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REVIEW

The management of pediatric severe traumatic brain injury: Italian Guidelines

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ABSTRACT

INTRODUCTION: The aim of the work was to update the "Guidelines for the Management of Severe Traumatic Brain Injury" published in 2012, to reflect the new available evidence, and develop the Italian national guideline for the management of severe pediatric head injuries to reduce variation in practice and ensure optimal care to patients.

EVIDENCE ACQUISITION: MEDLINE and EMBASE were searched from January 2009 to October 2017. Inclusion criteria were English language, pediatric populations (0-18 years) or mixed populations (pediatric/adult) with available age subgroup analyses. The guideline development process was started by the Promoting Group that composed a multidisciplinary panel of experts, with the representatives of the Scientific Societies, the independent expert specialists and a representative of the Patient Associations. The panel selected the clinical questions, discussed the evidence and formulated the text of the recommendations. The documentarists of the University of Florence oversaw the bibliographic research strategy. A group of literature reviewers evaluated the selected literature and compiled the table of evidence for each clinical question.

EVIDENCE SYNTHESIS: The search strategies identified 4254 articles. We selected 3227 abstract (first screening) and, finally included 67 articles (second screening) to update the guideline. This Italian update includes 25 evidence-based recommendations and 5 research recommendations.

CONCLUSIONS: In recent years, progress has been made on the understanding of severe pediatric brain injury, as well as on that concerning all major traumatic pathology. This has led to a progressive improvement in the clinical outcome, although the quantity and quality of evidence remains particularly low.

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KEY WORDS: Brain injuries, traumatic; Glasgow Coma Scale; Pediatrics; Guideline.

Introduction

Traumatic brain injury (TBI) is the leading cause of death and disability in children and the most frequent traumatic disease in pediatric population.

TBI is classified in three categories of severity based on the Glasgow Coma Scale (GCS): mild (GCS, 14-15), moderate (GCS 9-13) and severe (GCS≤8).[1]

The rate of TBI identified on Computed Tomography (CT) is 5% for children with mild injuries, 27% for those with moderate injuries, and 65% for those with severe injuries.[1, 2]

A wide number of publications, guidelines and clinical prediction rules were published to aid physicians to manage mild head injuries.

In 2004 the S.A.R.N.eP.I (Società di Anestesia e Rianimazione Neonatale e Pediatrica Italiana [Italian Society of Neonatal and Pediatric Anesthesia and Intensive Care], Rome, Italy) published the Italian Guideline on the management of severe TBI. After this publication, many articles on the same topic were issued including the guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents.[3]

Evidence-based medicine is playing an increasing role in the direction of medical practice. A management decision based on solid evidence that allows to understand not only the evidence supporting various therapeutic options but also the rigor of the evidence should offer the highest degree of confidence that the correct choice has been made. For this reason, we decided to update the clinical practice guideline on the management of severe TBI in children to reflect the new available evidence and develop the Italian national guideline for the management of severe pediatric head injuries to ensure the optimal care to patients. The present guideline is an attempt to assist physicians in the management of children younger than 18 years of age after a severe head injury. This guideline addresses key issues relating to the management of severe TBI in pediatric patients (age<18 years) with a Glasgow Coma Scale score of 3-8. The guidelines on severe pediatric brain injury proposed by our group results as an update to the "Guidelines for the Management of Severe Traumatic Brain Injury" published in 2012.[3]

This document should not be considered as a stand-alone tool of guidance in the management of pediatric severe head injury. Moreover, the assessment and management of cervical spine injuries that may be associated with head trauma will not be specifically addressed in this document. Finally, this document should not only be used as a roadmap to improve treatment, but also as a template from which to generate high quality research for future use.

Evidence acquisition

Development process

The guideline development process was started by the Promoting Group (PG) including the SARNePI and SIAARTI (Società Italiana di Anestesia Analgesia Rianimazione e Terapia Intensiva [Italian Society of Anesthesia, Analgesia and Intensive Care], Rome, Italy) Societies and by the Meyer Children's University Hospital of Florence. The PG composed a multidisciplinary panel of experts (PoE), with the representatives of the Scientific Societies, the independent expert specialists and a representative of the Patient Associations. The PG in agreement with the PoE has addressed the work towards an update of the previous "Guidelines for the acute medical management of severe traumatic brain injury in infant, children and adolescent, second edition (2012)."[3]

The PoE selected the clinical questions, discussed the evidence and formulated the text of the recommendations. The documentarists of

the University of Florence oversaw the bibliographic research strategy. A group of literature reviewers composed of anesthesiologists, neurologists, neurosurgeons, pharmacists, biologists and epidemiologists evaluated the selected literature and compiled the table of evidence (ToE) for each clinical question. The scientific secretariat oversaw the organization, management of work groups, programming, and supervision.

