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GUIDELINES

Management of intracranial hypertension following traumatic brain injury: a best clinical practice adoption proposal for intracranial pressure monitoring and decompressive craniectomy

Joint statements by the Traumatic Brain Injury Section of the Italian Society of Neurosurgery (SINch) and the Neuroanesthesia and Neurocritical Care Study Group of the Italian Society of Anesthesia, Analgesia, Resuscitation and Intensive Care (SIAARTI)

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ABSTRACT

No robust evidence is provided by literature regarding the management of intracranial hypertension following severe traumatic brain injury (TBI). This is mostly due to the lack of prospective randomized controlled trials (RCTs), the presence of studies containing extreme heterogeneously collected populations and controversial considerations about chosen outcome. A scientific society should provide guidelines for care management and scientific support for those areas for which evidence-based medicine has not been identified. However, RCTs in severe TBI have failed to establish intervention effectiveness, arising the need to make greater use of tools such as Consensus Conferences between ex-

perts, which have the advantage of providing recommendations based on experience, on the analysis of updated literature data and on the direct comparison of different logistic realities. The Italian scientific societies should provide guidelines following the national laws ruling the best medical practice. However, many limitations do not allow the collection of data supporting high levels of evidence for intracranial pressure (ICP) monitoring and decompressive craniectomy (DC) in patients with severe TBI. This intersociety document proposes best practice guidelines for this subsetting of patients to be adopted on a national Italian level, along with joint statements from "TBI Section" of the Italian Society of Neurosurgery (SINch) endorsed by the Neuroanesthesia and Neurocritical Care Study Group of the Italian Society of Anesthesia, Analgesia, Resuscitation and Intensive Care (SIAARTI). Presented here is a recap of recommendations on management of ICP and DC supported a high level of available evidence and rate of agreement expressed by the assemblies during the more recent consensus conferences, where members of both groups have had a role of active participants and supporters. The listed recommendations have been sent to a panel of experts consisting of the 107 members of the "TBI Section" of the SINch and the 111 members of the Neuroanesthesia and Neurocritical Care Study Group of the SIAARTI. The aim of the survey was to test a preliminary evaluation of the grade of predictable future adherence of the recommendations following this intersociety proposal. The following recommendations are suggested as representing best clinical practice, nevertheless, adoption of local multidisciplinary protocols regarding thresholds of ICP values, drug therapies, hemostasis management and perioperative care of decompressed patients is strongly recommended to improve treatment efficiency, to increase the quality of data collection and to provide more powerful evidence with future studies. Thus, for this future perspective a rapid overview of the role of the multimodal neuromonitoring in the optimal severe TBI management is also provided in this document. It is reasonable to assume that the recommendations reported in this paper will in future be updated by new observations arising from future trials. They are not binding, and this document should be offered as a guidance for clinical practice through an intersociety agreement, taking in consideration the low level of evidence.

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KEY WORDS: Traumatic brain injuries; Decompressive craniectomy; Consensus development conference; Guideline.

Introduction

Traumatic brain injury (TBI) represents a socioeconomic issue worldwide. According to the Global Burden of Disease Project[1] the global incidence rate of TBI is 939 cases (95% CI: 874-1005) per 100,000 people.

Nevertheless, no robust evidence is provided by literature regarding the management of intracranial hypertension following TBI. This is mostly due to the lack of prospective randomized controlled trials (RCTs), the presence of studies containing extreme heterogeneously collected populations and controversial considerations about chosen outcomes.[2]

CENTER-TBI based studies have shown substantial variation in structures, practice preferences and processes of TBI care, even among high-volume, specialized neurotrauma centers. This heterogeneity provides an opportunity to study the effectiveness of specific aspects of TBI care and to identify best practices.[3, 4]

A scientific society should provide guidelines for care management and scientific support for those areas for which evidence-based medicine has not been identified. However, RCTs in TBI have failed to establish intervention effectiveness,[5-10] arising the need to make greater use of tools such as Consensus Conferences between experts, which have the advantage of providing recommendations based on experience, on the analysis of updated literature data and on the direct comparison of different logistic realities. With this approach it is possible to create non-binding indications through dogmatic guidelines while conveying solutions of common sense at a high scientific level, applicable in daily reality.

This document proposes best practice guidelines to be adopted on a national Italian level, along with joint statements from the Italian Society of Neurosurgery (SINch), endorsed by the Italian Society of Anesthesia, Analgesia, Resuscitation and Intensive Care (SIAARTI).

Epidemiological data

In 2016, there were 27,08 million (95% CI 24.3-30.33) new cases of TBI worldwide; of those, 5.48 million people suffered severe TBI, resulting in roughly 73 cases per 100,000 people. These numbers are on the rise, along with years of life lived with disability (YLD) (8,1 million YLDs worldwide, 111 YLD per 100,000 people).[11]

Epidemiology in Europe has been assessed in a cross-sectional analysis by Majdan *et al*.[12] who obtained Eurostat TBI related data during the year 2012. The authors identified 1 375 974 TBI-related hospital discharges, 61% of whom were men and 39% were female. Regarding age, 55% of patients were 0-44 years old, and 29% were 65 years or older, with a female proportion higher in this age group. More than 33,400 deaths resulting from TBI were identified in the 25 countries, with a strong male prevalence (68%). Many deaths in the included countries oc-

curred in patients 65 years or older: 7599 (72%) of deaths occurred in this age group in female patients.

In Italy, the annual hospital TBI-related discharges were 134.3 per 100,000, with 7.6-8 deaths (N.=4743) due to TBI alone.[12]

A more detailed insight in the problem from a rehabilitation point of view was provided[13, 14] through a systematic collection of data from the National Registry of acquired severe brain injury (ABI): TBI accounts for 44.3% of the 1469 patients enrolled from 2008 and 2011 (others being non-traumatic severe brain injuries [NTBI]); their mean age was 43.6 years old *versus* 56.7 of the NTBI; patients with TBI presented a lower disability rating scale at admission and discharge, and returned home more frequently than the NTBI group.

Overall, the burden of TBI-related deaths, YLD and years of life lost is substantial in Europe and must not be overlooked.[15]

An important cause of TBI are motor vehicle accidents, which represent the first cause of death in the young population (14-44 years), but there has been a shift in the age of the affected population towards older groups, with falls reported as main cause of TBI, as mainly observed in high income countries. The changing epidemiological pattern emphasizes the need of a prevention policy targeting especially the elderly population, with a focus on falls prevention.[16]

Literature data

Following analysis of the literature, the latest guidelines and experts' consensus, an achievement of a discreet but not high agreement is reported concerning the possibility of maintaining intracranial pressure (ICP) guided therapy immediately following decompressive craniectomy (DC) as good quality of care for TBI.

Intracranial hypertension has been demonstrated as being an independent risk factor for mortality and morbidity following TBI, thus making elevated ICP management a key pillar of TBI treatment,[2, 17, 18] but debate has spread across the literature regarding its real impact on outcome and mortality. The issue of contention is whether maintaining monitored ICP below a universal threshold, as manifested in our current concepts and practices, improves recovery.[9]

When despite all best medical efforts, the intracranial pressure cannot be properly managed, neurosurgeons can perform a DC with the ultimate goal of ICP reduction and improvement of cerebral compliance. This is one of the most questioned neurosurgical procedures,[19] mostly in regard to the many severe disabilities that were observed as outcomes.

In the last decade, two major international RCTs, (DECRA and RESCUE-ICP)[5, 7] sparked even more debate in the neurosurgical community devoted to TBI management.

An effective impact on reduction of intracranial hypertension following bifrontal secondary DC was reported in the DECRAtrial,[5] with no favorable impact on outcome. DECRA has been widely criticized for various reasons,[20] but it could be intended as a valuable trial, which addressed a very specific issue; on the basis of its findings, we are able to conclude that bifrontal DC should not be used as a neuroprotective measure for moderate post-traumatic intracranial hypertension in well-resourced settings.

