseline and in the doses administered, as well as the fact that the study lacked the sufficient statistical power to detect differences in neurological outcomes.[55]A Cochrane systematic review[56] evaluated randomised clinical trials studying barbiturates as part of the treatment of severe TBI, and has been updated periodically. The latest update, in 2012, concludes that there is insufficient evidence supporting the utility of barbiturates in severe TBI. Barbiturates cause hypotension in one in 4 patients, offsetting any reduction in ICP.[56] The current BTF guidelines recommend high doses of barbiturates only in cases of IH refractory to maximum standard medical and surgical treatment, and recommend against their use for prophylaxis. The guidelines also stress the importance of haemodynamic stability before and during treatment with barbiturates.[8]

A recent retrospective study into the use of barbiturates in patients with TBI from 13 European centres found that fewer than 20% of patients received these drugs, with only 6% of these receiving high doses. High-dose barbiturate therapy was associated with a reduction in ICP, but also caused haemodynamic instability; furthermore, no significant differences in long-term outcomes were observed between the barbiturate and the control groups.[57]

One important issue for consideration in evaluating barbiturates and their use to treat TBI is that their capacity to reduce ICP varies according to individual patient characteristics, lesion type, and time of administration. Cormio et al.[46] reported that 15% of patients treated with barbiturates in their cohort did not respond to the treatment, and 40% only responded partially; this may be explained by the considerable variations in brain metabolism between patients and brain regions.[46] Considerable differences have also been reported in brain tissue oxygenation after pentobarbital administration: although an increase in $PbtO_2$ is generally observed, some patients with more severe involvement may develop an inverse response, with a decrease in $PbtO_2$.[50]

MMM incorporating such variables as pressure reactivity index, $PbtO_2$, and brain metabolism may be a valuable tool in evaluating barbiturate therapy, and may assist in determining how different haemodynamic, pathophysiological, and brain profiles respond to treatment.[47,49,50] However, the most suitable tests and equipment for MMM are not currently available at all centres.

Conclusion

Although several important questions remain unanswered, the available evidence on these 3 forms of treatment does not support their use as early prophylactic or neuroprotective therapy. Regarding DC, we know that its use as a last-tier intervention may decrease mortality rates; however, this benefit is associated with an increased risk of severe disability. Therefore, this approach is not considered appropriate. Based on the available evidence, similar conclusions may be drawn regarding TH. It is apparent that early application of TH provides no benefit and does not decrease mortality rates. Currently, TH should not play a role in the treatment of TBI, although it may potentially be useful in cases of refractory IH or as a last resort in progressive approaches to the management of severe TBI.[38,40]

Barbiturates play an important role as a rescue therapy to reduce ICP. However, given the high number of secondary effects and the haemodynamic instability they cause, current guidelines recommend that their use be restricted to refractory cases, which has led to a reduction in their use.[8,57] Given that the last clinical trial evaluating the general efficacy of barbiturates was conducted more than 25 years ago, further research analysing their effects on mortality and quality of life may be useful, especially in the light of the latest results reported for DC and TH. A more sophisticated approach including analysis of different physiological variables may help to explain the variations in treatment response associated with different patient profiles.[46,50,57]

These types of treatment should not be overlooked, as the therapeutic options for IH and severe TBI remain limited. Overall, we believe that in the light of the current evidence, these approaches should be considered exclusively as rescue therapy, and their use should be restricted to patients who do not respond to the other types of treatment. The clinical trials reviewed underscore the need to review the classic thresholds for ICP monitoring. Furthermore, the development and integration of different physiological variables in MMM is highly important for future research into the management of IH and severe TBI.

Conflicts of interest

The authors have no conflicts of interest to declare.

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