Search strategy

The research strategies adopted in the original guidelines[3] have been replicated, on the EMBASE and MEDLINE databases. The literature review aimed at identifying the evidence base for the guideline update, was searched for the period between 01 January 2009 and 31 October 2017, with the following fixed key words: (craniocerebral trauma[MeSH Terms] OR head injur* OR brain injur*).

Specific search strategies combined with fixed term were run for each question.

Study selection

The list of generated titles and abstracts generated was screened for the assessment of relevance. A second screening was performed on the full text of the selected articles. The included studies were assessed with the tools used in the original guideline and summarized in a ToE.

Papers were selected among systematic reviews or meta-analysis, randomized controlled trials, observational studies (cohort and case-control). Narrative reviews or editorial and letters to the editors were excluded (Supplementary Digital Material 1: Supplementary Table I).

We selected studies published in English, conducted on pediatric populations (0-18 years) or on mixed populations (pediatric/adult) with available age subgroup analyzes.

Results were supplemented with literature identified from reference lists or recommended by peers.

Quality assessment and grading system

The quality assessment of each study was assigned considering the design and the possible presence of bias.

We classified as evidence class I the RCTs (Randomized control trials) of good quality with adequate randomization, allocation concealment, blindness, ITT (Intention to treat) analysis, and lost to follow-up.

Class II was assigned to RCT of moderate / poor quality, or to good quality cohort or case-control studies. Class III, finally, concerns observational studies of poor quality, and case-series.

The overall quality of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method,[4] also adopted by the original guideline.[3] The method assesses, for each selected outcome, the quality of evidence, the inconsistency among different studies, the indirectness and the imprecision.

The recommendations provided by the original document[3] have therefore been updated considering: 1) the quality and quantity of the evidence already available for each clinical question; 2) the quality and amount of the evidence selected by the update work; and 3) the opinion of the PoE.

The grading of the recommendations was expressed through the wording. The term "must" expresses a conviction greater than that expressed by the term "should be," which in turn expresses a conviction greater than that expressed by the term "can be" and the choice between the three terms is a direct function of the overall quality of the evidence and opinion of the PoE.

The weight given to the opinion of the PoE was inversely proportional to the quality and amount of available evidence.

Evidence synthesis

The search strategies identified 4254 articles. We selected 3227 abstract (first screening) and, finally included 67 articles (second screening) to update the guideline (Figure 1).

Included studies

This Italian Guidelines includes 25 evidence-based recommendations and five research recommendations. Recommendations on Hyperventilation (question 10) and Steroids (question 11) do