The RESCUE-ICP trial[7] showed a clear effect on the reduction of mortality in DC patients, as the procedure has demonstrated to be beneficial in improving overall survival when applied as last-tier treatment, compared to medical therapy. The indisputable role that DC has in reducing ICP values at more physiological levels does not translate into a direct and certain positive effect on the outcome. The reduced mortality has been turned into a high rate of disability, with better results at 12-month follow-up. As this last observation, the rehabilitation facilities play a fundamental role to hypothesize the best possible outcome, provided that the patients are able to perform the rehabilitation program. Thus, as clinicians, we have to bear in mind that prognostication on a single-patient level remains non-univocal.

The latest guidelines of the Brain Trauma Foundation (BTF),[2] published before the results of the RESCUE-ICP trial,[7] further fueled the need for scientific comparison, clearly stating that the scarcity of scientific evidence on head trauma, does not allow precise guidelines, but only recommendations that must be integrated into the considerations of daily clinical practice and local protocols. More recently, an update of the 2017 BTF recommendations with three new level-IIA recommendations are provided following the adjudication and consideration of the evidence provided by RESCUE-ICP[21] as well as DECRA's recently published 12-months outcome data.[6]

A high-grade evidence (Level II) study[22] regarding the management of ventriculoperitoneal shunt (VPS) for any kind of hydrocephalus has recently been reported. Although not published within the context of neurotraumatologic literature, this study represents the largest multicenter, single-blinded, randomized controlled trial regarding the use of standard *vs.* antibiotic-impregnated (0.15% clindamycin and 0.054% rifampicin) *vs.* silver-impregnated VPS (BASICS), and its results are rather interesting.

The BASICS trial demonstrated that antibiotic shunts significantly reduce the risk of infection compared with standard shunts in patients of all ages. Silver shunts are associated with the same number of infections as standard shunts. Antibiotic shunts would reduce the risk of infection and be substantially cost-effective, and thus they should be the first choice for patients with hydrocephalus undergoing insertion of their first ventriculoperitoneal shunt. The benefits and implications, both from an efficacy and health economic standpoint, are most pronounced in young patients, this group maybe is more affected by post-traumatic or post-hemorrhagic hydrocephalus. The global implications of these findings require consideration of their generalizability across different health-care systems.[22]

Role of Consensus Conferences

When there is such an impactful lack of evidence, the Consensus Conference represents an effective tool to identify areas of uncertainty in progress and areas of agreement. During the Conference, the panel of experts could discuss on which points they agreed, and on which points they disagreed, and why, in order to provide a final document, representing the common agreement on actual daily practice.

In October 2013, a group of neurosurgeons and neurointensivists met in Milan, Italy to discuss and provide consensus regarding practical applications of ICP monitoring in severe adult TBI. The report from the Milan Consensus Conference, supported by SINch and European Association of Neurosurgical Societies (EANS) addresses four topics on ICP indications: 1) in diffuse brain injury, 2) in cerebral contusions; 3) secondary DC; 4) after evacuation of intracranial traumatic hematoma.[20]

A systematic review reported in 2014 by the International Multidisciplinary Consensus Conference on Multimodality Monitoring provided recommendations regarding strategies for the optimal management of TBI.[23] The high quality of evidence has supported recommendations mainly about indications and methods for ICP monitoring. Information concerning injury severity/prognosis or improved outcomes based on ICP monitoring is supported by moderate quality of evidence. The optimal ICP treatment threshold has been supported only by low quality evidence. Defined clinical or computed tomography (CT) findings with a predictive value for developing intracranial hypertension to guide ICP monitoring decision making about could be based only on low quality of evidence.

The University of Cambridge, in September 2017, organized and hosted the International Consensus Conference on the role of the DC in the management of TBI, jointly with the World Federation of Neurosurgical Societies (WFNS), GlobalNeuro and the NIHR Global Health Research Group on Neurotrauma.[8] Delegates, with a wide geographical representation discussed on use of DC after TBI. There were six topics of the consensus meeting: 1) primary DC for mass injury; 2) secondary DC for intracranial hypertension; 3) perioperative treatment of DC patients; 4) surgical technique; 5) post-DC skull reconstruction; 6) DC in low and middle income countries.

Both consensuses provided a list of statements, representing an international agreement on management of intracranial hypertension following TBI.

The first in-person meeting, the Severe TBI Consensus Conference (SIBICC), was held in April 2019 in Seattle, Washington, USA. Consensus-efforts generated a list of interventions to be in place in the course of severe TBI care in the Intensive Care Unit (ICU) admitted patients. As reported by the authors there is insufficient research to allow evidence-based development of a care plan. Thus, an amalgamation of individual treatments coming from daily experiences and literature observations into a management algorithm of a treatment approach derived from an expert consensus remains the best current method for developing recommendations, despite its limitations and weaknesses.[21, 24] These recommendations are currently being integrated by the American College of Surgeons Committee on Trauma in the American College of Surgeons-Trauma Quality Improvement Program document. Nevertheless, the authors considered this algorithm as a suggested treatment method without proven superiority over other applicable methods.

Thus, the SIBICC reported recommendation against the use of:

- mannitol by non-bolus continuous intravenous infusion;
- scheduled infusion of hyperosmolar therapy;
- lumbar cerebral spinal fluid (CSF) drainage;
- furosemide;
- routine use of steroids;
- routine use of therapeutic hypothermia to temperatures below 35 °C;
- high-dose propofol to attempt to reach burst suppression;
- routine induced hypocapnia ($PaCO_2$ below 30 mmHg/4.0 kPa);
- routine high cerebral perfusion pressure (CPP) threshold above 90 mmHg.

Despite an elevated rate of agreement (≥80% consensus) has supported this recommendation, the panel agreed

that there may be circumstances where the above listed items might be used by an experienced and expert clinician in infrequent and carefully considered situations.

Proposal of adoption as best medical practice on an Italian national level

The Italian scientific societies should provide guidelines following the national laws ruling the best medical practice. Nevertheless, guidelines are based on strong evidence supported by randomized controlled trials. However, many limitations do not allow the collection of data supporting high levels of evidence for patients with TBI, as reported in the last edition of the Brain Trauma Foundation Guidelines.[2]

Members of SINch and SIAARTI have been active participants and supporters of all reported consensus conferences. Due to the low level of evidence, experience and practical suggestions from authors' were derived from the participation at international meetings, helpful in treating traumatic brain injured patients.

Presented here is a recap of recommendations supported a high level of available evidence and rate of agreement expressed by the assembly during the different consensus conferences.[4, 8, 20, 23]

The following recommendations are suggested as representing best clinical practice, nevertheless, adoption of local multidisciplinary protocols regarding thresholds of ICP values, drug therapies, hemostasis management and perioperative care of decompressed patients is strongly recommended to improve treatment efficiency, to increase the quality of data collection and to provide more powerful evidence with future studies.

It is reasonable to assume that the recommendations reported in this paper will in future be updated by new observations arising from future trials. They are not binding, and this document should be offered as a guidance for clinical practice through an intersociety agreement, taking in consideration the low level of evidence.

Intracranial pressure monitoring proposed recommendations

ICP1

Monitoring ICP not only represents the measurement of a single numerical parameter, but also a dynamic value expressed in a time range. The indication to consider a threshold of raised ICP as an hourly dose for ICP 25-30 mmHg, dose-minutes for ICP 30-40 mmHg is proposed. Nevertheless, no absolute cut-off ICP value for determining level of treatment for all severe TBI patients or individual subgroups has been reported.

ICP2

Continuous ICP and CPP monitoring should be preferred in place of the instantaneous interpretations of ICP values in the context of monitoring trends.

ICP3

In comatose TBI patients the indications for monitoring ICP should be based on neuroradiological observations mismatched with clinical findings in a multidisciplinary agreement among neurosurgeons and neurointensivists.

ICP4

In comatose TBI patients, in of the presence of a normal CT scan, there is no indication for ICP monitoring; early negative CT scan can subsequently worsen, therefore a second CT is recommended - scheduled if the result of the neurological examination remains stable, urgent in case of worsening.