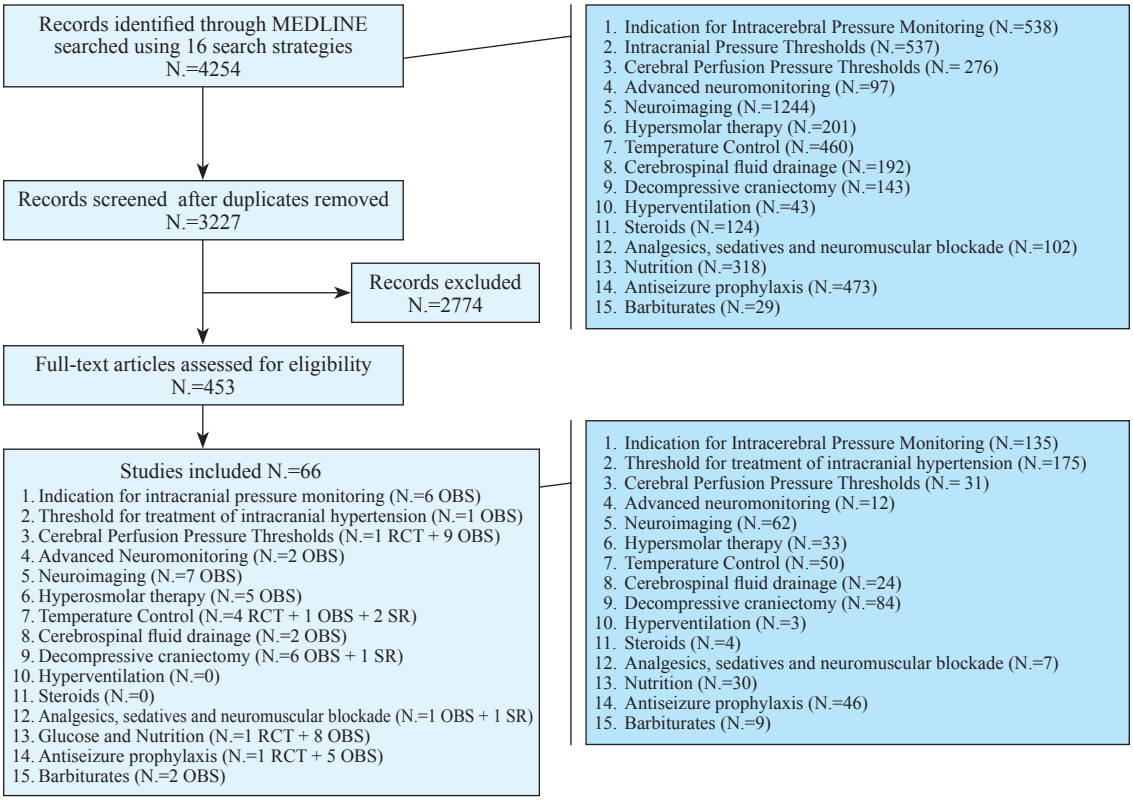

Figure 1.—Flow-chart of the research progress for the systematic review.

not differ by the guideline published by Kochanek *et al*.[3] because of the absence of new evidence. Table I[5-69] shows the included studies for each clinical question, with design and number of enrolled patients. Supplementary Digital Material 2 (Supplementary Table II) and Table II provide the evidence-based recommendations and the recommendations for research. Recommendations have a sequential numbering, whereas recommendations for research are identified by letter R followed by a progressive number. The online Italian guideline document[70] includes a section on each topic consisting of an Introduction regarding the results of the US document, Summary of the Evidence, Discussion of the PoE, Evaluation of the Evidence, Recommendations and Bibliography.

Indication for intracranial pressure monitoring

Alkhoury *et al*.[5] show a reduction in mortality in individuals ICP (Intracranial pressure) monitoring only in the subgroup with GCS = 3. The study retrospectively analyzes more than 4000 subjects aged <17 years and GCS <9. Other observational studies fail to demonstrate the effectiveness of monitoring[6, 7, 9, 10] or report the causes of missing monitoring.[8] The overall quality of the evidence is low, including retrospective studies. There are some suggestions on the effectiveness of the ICP monitoring in very serious patients.

Threshold for treatment of intracranial hypertension

Values of SJO2 (jugular oxygen saturation), PJO2 (jugular oxygen partial pressure), EVLWi (extravascular lung water), PVPi (pulmonary vascular permeability), FO (fluid overload) and CEO2 (cerebral extraction of oxygen) are investigated in 56 children with GCS<8 by Lubrano *et al*.[11] The authors show pathological threshold at 15 mmHg of ICP and worsening at 13 mmHg.

The overall quality of the evidence is low but confirm the use of threshold values for ICP treat-

TABLE I.—*Included studies by clinical question, design and sample size.*

Chapter	Study	Design	Sample size
Indication for intracranial pressure monitoring	Alkhoury *et al*.[5]	Retrospective	4141
	Bennett *et al*.[6]	Retrospective	3084
	Davidson *et al*.[7]	Retrospective	99513
	Roumeliotis *et al*.[8]	Retrospective	64
	Wainwright *et al*.[9]	Retrospective	32
	Young *et al*.[10]	Prospective	12
Threshold for treatment of intracranial hypertension	Lubrano *et al*.[11]	Prospective	56
Cerebral perfusion pressure thresholds	Hutchison *et al*.[12]	RCT	225
	Allen *et al*.[13]	Prospective	2074
	Brady *et al*.[14]	Prospective	21
	Mehta *et al*.[15]	Retrospective	22
	Lewis *et al*.[16]	Prospective	36
	Guiza *et al*.[17]	Prospective	99
	Miller *et al*.[18]	Prospective	85
	Guiza *et al*.[19]	Retrospective	79
	Nagel *et al*.[20]	Retrospective	10
	Young *et al*.[10]	Prospective	12
Advanced neuro-monitoring	Figaji *et al*.[21]	Prospective	28
	Zuluaga *et al*.[22]	Prospective	30
Neuroimaging	Bata *et al*.[23]	Retrospective	71
	Buttram *et al*.[24]	Retrospective	105
	Choi *et al*.[25]	Retrospective	68
	Cohen *et al*.[26]	Retrospective	90
	Oh *et al*.[27]	Retrospective	503
	Qualls *et al*.[28]	Retrospective	63
	Sheridan *et al*.[29]	Retrospective	54
Hyperosmolar therapy	Bennett *et al*.[30]	Retrospective	6238
	Brenkert *et al*.[31]	Retrospective	56
	Piper *et al*.[32]	Retrospective	32
	Rallis *et al*.[33]	Retrospective	14
	Roumeliotis *et al*.[34]	Retrospective	16
Temperature control	Beca *et al*.[35]	RCT	55
	Adelson *et al*.[36]	RCT	77
	Li *et al*.[37]	RCT	22
	Bayir *et al*.[38]	RCT	28
	Sundberg *et al*.[39]	Retrospective	226
	Crompton *et al*.[40]	Review	454
	Zhang *et al*.[41]	Review	442
Cerebrospinal fluid drainage	Andrade *et al*.[42]	Prospective	58
	Ngo *et al*.[43]	Retrospective	66
Decompressive craniectomy	Desgranges *et al*.[44]	Retrospective	12
	Güresir *et al*.[45]	Retrospective	34
	Prasad *et al*.[46]	Retrospective	71
	Rubiano *et al*.[47]	Prospective	36
	Pérez Suárez *et al*.[48]	Retrospective	14
	Thomale *et al*.[49]	Retrospective	53
	Weintraub *et al*.[50]	Review	-
Analgesics, sedatives and neuromuscular blockade	Shein *et al*.[51]	Prospective	16
	Spritzer *et al*.[52]	Review	184
Glucose and nutrition	Merhar *et al*.[53]	RCT	25
	Melo *et al*.[54]	Retrospective	286
	Mtaweh *et al*.[55]	Prospective	13
	Seyed Saadat *et al*.[56]	Cross-sectional	122
	Taha *et al*.[57]	Retrospective	109
	Sharma *et al*.[58]	Retrospective	112
	Melo *et al*.[59]	Retrospective	340
	Elkon *et al*.[60]	Retrospective	271
	Smith *et al*.[61]	Retrospective	57
Antiseizure prophylaxis	Pearl *et al*.[62]	Nonrandomized trial	40
	Christensen *et al*.[63]	Retrospective	1605216
	Bansal *et al*.[64]	Retrospective	72
	Chung *et al*.[65]	Prospective	34
	Liesemer *et al*.[66]	Retrospective	275
	Strazzer *et al*.[67]	Retrospective	203
Barbiturates	Mellion *et al*.[68]	Retrospective	36
	Glick *et al*.[69]	Prospective	6

TABLE II.—*Research recommendation developed from the panel of expert.*

Chapter	Research recommendation
Cerebral perfusion pressure threshold values	R1 - The development of studies conducted on pediatric populations with severe brain trauma, aimed at establishing threshold values of CPP according to age, is recommended. These studies could be conducted within the common clinical practice (observational studies) and provide for the evaluation of CPP with reference to relevant clinical end points
Advanced neuromonitoring	R2 - The development of studies conducted on pediatric populations with brain trauma is recommended, aimed at establishing the efficacy and timing of monitoring of cerebral oxygenation
Neuroimaging	R3 - The development of studies aimed at defining the role and timing of MRI in pediatric brain injury is recommended.
Hyperosmolar therapy	R4 - The development of specific studies to evaluate the effect of hyperosmolar therapy on intracranial hypertension in the pediatric patient with severe trauma is recommended. These studies will have to investigate the different dosages and the different concentrations
Glucose and nutrition	R5 - Prognostic studies aimed at estimating the effects of different blood glucose values on unfavorable outcomes in pediatric patients with severe brain injury are required. Furthermore, studies aimed at evaluating the efficacy of monitoring and correction of hyperglycemia on clinical outcomes in pediatric patients with severe head trauma are required.

ment and suggests the threshold to 15 mmHg compared to the value of 20 mmHg recommended by the original guideline.