ICP5

In comatose TBI, in case of traumatic subarachnoid hemorrhage (tSAH) and/or small petechial foci of hyperdensity/hemorrhages on first CT scan, there is no indication for ICP monitoring, waiting for a second CT - scheduled when the neurological exam is stable or urgent in case of worsening.

ICP6

In comatose TBI patients at any CT scan there is indication of ICP monitoring in case of one of the following:

- radiological progression;
- midline shift >5 mm;
- effacement of basal cisterns;
- disappearing cortical sulci;
- not distinguished gray/white matter;
- diffuse hypodensity.

ICP7

ICP monitoring is indicated in comatose TBI patients with cerebral contusions in whom the interruption of sedation to check neurological status is dangerous and when the clinical examination is not completely reliable. The probe should be positioned on the side of the larger contusion,

whenever possible. In case of large bifrontal contusions and hemorrhagic masses near the brainstem ICP monitoring should be taken into consideration irrespective of the initial Glasgow Coma Scale (GCS).

ICP8

ICP monitoring is generally recommended following a DC in order to assess the effectiveness of DC in terms of ICP control and in order to guide further therapy. No evidence about the post-DC threshold ICP values.

ICP9

ICP monitoring after evacuation of an acute supratentorial intracranial hematoma should be considered for salvageable patients at increased risk of intracranial hypertension with particular perioperative features.

ICP10

Intraparenchymal and intraventricular ICP monitoring devices provide reliable and accurate data. In the presence of hydrocephalus, use of an external ventricular drainage when safe and practical is preferred to parenchymal monitoring.

ICP11

The duration of ICP monitoring should be as long as the patient needs it. The risk of infections is overwhelmed by the benefits of the monitoring, keeping as reference no more than 5 days in the case of stable normal values.

ICP12

Following ICP monitoring, whenever first permanent shunting is needed, adopting antibiotic-impregnated ventriculoperitoneal shunts should be preferred.

ICP13

When interpreting ICP monitoring, individual patient interactions, which may influence ICP values, must take into consideration the following:

- different injury patterns;
- intrathoracic/intra-abdominal pressure;
- individual physical properties of the injured brain;
- individual cerebral metabolic demands.

ICP14

In elderly patients there is uncertainty about the benefits of ICP monitoring due to:

- the increased brain compliance due to cerebral atrophy can accommodate a larger volume of blood collection without signs of neurological deterioration;
- the higher poor outcome and increased mortality after DC;
- the mean age of the most reported RTC or retrospective series is less than 65 years.

Decompressive craniectomy proposed recommendations

DC1

In comatose TBI patients the indications for DC should be based on neuroradiological observations, clinical findings and neurophysiological findings (when indicated) in a multidisciplinary agreement among neurosurgeons and neurointensivists.

DC2

For primary DC the removal of the bone flap follows removal of intracranial blood collection, with or without previous ICP monitoring.

DC3

For secondary DC the removal of the bone flap is based on ICP monitoring. The bone removal (bifrontal/fronto-temporo-parietal unilateral/bilateral hemicraniectomy) could be associated with one or more the following:

- subtemporal decompression;
- non-primary dural closure;
- wide duraplasty.

DC4

The intraoperative judgment of the surgeon should still play the main role to decide whether:

- to leave the bone flap or performing a DC;
- to evacuate intracranial hematoma.

DC5

To consider a bone flap as a lateral DC the dimensions should be not less than 12×15 cm or 15 cm in diameter, recommended in order to reduce mortality and improve neurological outcome in patients with severe TBI (Level IIA recommendation based on a moderate-quality body of evidence). A craniectomy smaller than the above-mentioned dimensions will be therefore considered just a simple surgical bone removal, rather than a standard decompressive craniectomy. Thus, smaller craniectomies shall

be excluded from any speculative research effort about management or outcome effectiveness of decompressive surgery.

DC6

Primary DC remains a treatment option following initial craniotomy, but exact indications require further refinement, due to insufficient evidence regarding preoperative clinical and/or neuroradiological decompressive criteria. Reduced mortality rate has been substituted by a high rate of disability, prognostication on a single-patient level remains non-univocal.

DC7

Secondary DC is suggested to reduce ICP and duration of intensive care, both for early and late refractory ICP elevation — but with an uncertain effect on favorable outcome (recommendations based on a moderate-quality body of evidence - Level IIA).

DC8

The underlying brain pathology and pathophysiology have a deep impact on final outcome. A routine use of secondary DC is not recommended and it should be applied selectively as there is yet uncertainty about which subgroups of patients with severe TBI will really benefit.

DC9

Secondary DC performed for late refractory ICP elevation is recommended to improve mortality and favorable outcomes. Nevertheless, secondary DC is not recommended to improve mortality and favorable outcomes when performed for early refractory ICP elevation (recommendations based on a moderate-quality body of evidence - Level IIA).

DC10

During management of a patient undergoing DC there is a need to conduct frank yet respectful discussions with family members/caregivers regarding the risks, benefits, alternatives, potential prognosis and time to recovery; this communication should be undertaken since inception of treatment and maintained all along the therapeutic process.

DC11

If the ICP can't be controlled by the DC medical therapy must be continued while searching for reversible reasons for intracranial hypertension: EEG, CSF troubles etc.; consider a brief suspension of sedation to evaluate the neurological clinical condition, accepting the risk of a slight elevation of the ICP.

DC12

A postoperative CT within 24 hours of surgery might be useful, not mandatory, to document initial efficacy of surgery.

Survey results

The listed recommendations have been sent to a panel of experts consisting of the 107 members of the TBI Section of the SINch and the 111 members of the SIAARTI Neuroanesthesia and Neurocritical Care Study Group. The aim of the survey was to test a preliminary evaluation of the grade of predictable future adherence of the recommendations following this intersociety proposal.

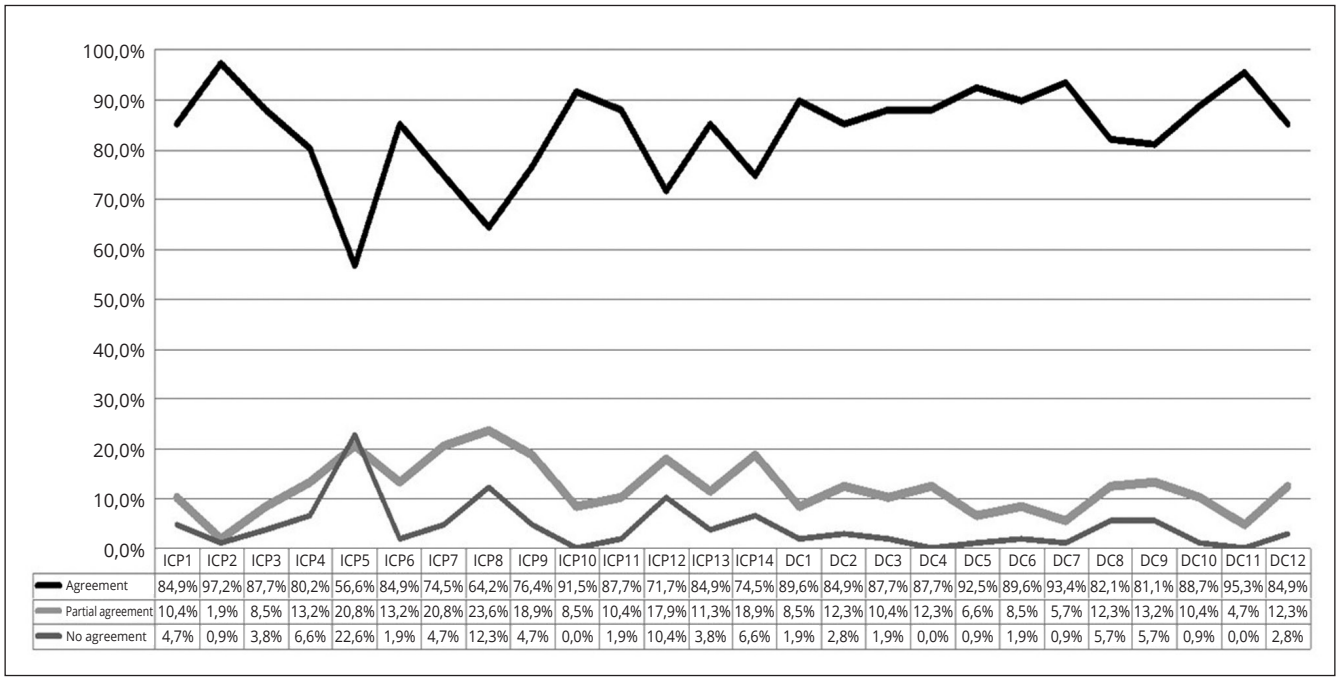
An e-mail containing an internet link (SurveyMonkey, a cloud-based online survey software) active between 15th January and 16th February 2020 to a questionnaire was sent to the mailing list of both groups. Sixty of 107 (56%) of the TBI Section and 45 of 111 (40%) of the SIAARTI Neuroanesthesia and Neurocritical Care Study Group filled in the questionnaire.

In the questionnaire panelists are asked to rate the agreement for each recommendation using their own best clinical judgement. The three options were "I agree," "I partially agree," and "I disagree," where "I agree" means that the proposed recommendation will most likely be adopted in daily clinical practice and "I disagree" that the proposed recommendation is unlikely to or will not be adopted.

A further three-point scale assessed the degree of conviction of the answers and for each option the grade of certainty of the answer has been expressed by three options: "no doubt," "fair certainty," "poor certainty."

The threshold of 70% of "agree" has been evaluated to define as a reached agreement and all but two recommendations achieved this result. Further remarkable results are the achieved grade of 80% of agreement in 20 of 26 recommendations (77%) and the achievement of disagreement less than 10% for all recommendations but three (Figure 1).

The degree of certainty of the answers expressed by panelists showed more heterogeneous results (Figure 2). "No doubt" achieved more than 80% just for ICP2 and DC1, less than 80% but more than 70% for seven of 26 (26.9%) and less than 70% in 17 of 26 (65.4%) of rec-



	ICP1	ICP2	ICP3	ICP4	ICP5	ICP6	ICP7	ICP8	ICP9	ICP10	ICP11	ICP12	ICP13	ICP14	DC1	DC2	DC3	DC4	DC5	DC6	DC7	DC8	DC9	DC10	DC11	DC12
Agreement	84,9%	97,2%	87,7%	80,2%	56,6%	84,9%	74,5%	64,2%	76,4%	91,5%	87,7%	71,7%	84,9%	74,5%	89,6%	84,9%	87,7%	87,7%	92,5%	89,6%	93,4%	82,1%	81,1%	88,7%	95,3%	84,9%
Partial agreement	10,4%	1,9%	8,5%	13,2%	20,8%	13,2%	20,8%	23,6%	18,9%	8,5%	10,4%	17,9%	11,3%	18,9%	8,5%	12,3%	10,4%	12,3%	6,6%	8,5%	5,7%	12,3%	13,2%	10,4%	4,7%	12,3%
No agreement	4,7%	0,9%	3,8%	6,6%	22,6%	1,9%	4,7%	12,3%	4,7%	0,0%	1,9%	10,4%	3,8%	6,6%	1,9%	2,8%	1,9%	0,0%	0,9%	1,9%	0,9%	5,7%	5,7%	0,9%	0,0%	2,8%

Figure 1.—Agreement rate expressed by the panelists in the intersociety survey. The black line represents the rate of agreement achieved for each recommendation, for ICP5 and ICP8 agreement is below 70%, for ICP12 and ICP 14 it is between 70% and 80%. The rate of disagreement is lower than 10% for all recommendations but three, namely ICP5 (22.6%), ICP8 (12.3%), and ICP12 (10.4%) (dark grey line). The rate of partial agreement (light grey line) followed the trend of disagreement, but with a higher rate, as the maximum and minimum value of 23.6% (ICP8) and 0.9% (ICP2). The graph shows the rate of agreement for each recommendation.

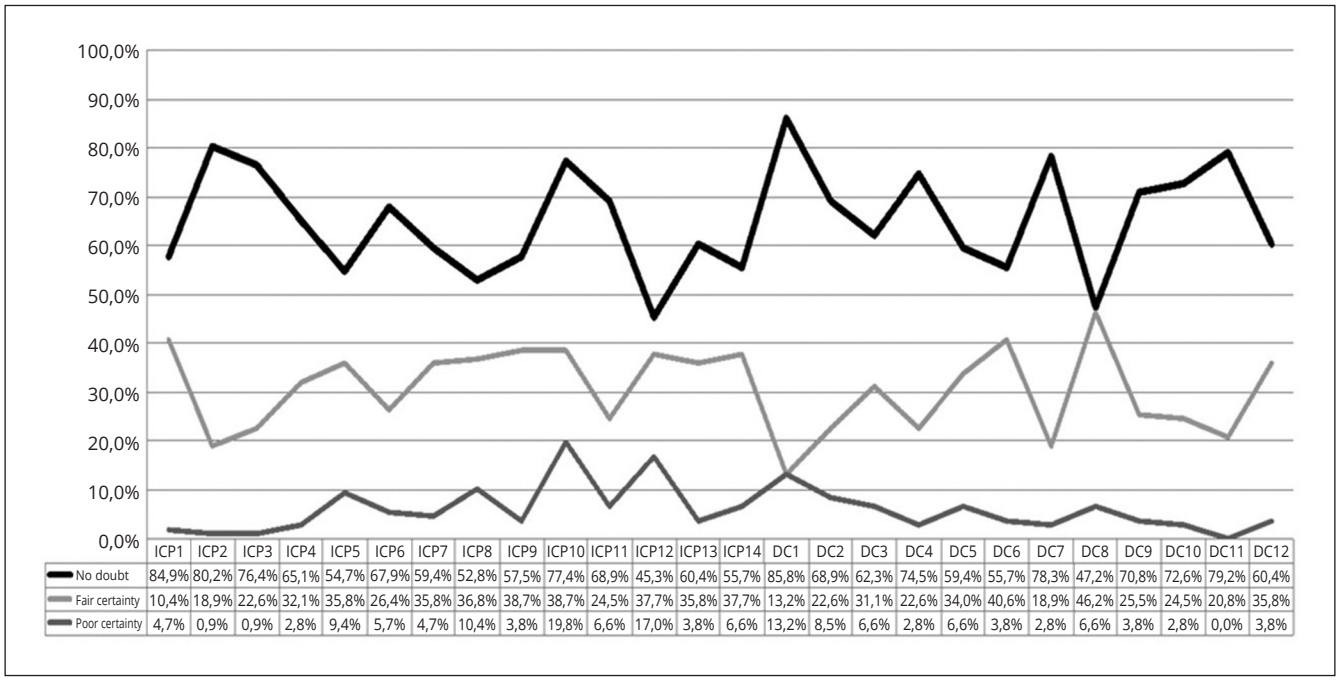
ommendations. The panelists expressed a "fair certainty" with a rate of over 30% for 15 of 26 (57.7%), recommendations. The "poor certainty" usually has been reported below 10%, except for four (15.4%) (Figure 2).

The panel of experts was therefore asked for a further subjective evaluation, in relation to a more personal perspective. It is objectively conceivable that the highest degree of agreement and absence of doubt can be associated with solid scientific knowledge, supported by clinical practical experience. A reduced scientific certainty, mainly related to the lack of evidence, or maybe some reduced grade of effectiveness in medical or surgical treatments observed in personal experience could justify the low level of judgment for the clinical scenario described in the recommendations.

These considerations could be related to the observed higher grade of agreement for recommendations on DC than on ICP with an agreement >70% (12/14 *versus* 12/12, respectively). Moreover, the grade of certainty for ICP group recommendations has been basically little lower than DC group recommendations.

The lower grade of agreement (56.6%) and the higher grade of disagreement (22.6%) have been achieved in the single recommendation ICP5, despite the message expressed in ICP5 has been reported for the first time in the Milan Consensus Conference[20] published in 2014. At that time, the absence of indication of ICP monitoring in case of tSAH and/or small petechial foci of hyperdensity/hemorrhages on first CT scan represented a new recommendation based on the panelist's experience of that Consensus, not aligned to the old indication for ICP monitoring suggested by the-BTF guidelines.[2] Nevertheless, in this survey, the grade of no doubt about this disagreement is low (54.7%), therefore there is a need of further time of clinical application to be highly accepted by the neuro-traumatological community.