Cerebral perfusion pressure thresholds

The study of Hutchison *et al*.[12] shows an increased risk of unfavorable outcome (Pediatric Cerebral Performance Category Score of 4-6) in a post hoc analysis on patients with low cerebral perfusion pressure (CPP) randomized to hypothermia (N.=108), compared with normothermia (N.=117).

Three observational studies[13, 15, 17] observe more favorable outcomes in patients with CPP over 40-50 mmHg. Time spent within optimal CPP values and difference between optimal and real CPP values are the main determinants of survival in the study of Guiza *et al*.[19] on 79 patients with TBI.

Three small studies[14, 16, 20] based on 36, 10 and 21 patients measure the prognostic value of the Pressure-reactivity index by correlating CPP values with unfavorable outcomes and obtaining contrasting results, while Miller Ferguson *et al*.[18] estimate predictive models of uncertain significance.

The observational study of Young *et al*.[10] confirms the usefulness of the multi-modality monitoring in TBI patients.

The overall quality of the evidence is low; since only III class observational studies and a *post-hoc* analysis of a moderate quality RCT are available (the analysis is conducted in violation of randomization).

The evidences seem to confirm that it is possible to consider a threshold value of CPP based on age by selecting the best option for each age group: CPP values above 50-60 mmHg in adults, above 50 mmHg between six and 17 years and over 40 mm Hg between 0 and five years.

Advanced neuro-monitoring

Figaji *et al*.[21] examine the effect of the increase in inspired oxygen fraction (FiO2) on brain tissue oxygenation (PbO2) in 28 children aged <15 years with severe TBI (GCS≤8). The deltaPbO2/deltaPaO2 is slightly higher in patients who have catheter placed close to contusion compared to patients who have catheter placed in normal-appearing white matter. The deltaPbO2/deltaPaO2 ratio is inversely related to outcome.

Zuluaga *et al*.[22] fail to demonstrate any correlation between intracranial pressure and cerebral oxygen saturation in 30 patients. The panel considers the parameter of oxygenation of the brain tissue (PbO2) still little studied (although potentially of high prognostic value).

Several panel members mention the near-infrared spectroscopy (NIRS) as a tool capable of capturing changes in intracranial dynamics such as intracranial hypertension and therefore useful for advanced neuro-monitoring. However, the usefulness of this method remains to be defined. The body of evidence relating to a possible role of advanced neuro-monitoring is low quality and does not allow the formulation of adjunctive recommendations.

Neuroimaging

The impact of repeated computed tomography (CT) on clinical management of 71 children aged <18 years with severe (but not mild) TBI is documented by Bata *et al*..[23] Buttram *et al*.[24] show the poor concordance of CT and MRI (Magnetic Resonance Imaging) in 105 children with mild, moderate and severe TBI. Choi *et al*.[25] apply the MRI susceptibility-weighted imaging (SWI) in 68 pediatric TBI patients, showing a worse prognosis in patients with additional hemorrhagic sites in different brain regions observed indiscriminately with SWI or FLAIR (axial fluid-attenuated inversion recovery). The prognosis is worse especially in subjects with severe TBI. Cohen *et al*.[26] and Oh *et al*.[27] study the effects of the introduction of the cervical spine MRI (cMRI) in the clinical course of the hospital, while Quallas *et al*.[28] and Sheridan *et al*.,[29] estimate the diagnostic accuracy of CT and MRI in populations with TBI, for the detection of unstable CSI (Cervical Spine Injuries) and for the confirmation of TBI. The quality of evidence is low, and a routine repeat head CT scan may not change the surgical management.

Hyperosmolar therapy

A reduction in ICP and an increase in CPP in the first 120 minutes after treatment with Hypertonic Saline (HTS) at 7.5% is observed by Rallis *et al*.[33] in 29 patients and 136 episodes studied. The retrospective works by Bennet *et al*.,[30] Brenkert *et al*.,[31] Piper *et al*.[32] and Roumeliotis *et al*.[34] do not provide relevant information. The quality of the evidence is moderate.

Questions have been raised about the different concentrations of HTS. However, the panel confirms the recommendation given in the original document and to solicit specific studies on this topic.

Temperature control

A randomized study[35] assesses the efficacy of early and continued (72 h) hypothermia in children with severe head injury. Twenty-four patients are assigned to the intervention group (cooling 32°-33°) and twenty-six to the control group. No difference is documented at 12 months of follow-up. Adelson[36] fails to demonstrate differences between 38 treated with normothermia and 39 treated with hypothermia, neither in terms of mortality, nor in terms of Glasgow Outcome Scale (GOS) and GOS-e Peds (GOS - extended pediatrics), nor in terms of adverse events.

The randomized studies of Li *et al*.[37] and Bayir *et al*.[38] show the efficacy of hypothermia on non-clinical outcomes after short follow-up period. In a retrospective study[39] based on 226 pediatric patients, the hypothermia is a risk factor for mortality in traumatized pediatric patients. Crompton *et al*.[40] and Zhang *et al*.[41] in their systematic review conclude that therapeutic hypothermia increases mortality and unfavorable neurological and cardiac outcome in children. After the completion of our bibliographic research, the committee become aware about the early termination because of futility of the cool kids' trial of hypothermia in pediatric TBI.

The overall quality of the evidence is moderate, given the presence of RCTs and observational studies with substantial agreement of results. The evidence clearly shows that hypothermia, in the pediatric population, is not effective.

Cerebrospinal fluid drainage

The prospective study of De Andrade *et al*.[42] assesses the efficacy of the continuous ventricular drainage of cerebrospinal fluid in a mixed population with irrelevant results. Ngo *et al*.[43] retrospectively describe the indications and complications of external ventricular drainage (EVD) in children.

The overall quality of the evidence is low. Original guideline is also based on expert opinion, in lacking clinical studies.

Experts disagree to consider lumbar drainage in refractory intracranial hypertension. Ventricular drainage through EVD may help to control ICP in selected cases.

Decompressive craniectomy

Desgranges *et al*.,[44] Guresir *et al*.,[45] Suarez *et al*.[48] and Thomale *et al*.[49] retrospectively analyze small case-series without obtaining significant results. The retrospective study of Prasad *et al*.[46] shows a better survival (58% *vs.* 42%) in patients subjected to early *vs.* late decompressive crani-

ectomy (DC) (<2h *vs.* >2 h from the increase in ICP). Prasad *et al*.[46] suggests the inadequacy of the 20-mmHg limit of ICP for indication to surgical decompression for younger children. Rubiano *et al*.,[47] in a prospective observational study with historical controls, shows similar results, documenting association between efficacy and timeliness of intervention of the DC. The review of Weintraub *et al*.[50] cites one RCT showing the benefit of DC on ICP and overall outcome in children. The overall quality of evidence is low.

Hyperventilation

No studies selected. The panel agrees to maintain the recommendation of the original guideline.

Steroids

No studies selected. The panel agrees to maintain the recommendation of the original guideline.

Analgesics, sedatives and neuromuscular blockade

Shein *et al*.[51] document the use of fentanyl and pentobarbital in 196 doses administered to 16 patients with severe traumatic brain injury. Fentanyl, hypertonic saline and pentobarbital reduce the ICP; fentanyl reduces CPP and hypertonic saline solution increases CPP.

The review of Spritzer *et al*.,[52] including one RCT enrolling mixed population with moderate to severe TBI, shows favorable effects of the amantadine compared to placebo, on the Disability Rating Scale and Coma Recovery Scale-Revised (CRS-R). The effect of amantadine does not persist after drug discontinuation. The overall quality of evidence is low.

Glucose and nutrition

Merhar *et al*.[53] shows significant effects of high-protein diet (4 g/kg/d) on weight of 25 patients with gestational age>32 weeks with anoxic perinatal trauma. No effects are shown on head circumference and height. Higher serum levels of urea are observed in the arm of high-protein diet, compared with control arm (standard diet). The study reports data at the 3rd month of follow-up (originally designed for 12 months of follow-up) and the etiology of the trauma was anoxic.

Taha *et al*.[57] retrospectively analyze 89 patients showing that an early start of nutritional support and the achievement of full caloric intake are both positively correlated with earlier discharge from intensive care. Melo *et al*.[54] show an excess of 6-month mortality in 286 subjects (retrospectively evaluated) with GCS≤8, as a function of post-traumatic hyperglycemia. These results are confirmed by the cross-sectional study of Seyed Saadat *et al*.[56] based on 122 patients with GCS≤8 and by the retrospective study of Elkon *et al*.,[60] based on 271 pediatric subjects.