Recommendation ICP8 achieved a grade of agreement lower than 70% (64.2%), but always with a low grade (52.8%) of no doubt about this disagreement. The current indication of ICP monitoring following DC is supported mainly for speculative approaches than daily clinical practice, as post-DC ICP values to drive the therapeutic steps need to be defined.[25, 26] Therefore, the moderate agreement of the panelists could be reasonable. Nevertheless, as suggested in the recent literature, ICP monitoring after DC for TBI provides prognostic information, thus hopefully there will be an increased adherence to this recommendation.



	ICP1	ICP2	ICP3	ICP4	ICP5	ICP6	ICP7	ICP8	ICP9	ICP10	ICP11	ICP12	ICP13	ICP14	DC1	DC2	DC3	DC4	DC5	DC6	DC7	DC8	DC9	DC10	DC11	DC12
No doubt	84,9%	80,2%	76,4%	65,1%	54,7%	67,9%	59,4%	52,8%	57,5%	77,4%	68,9%	45,3%	60,4%	55,7%	85,8%	68,9%	62,3%	74,5%	59,4%	55,7%	78,3%	47,2%	70,8%	72,6%	79,2%	60,4%
Fair certainty	10,4%	18,9%	22,6%	32,1%	35,8%	26,4%	35,8%	36,8%	38,7%	38,7%	24,5%	37,7%	35,8%	37,7%	13,2%	22,6%	31,1%	22,6%	34,0%	40,6%	18,9%	46,2%	25,5%	24,5%	20,8%	35,8%
Poor certainty	4,7%	0,9%	0,9%	2,8%	9,4%	5,7%	4,7%	10,4%	3,8%	19,8%	6,6%	17,0%	3,8%	6,6%	13,2%	8,5%	6,6%	2,8%	6,6%	3,8%	2,8%	6,6%	3,8%	2,8%	0,0%	3,8%

Figure 2.—Certainty rate expressed by the panelists in the intersociety survey. Despite the "poor certainty" (dark gray line) being below 10% in 22/26 (84.6%) and below 20% in 4/6, the grade of a partial or absolute certainty achieved a very heterogeneous result. The absence of doubts (black line) about the certainty of the answer achieved less than 50% in ICP12 (45.3%) and DC8 (47.2%), between 50% and 60% in ICP1 (57.5%), ICP5 (54.7%), ICP7 (59.4%), ICP8 (52.8%), ICP9 (57.5%), ICP14 (57.7%), DC5 (59.4%), DC6 (55.7%), and between 70% and 80% for 7/26 and more than 80% just for 2/26 recommendations. "Fair certainty" (light gray line) achieved a rate over 30% for 15/26 recommendations (57.7%).

In this survey the main stakeholders of TBI management of the SINch and SIAARTI expressed an acceptable agreement with the proposal recommendations. Heterogeneous results reflect the current grade of evidence available in literature.

In these terms the main aim of this report is to spark discussion in each professional context, as to develop local protocols for daily practice guidance, with adoption of the listed recommendations better adapted to the needs and resources of the environment in which they must be applied.

Update on advanced monitoring in TBI

ICP monitoring is widely considered the cornerstone of TBI care. The most recent BTF guidelines[2] have increased the threshold for ICP treatment from 20 to 22 mmHg. However, the concept of the threshold of ICP has been largely discussed by several authors[20, 27] suggesting that the definition of a numeric threshold of ICP does not take in account the complete pathophysiological features of brain injured patients. In this context, multimodal neuromonitoring, providing advanced information on cerebral dynamics, might enable clinicians to make individualized management decisions to prevent secondary ischemic brain injury. Moreover, multimodal neuromonitoring might help in the decision to invasively monitor traumatic brain injured patients in borderline situations where ICP monitoring would be desirable, but not strongly indicated.

Indeed, the results of our survey reflect the fact that ICP monitoring only may not be sufficient enough in order to guarantee a complete picture of all the pathophysiological processes which may ensue following brain injury due to the extreme heterogeneity of TBI patients, individual cerebral autoregulatory (CVA) ranges and coexisting pathophysiological processes. A recent report from Center TBI has described inadequacy of current TBI therapies in modulating impaired autoregulation.[3, 4]

These findings support the need for investigation into the molecular mechanisms involved, or individualized physiologic targets (ICP, CPP, or CO_2) in order to treat impairment of cerebral autoregulation (CA) and other pathophysiological processes actively.

While several invasive and non-invasive techniques are nowadays available to monitor ICP, their use is quite heterogeneous, even among very specialized units.[28]

Even though a thorough explanation of these techniques is beyond the scope of this paper, we would like to provide a rapid overview of their role in the optimal CPP/ICP management.[2, 29, 30]

Non-invasive monitoring

Pupillometry

Pupillary examination is a fundamental component of neurological evaluation in the intensive care unit, including size, symmetry and the assessment of the pupillary light reflex.[31]

To date, in clinical practice, pupillary assessment is based on a qualitative-operator dependent examination, using manual flash penlights or lamps. However, automated infrared pupillometry technique is recently gaining interest as a non-invasive quantitative tool for pupillary examination.[32, 33]

There are two devices currently used: theNeurOptics® NPi-200 (Neuroptics, Irvine, CA, USA) and the Neuro-Light- Algiscan® (ID-Med, Marseille, France).

Automated pupillometry consists in an infrared light-emitting diode, with a digital camera that senses the reflected infrared light from the iris showing variables such as pupillary size, asymmetry, constriction variation to light stimulation latency, constriction and dilation velocity. The Neuroptics® NPi-200 also allows to calculate the Neurological Pupil Index (NPi), which is a scalar value that is calculated using an algorithm derived from the basic variables.

There are several applications of automated pupillometry in the intensive care unit. Indeed, recent studies have shown significant clinically divergence between subjective manual and objective quantitative pupillometric examination.[34, 35] In this context, the routine use of automated pupillometry in the daily assessment of pupillary reactivity could be of extreme importance for a precise and early evaluation of neurological complications and to detect secondary brain damage, especially in sedated patients. In particular, in the context of traumatic brain injury, NPi<3 seems to be associated with increased ICP>20 mmHg.[36, 37] In a recent study comparing noninvasive methods to assess ICP, NPi proved to have a good accuracy in the detection of intracranial hypertension.[38]

Finally, pupillometry has shown to have an important role in the coma prognostication in the early ICU phase; in particular, PLR at day three following cardiac arrest has shown to be a strong predictor of poor outcome.[39-41] In summary, automated pupillometry enables a precise and quantitative evaluation of pupillary light reflexes at the patient bedside, and should be integrated in the clinical assessment of brain injured patients.

Optic nerve sheath diameter (ONSD)

The measurement of the ONSD has recently emerged as a promising tool to assess non-invasively ICP. The optic nerve is a part of the central nervous system, and it is surrounded by the subarachnoid space containing CSF. Therefore, when the pressure in the CSF increases, it can be transmitted along the optic nerve sheath, and as the retrobulbar optic nerve sheath is distensible can cause its dilation.[42] Direct measurement of the diameter of the ONS may provide an early and reactive measure of ICP increase.

The ONSD has shown a good correlation with ICP in magnetic resonance imaging, CT and ultrasound studies.[43-45] In particular the sonographic measurement of ONSD has shown to be a reliable, bedside and repeatable tool to evaluate changes in intracranial pressure when invasive methods are not available or contraindicated. Using a high frequency probe of at least 7.5 MHz over the closed upper eyelid, with the patients placed in supine position, the optic nerve is detected as an hypoechogenic line, closely surrounded by the echogenic pia mater; the subarachnoid space appears anechogenic or hypoechogenic and is surrounded by hyperechogenic dura mater and periorbital fat. ONSD should be measured in its retrobulbar segment, 3 mm behind the ocular globe, corresponding to the anterior part of the ONSD that can dilate in case of raised pressure. A diameter varying from 5 to 6 mm[46] has been evaluated as corresponding to the threshold of ICP=20 mmHg.