Correlations between trauma (and its severity) and hyperglycemia are demonstrated by studies by Melo *et al*.[59] and Sharma *et al*.[58] Finally, Smith *et al*.[61] demonstrates an association between late hyperglycemia (between 49- and 169-hours post-trauma) and unfavorable outcomes (at six months), in a retrospective study on 57 children. Metabolic differences show no prognostic significance in subjects with severe TBI (GCS <9) in the study of Mtaweh *et al*.[55] The only RCT available enrolls individuals with non-traumatic cerebral injury (indirectness) and selective reporting. The overall quality of the evidence is low.

Antiseizure prophylaxis

Pearl *et al*.[62] report 40 patients (6-17 years) with one or more risk factors for developing post-traumatic epilepsy (PTE) in a phase II study. Twenty patients are treated with levetiracetam 55 mg/kg bid, for 30 days, starting at 8h after the trauma and then followed for two years. Twenty untreated patients constitute the control group. No differences in the incidence of infections, mood disorders or behavioral problems are observed. One in twenty treated patients develops PTE. Christensen *et al*.[63] and Bansal *et al*.[64] retrospectively assign correlation between trauma and seizures. In the prospective observational study by Chung & O'Brien,[65] very frequent early post-traumatic seizures are reported among the 34 TBI patients treated with levetiracetam. The retrospective observational study by Liesemer *et al*.[66] documents the efficacy of antiepileptic drugs (AEDs) in reducing early post-traumatic seizures in 275 children with traumas with different mechanism of injury. The retrospective observational study of Strazzer *et al*.[67] fails to demonstrate the efficacy

of prophylaxis with phenobarbital in preventing PTE in children and adults less than 30 years old. However, an increased risk of PTE is observed after discontinuation of prophylaxis.

In conclusion, only one non-randomized study of moderate quality and five observational studies of low quality are available. An increased risk of seizures following the prophylactic AED withdrawal is reported, but no clear evidence is available on the efficacy of the antiseizure prophylaxis with following TBI.

Barbiturates

Mellion *et al*.[68] retrospectively follow 36 pediatric patients with refractory intracranial hypertension (RICH) treated with barbiturates for at least six hours, of which 10 with controlled RICH and 26 with uncontrolled RICH. Patients with controlled RICH have better survival and higher pediatric cerebral performance category (PCPC) scores than patients with uncontrolled RICH.

In the observational study by Glick *et al*.[69] six patients treated with barbiturates for 72h after surgery are followed for six months - one year. No significant results are reported. The overall quality of evidence is low.

Discussion

Monitoring recommendations

Monitoring recommendations concern three types of monitoring: ICP monitoring, advanced neuromonitoring and neuroimaging. The panel discusses the importance of ICP monitoring, highlighting the complexity of the organizational path. Many determinants of the choice of monitoring are debated, including GCS score, timing and type of trauma. Currently, ICP monitoring can be considered in pediatric patients with severe TBI. Regarding the advanced neuromonitoring the panel adds two new recommendations. The first regarding the application of NIRS as a tool capable to capture changes in intracranial dynamics. The other is a research recommendation aims to study efficacy and timing of the oxygenation of the brain tissue.

Neuroimaging recommendation does not change from the previous one and the panel discuss about the difficult evaluation of the risk/benefit ratio of neuroimaging techniques, sharing the practice of using CT in hyper-selected cases of head trauma and the need for more information about the role and timing of MRI.

Threshold recommendations

These recommendations are related to threshold values for ICP e CPP that are monitored during the management of patients with severe TBI. There are no important changes to the recommendations from the second edition of Guidelines for the Management of Severe Traumatic Brain Injury" published in 2012. The panel adds only some clarifications that consider also different thresholds for ICP and CPP in relation to age and clinical course of the TBI. Both ICP and CPP are not static measurements but dynamic values to be considered in a time-period. In general, the management aims to maintain the ICP below 20 mmHg.

Treatment recommendations

There are 17 recommendations regarding specific treatments for the in-hospital management of TBI. Regarding Hyperosmolar therapy, Hyperventilation, Corticosteroids and Barbiturates the experts confirm the recommendations given in the original document, because no new studies have been selected and the one selected is of low quality. The most important change from the previous guidelines regards the temperature control. This recommendation is based on moderate quality of the evidence, including RCT and observational studies with substantial agreement of results. The evidence clearly shows that hypothermia, in the pediatric population, is not recommended.

The 8th and 9th questions concern neuro-surgical treatments: cerebrospinal fluid (CSF) drainage and decompressive craniectomy (DC).

CSF drainage is considered as an aid to reduce the ICP basing on the ICP monitoring. It is performed through an EVD, which must be maintained as long as it is required by the clinical and radiological evolution.

Regarding the DC, the panel agrees with the recommendation elaborated by the original document and points out that it refers to craniectomy performed in patients with signs of neurological deterioration and intracranial hypertension refractory to medical treatments. The experts add

another recommendation with respect to some ethics aspects like the importance of discussing with families about the opportunity, risks, benefits and possible alternatives to the DC.

The 8th and 9th questions consider the possibility of persistent vegetative outcomes.

The panel agrees that the decision for any surgical treatment should be based on the agreement resulting from a multidisciplinary (neurosurgical and neuro-anesthetist) assessment of the patient. The decision whether a patient must be treated, should be documented by specialists taking care of the patient and that have a role in this decision.

The neurosurgeon is the specialist who decides all the issue connected to the surgical procedure (*e.g.,* the extension and modality of DC).

The topic related to analgesics, sedatives and neuromuscular blockade includes three recommendation based on the opinion of experts, because of the only available studies are of low quality. The panel discuss about the recent changes in clinical practice that made the recommendation of the original document obsolete. The widespread habit of using off-label drugs (fentanyl, midazolam and propofol) is proof of this. A substantial agreement has emerged on the need for analgesia and sedation accompanied by careful monitoring. The indication for neuromuscular blockade is instead left to individual evaluations. According to the panel, monitoring can be carried out with the help of tools such as validated clinical scales (Comfort Behavioral Scale and State Behavioral Scale). The topic on glucose and nutrition includes low quality observational studies and one RCT with serious problems of directness. The panel discusses the role of glycemia values as a prognostic indicator for the pediatric patient with severe brain injury. The value of early and late hyperglycemia as an unfavorable prognostic factor has also been recognized, even if the studies supporting this prognostic value do not directly demonstrate the efficacy of corrective measures on glycaemia in the management of the pediatric patient with severe brain injury. For this reason, the panel points out the importance of research. There is no evidence to support the effectiveness of early enteral nutrition and the use of a high-protein diet. The last topic concerns antiseizure prophylaxis.

The panel does not recommend antiseizure prophylaxis, because the studies do not demonstrate its role in preventing seizures and improving outcome.

Conclusions

In recent years, progress has been made on the understanding of severe pediatric brain injury, as well as on all major traumatic pathology. This has led to a progressive improvement in the clinical outcome, although the quantity and quality of evidence remains particularly low. The scarcity, however, of qualitatively acceptable studies on pediatric populations makes the clinical management of pediatric head trauma difficult and often leads, in an inappropriate manner, to extrapolate data derived from studies on adults.

However, we should acknowledge the opportunity of using data from adult populations, after having evaluated the coherence of these information with those from the pediatric population and after the evaluation by the panel of experts.

Considering the lack of evidence on specific topics, our recommendations for research development on specific topics could help to fill the knowledge gap resulted by the literature search performed to complete this guideline.

In conclusion, this guideline provides updated evidence-based guidance on the management of pediatric severe traumatic brain injury. The assessment and management of cervical spine injuries that may be associated with head trauma and the knowledge translation process to implement this guideline are not covered by this guideline.

Key messages

- In subjects with TBI, evidence of low quality suggests threshold values of ICP between 15 and 20 mmHg and CPP between 40 and 50 mmHg.
- Therapeutic hypothermia in patients with TBI is not effective and there are some suggestions about harm induced by the practice. Evidences of moderate quality are available related to pediatric and adult population.

• Antiseizure prophylaxis in patients with TBI is not recommended. The available evidences are ambiguous and strongly biased. In addition, the rationale of prophylactic practice is not clear.

• We recommend further pragmatic studies on monitoring and the use of threshold values of different parameters. Studies defining the role of MRI and other imaging techniques are also needed.

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