There are some limitations in the use of ocular sonography: these include the need for training, intra and interobserver operator, the risk of artifacts and the poor reliability in patients with SAH.[47] As a consequence, ONSD should not be used to substitute invasive ICP measurement, but it can be a useful simple and rapid method which may offer opportunities to estimate the risk of raised ICP, and maybe to better individualized treatment in the very early management of brain injured patients.

Transcranial Doppler (TCD) ultrasonography

Rune Aaslid's introduction of TCD in 1982 constitutes an important step for non-invasive bedside study of intracranial blood vessel flow and velocity.[48] Using a low-frequency ultrasound probe (*e.g.*, 2 MHz) through specific insonation windows, it is possible to gain access to the arteries that shape the Circle of Willis.[48] Afterwards, high-resolution ultrasonic systems and high-performance

sector transducers have opened up new perspectives for transcranial examination in adults. During the last two decades transcranial color-coded duplex ultrasonography (TCCD) found its important role in the diagnosis of intracranial space occupying lesions and assessment of intracranial pressure, intracranial hemorrhage, hydrocephalus, midline shift and cerebrovascular diseases in both acute and chronic clinical settings.[42, 49] Pulsatility index (PI) is a TCD derived parameter correlated to ICP and it is defined as: systolic flow velocity (FV) – diastolic FV/mean FV. PI is related to ICP as follows (sensitivity: 89%, specificity: 92%): ICP=(10.93×PI) − 1.28.[50] With A PI >2.13 correlating to an ICP >22 mmHg, whereas PI <1.2 corresponds to an ICP of approximately 12 mmHg.

The main advantage of PI is that it is not affected by the angle of insonation, but on the other hand a decreased PaCO2 or an increased arterial blood pressure alterations could lead to misinterpretation. Further investigation reconsidered its reliability in assessing ICP because absolute accuracy seemed to be too poor with critical cut off not reliable enough.[51]

Czosnyka *et al.* proposed and validated a new non-PI-related formula measuring arterial flow velocities on mean cerebral artery through the temporal window:

$$CPP = (\text{diastolic FV/mean FV}) \times MAP + 14$$

which proved to have a good accuracy compared to invasive CPP estimation, finding a difference lower than 10 mmHg in 89% of measures and lower than 13 mmHg in 93%, despite not being precise enough for ICP.[52]

In 2017, the prospective multicenter pilot study IMPRESSIT enrolled 38 patients, with one hundred fourteen paired of invasive and TCD derived ICP measurements providing preliminary evidence that ICP estimated with TCD may accurately exclude intracranial hypertension in patients with acute brain injury. ICP-TCD (sensitivity:100% for ICP above 20 mmHg, according to the recommended cutoff value available at the time the study took place; indeed the best threshold was at invasive ICP of 24.8 mmHg corresponding to an ICP-TCD sensitivity of 100% and a specificity of 91.2%.[53]

Given the results of the pilot study, a powered prospective international multicenter trial (IMPRESSIT 2), aiming at enrolling 490 patients, has been designed and is still ongoing, in order to properly address the issue (NCT02322970).

Brain midline shift (MLS) is a life-threatening complication present in various types of acute brain injuries and it is considered clinically significant when it exceeds 0.5 cm on head CT, predicting poor neurological outcome and requiring prompt surgical intervention. Third ventricle visualization can be considered as the point of reference for midline structure in the sonographic anatomy.[54] Ultrasound MLS compared to the gold standard determination shows a good correlation with CT measurements.[55] Moreover, a MLS>2.5 mm on transcranial ultrasound is considered significant and its detection may be helpful in order to determine the optimal timing to a new CT scan.[56]

Although TCD derived ICP cannot substitute invasive ICP measurement, it could be useful when indications are unclear or invasive methods are not available (*i.e.*, low-income countries) or contraindicated (*i.e.*, severe coagulopathy), representing a "triage" tool to discriminate patients at risk of developing intracranial hypertension.[57]

There are some limitations in the use of TCD, most important of which is a poor ultrasonographic window (*i.e.*, high bone attenuation, due to thicker cranial vault, leading to difficult views and uninterpretable transcranial Doppler image in 5-20% of patients.

Continuous electroencephalography(cEEG)

EEG provides information about brain electrical activity, even when brain function is depressed and cannot be explored otherwise, as in comatose patients. Since digital EEG recording became available, cEEG monitoring was proposed for continuous monitoring at bedside in the ICU.

Standardized Critical Care EEG Terminology (2012) was proposed by the American Clinical Neurophysiology Society.[58] This classification system simply categorizes EEG patterns observed in the neuro-ICU setting mainly by waveform and localization.

In the main term 1 EEG patterns are classified according to their localization into generalized, lateralized, bilateral independent, and multifocal patterns. Then, in the main term 2, patterns are classified according to their waveform morphology into periodic discharges (PDs), rhythmic delta activity (RDA), and spike-and-wave or sharp-and-wave (SW).

Seizure detection is the main indication for cEEG monitoring in these patients. When seizures are suspected, it should be initiated as soon as possible, as higher morbidity and mortality has been observed, and early treatments are likely to be more effective. Recording for at least 24 h is recommended, but in some cases shorter or longer periods may be necessary. Traditional 30-60 min EEG recordings identify non-convulsive seizures in only 45-58% of patients in whom seizures are eventually recorded. About 80-95% of patients with non-convulsive seizures can be identified within 24-48 h.[59]

Recently, the Neurointensive Care section of European Society of Intensive Care Medicine and American Clinical Neurophysiology Society revised indications for this monitoring in traumatic brain injured patients.[60, 61]

It is recommended:

• in all TBI patients with unexplained and persistent altered consciousness;

• in patients with GCS<8, to rule out non convulsive seizures, particularly in case of large cortical contusion/hematoma, depressed skull fracture or penetrating injury;

• to monitor depth of sedation and high-dose suppressive therapy.

No study has shown a role for ischemia detection in patients with traumatic brain injury.

Furthermore, it is recommended to assess level of consciousness in patients requiring intravenous sedation or pharmacologically induced coma. In particular, it is useful to monitor burst suppression, when it is necessary to control refractory intracranial hypertension or refractory status epilepticus. In these cases, the goal is to optimize seizure suppression, burst suppression, or complete suppression while avoiding oversedation, hemodynamic complications, and other systemic adverse effects. Standard montage should be obtained by using 21 electrodes. In Intensive Care Unit this could be time consuming and difficult, so that simplified montages have been described. A montage with eight recording electrodes uses four couples of electrodes: forehead FP1, FP2; central C3, C4; temporal T3, T4; and occipital O1, O2 (Figure 3).

There are some limitations in cEEG monitoring in ICU. In fact, it may be difficult to obtain in presence of skull dressing or intracranial catheters, and the positioning of electrodes may require several adjustments to reduce artifacts in time. Furthermore, for a correct cEEG reading, expertise is needed, and neurologist are not always available; actually, several papers show that even ICU physician or nurses can achieve an acceptable level in identifying main EEG patterns and detecting seizures.

Invasive monitoring

Partial pressure of oxygen in the brain tissue ($PbtO_2$)

It is widely acknowledged that sustained elevated ICP may be harmful as it leads to a reduction of the CPP and subsequently to cerebral hypoxia.[62] However, the ICP monitoring alone is not always able to detect all the hypoxic phases;[9, 63, 64] that is why multimodal neuromonitoring, which includes measurement of $PbtO_2$, is advisable as it allows detection of hypoxic crisis within the brain alongside changes in ICP/CPP.[65]

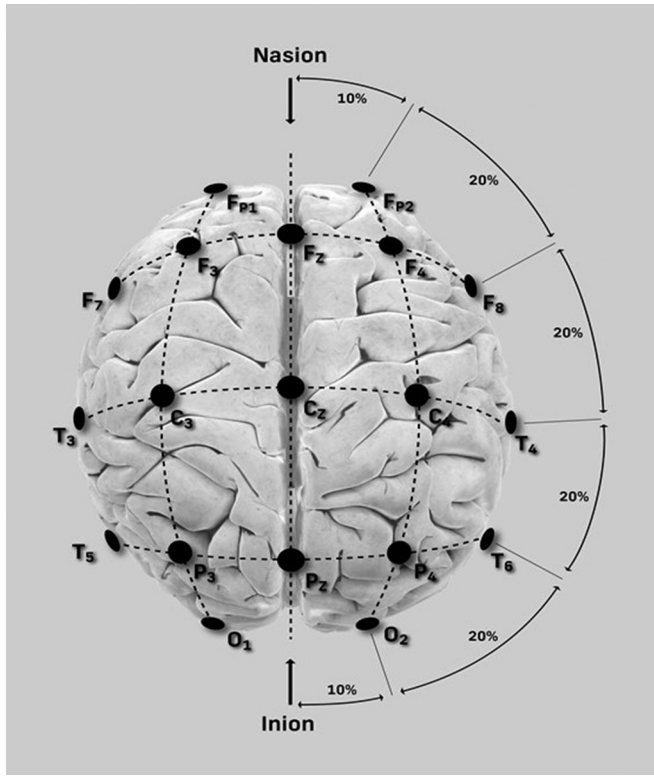


Figure 3.—International 10/20 system of electrode placement. The 10/20 system or International 10/20 system is an internationally recognized method to describe the location of scalp electrodes, based on the relationship between the location of an electrode and the underlying area of cerebral cortex.

$PbtO_2$ is measured by means of a dedicated probe inserted into the brain tissue through an intracranial bolt. It is therefore an invasive regional measurement that covers an area of brain parenchyma of about 15-20 mm^2. Such a small sampling volume makes location of the probe crucial for data interpretation and clinical significance. In TBI the probe is commonly placed in the frontal lobe of the least damaged hemisphere even though there is no full agreement among experts and no trial has been done to determine the best position.[66] This method permits to estimate the oxygenation of a larger area of undamaged tissue.[67] At the current state two types of probes exist, the Lycox (Integra LifeSciences Corporation, Plainsboro, NJ, USA), which is based on a miniature Clark's electrode, and the Neurovent (Raumedic, Helmbrechts, Germany) based on an optic technique. Both methods are reliable despite a drift in the values has been observed between the two probes with higher values reported by the Neurovent.[68] The proper functionality of the probe should be checked on a daily basis with an oxygen challenge test,

consisting in increasing the FiO_2 to 1.0 for 20 minutes and obtaining an increase of the $PbtO_2$ of 200% from the baseline.[65]

Normal values for $PbtO_2$ range from 20 to 25 mmHg and 15 mmHg is commonly considered as threshold for hypoxia.[69] Many single center studies have shown that TBI patients with $PbtO_2$ persistently below this limit presented worst outcome. Nevertheless, the only RCT conducted so far to study the correlation through $PbtO_2$ and outcome (BOOST-2 trial) was underpowered and it showed only a trend without statistic significancy with respect to the correlation between lower $PbtO_2$ and poor outcome.[70] Moreover, some recent evidence suggests that an even higher threshold for cerebral hypoxia should be targeted in order to obtain a better outcome.[71]

It is unlikely that the monitoring itself would bring a better care for the patients and several algorithms have been proposed for the treatment of cerebral hypoxia,[24, 65, 72] but there is still a gap in the clinical literature thus no validation through high quality trial is available at this date.[24]

Literature shows a positive correlation between $PbtO_2$ and cerebral blood flow (CBF):[73] in the normal brain an increase in MAP or in CPP leads to an increase in the $PbtO_2$.[74] Several studies on brain injured patients have shown that lower $PbtO_2$ correlates with a poorer outcome,[75, 76] whereas correcting a low $PbtO_2$ may improve the outcome.[70, 77, 78] Since it is considered as a surrogate for CBF, $PbtO_2$ has also been used to study cerebral autoregulation. ORx a correlation coefficient between $PbtO_2$ and CPP was created in order to monitor autoregulation at the bedside, however, though promising, data are still limited on the reliability and the potentials remain unclear.[79, 80]

$PbtO_2$ monitoring still presents many issues. First, the technique is invasive and requires a cautious placement (accounting also the critical importance of the brain area where the $PbtO_2$ is measured). Furthermore, there is no clear indication about the positioning of the probe and in which precise kind of TBI this monitoring may be beneficial. Second, bleeding rates are low and comparable to the usual ICP monitoring even if they have to be taken into account;[65, 81-83] no infection has been described with the use of this kind of probes.[65] Finally, issues related to the probes itself have to be accounted for. A low reliability in the first hour of placement is well known,[82] causing the inability to detect early hypoxic phase in the most critical moment of the TBI care. Also the different values given from the two available probes must be considered especially when using ORx or comparing the values itself.

Cerebral autoregulation

Cerebral autoregulation (CA) represents the ability of the brain to maintain cerebral blood flow constant and therefore protect the brain from potential damages caused by abrupt variation of perfusion pressure. This complex self-regulatory mechanism, finely tuned by different biochemical, metabolic and biophysical processes, warrants the brain a distinct protection against ischemic and hyperperfusion damages. It is known that autoregulation works within a specific pressure range (lower limit and upper limit of autoregulation) and that this range can be wide or narrow and that it can change from person to person; that CA shows both a static and a dynamic component.

Traumatic injuries can alter cerebral structural integrity leading to clumsy communication between metabolic demand and delivery and vice versa. Disruption of the autoregulatory system is therefore a multifactorial process, that makes the brain vulnerable to secondary damage and is related to poorer outcome in TBI patients.[84, 85]

In practical terms, autoregulation at bedside can only be estimated and not directly calculated, Cerebral autoregulation can be assessed either by studying the relationship between 'steady-state' changes in CPP (or in some cases, ABP) and CBF (static autoregulation) or by studying 'continuous' changes in CPP (or ABP) and CBF (dynamic autoregulation).

For ICU patients, the techniques considered suitable and safe are those that monitor CA and exploit CBF induced changes by spontaneous fluctuations of the ABP, more specifically time domain analysis of slow oscillations of these two signals have led to the creation of correlation coefficients such as TCD mean flow index (Mx), NIRS autoregulation index (TOx), pressure reactivity index (PRx) and oxygen reactivity index (ORx).

- Mx: moving correlation coefficient between mean CPP (or sometimes ABP) and mean flow velocity in the middle cerebral artery (both averaged over 10 seconds time period) measured during session of continuous TCD monitoring. A positive correlation indicates disrupted autoregulation while Mx negative or around zero describes intact CA.[86] Mx is calculated over session of TCD recordings of about one hour, so it does evaluate autoregulation but a continuous monitoring capable to detect changes at any time it is not feasible yet, moreover in order to have a CPP input variable an invasive ICP monitoring is necessary;
- TOx: correlation coefficient between mean ABP and NIRS oxygenation index;

• PRx: moving correlation coefficient between averaged values (over 10 seconds) between mean ABP and ICP. Instead of assessing the relationship between ABP and CBF, PRx assesses the relationship between ABP and ICP by taking the changes in ICP to represent changes in cerebral blood volume. When cerebral vessels are actively autoregulating, a decrease in ABP will dilate intracranial vessels, which will increase the cerebral blood volume. An increase in cerebral blood volume will cause either an increase in ICP (if on the steep portion of the intracranial pressure–volume curve) or no change in ICP (if on the flat portion of the pressure–volume curve). Conversely, with deranged autoregulation, a decrease in ABP will cause a passive constriction, reducing the cerebral blood volume and ICP.[87] Sorrentino *et al*. described critical values of PRx that maximized the difference between patients who died (PRx=0.25) and those with a more favorable outcome (PRx=0.05);[88]

• ORx is the moving correlation coefficient between mean ABP and PtiO2. Being $PbtO_2$ considered as an indicator of CBF.[89]

According to this kind of analysis, positive correlation between the variables indicates disrupted CA while an index close to zero or negative suggests a preserved CA.

Of these indexes the most studied and used for clinical purposes are Mx and PRx, calculation of these indexes requires a dedicated software. PRx and Mx have been suggested to describe different components of the autoregulatory mechanism and it has been suggested that Mx is a better predictor of functional outcome than of mortality.[88, 90] PRx is more discriminatory for survival *versus* mortality; however, both demonstrate U-shaped curves when plotted against CPP and moreover are directly responsive to alterations of ICP.[84, 91, 92]

According to the observation that plotting PRx *versus* CPP produces a U-shaped curved has led to the concept of CPP opt (Figure 4). This concept overcomes the rigid indication of the BTF of keeping CPP within a fixed ranged (60-70 mmHg) in TBI,[2] instead introduces a patient tailored approach. CPP opt is a range of CPP values within which the patient displays the lowest value of PRx: it is the CPP range where autoregulation can work at its best. Evidence supporting the use of CPP opt is for the time being mostly retrospective, but promising and showing a robust association between unfavorable outcome and deviation from calculated CPP opt in severe TBI patients.[93, 94]

Only two single center prospective studies have shown an improvement in the outcome in patients treated with a CPP individualized approach.[80, 95]

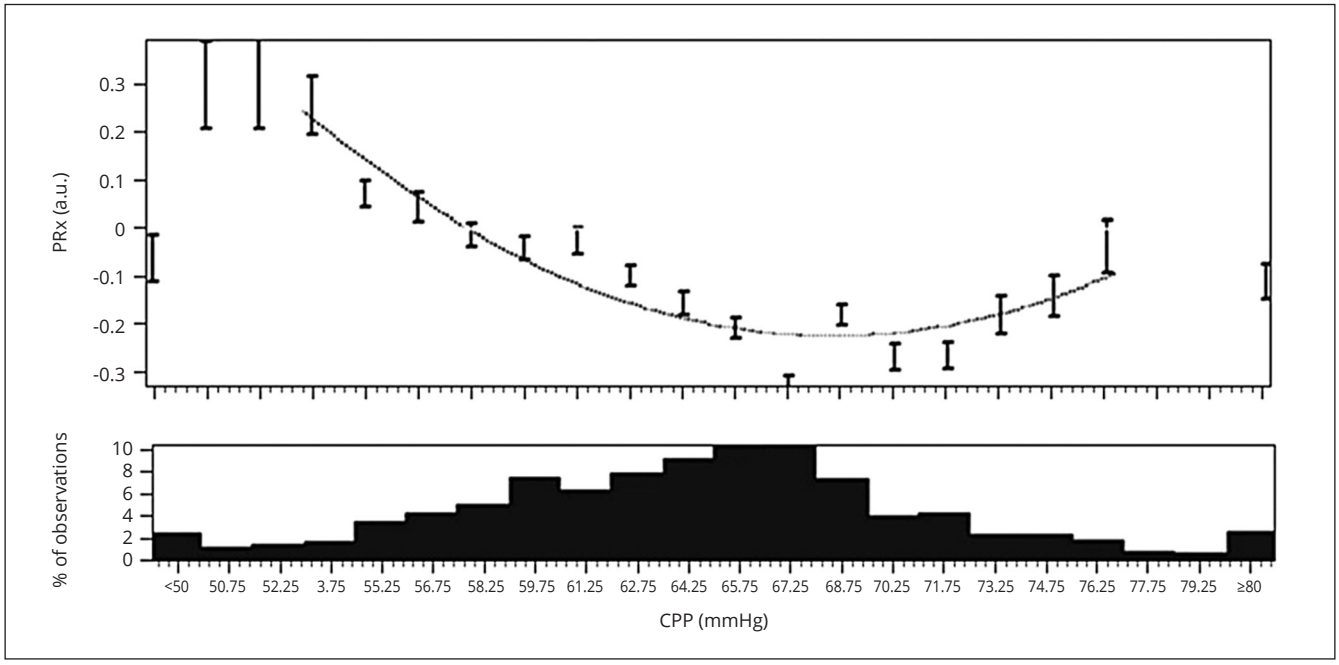


Figure 4.—Plot of PRx *versus* CPP: U-shaped curve defining CPP opt. Plots of PRx against cerebral perfusion pressure (CPP) show U-shaped behavior — the minimum reflecting optimal cerebral autoregulation (CPP opt). The point for which PRx is the lowest is determined by curve fitting. This point defines the optimal CPP (CPP opt), representing the CPP for which autoregulation is.

Currently a phase II multicenter trial (COGiTATE) with the aim of assessing the feasibility and safety of targeting CPP at CPP opt in TBI patients is ongoing and recruiting.[96]

Future perspectives

Systematic reviews and meta-analyses could be misinterpreted due to methodological flaws, and the conclusions have a low level of confidence. However, a general agreement seems to support the effect of DC to decrease mortality, reduce ICP and minimize days in the ICU and hospital, but with an unclear impact on outcome, depending on brain condition, clinical aspects of patients, surgical techniques, timing of surgery and neurointensive management.

Timing is only one of the several heterogeneous data across studies, nevertheless, it could be a crucial impact factor on outcome. Some neurosurgeons believe that DC should be performed as a last ditch procedure, so this potential delay in timing could be at least in part the cause of drastic complications and source of the observed poor outcomes.[97] However, the actual dramatic considerations available in literature on outcome following DC do not allow to be too aggressive, so the ideal timing is still an unanswered question of paramount importance. Trial of early DC with a pre-specified, controlled surgical approach has not been conducted.

Moreover, it is still not identified the ideal candidate for DC. Age, comorbidities, brain condition are not well stratified in the available trials. Therefore, results from the RESCUE-ASDH, the first study on a specific intermediate category of acute subdural hematoma patients whose brain isn't neither relaxed nor bulging, are awaited.[98]

The needs to find therapeutic solutions amongst this area of uncertainty could be the future challenge for TBI management, with the wisdom to distinguish the need of a real alternative approach from the need of a more proper indication of the actual care planning.

During the last years cisternostomy has been proposed as a promising surgical technique in managing rising ICP in TBI-affected patients especially in environments where close multimodality monitoring is impractical.[99]

The cisternostomy is not an experimental technique, but it is a well-established surgical procedure to decrease ICP in patients with acute aneurysmal subarachnoid hemorrhage treatment and skull base pathologies approaches.[100] There is a long track record for this surgery, and most of neurosurgical centers have access to well-trained vascular and skull base surgeons capable of performing this surgery.

The rationale to apply cisternostomy in reducing raised ICP in TBI patients is fascinating, and it is based on the theoretical studies on the glymphatic system.[101]

Following this theory, in TBI the pathologic origin of edema is a mechanical obstruction of CSF circulation due to subarachnoid hemorrhage. Thus, when the cisternal pressure increases, the cisternal CSF gets displaced through the Virchow Robin spaces into the brain resulting in CSF shift edema. A DC causes this edematous brain to herniate into the hemicraniectomy site, while the cisternostomy open the cisterns and reverse the pressure gradient.

Nevertheless, documented clinical studies are still limited and the assumption that brain edema formation might be caused by the obstruction of the glymphatic system remains unproven. However, the rule of CSF circulation through perivascular and interstitial space has been proposed in the past and recent studies about glymphatic dysfunction and neurological diseases.[100] Taking in account the experimental studies,[101] the developing of vivo evidence supporting the role of glymphatic system dysfunction in TBI is auspicable. with preclinical and clinical basic research.

The role of cisternostomy in a care planning of a TBI patient still needs to be defined as a safe and effective surgical therapeutic action due to the absence of any clinical trials.[102] Moreover, the therapeutic effectiveness due to the positive effect on reduced ICP values[103] cannot be related for all patients eligible for DC.

Proposed indications for cisternostomy included patients with moderate and severe TBI,[103-105] and need a better level of evidence. Currently cisternostomy should be considered a further surgical procedure to reduce raised ICP, more than an alternative treatment to DC. Following the glymphatic system theory, the cisternostomy could be more effective when the secondary injury has not started abruptly, since blood flow despite vasospasm is not completely blocked.

Thus, a randomized study about the efficacy of cisternostomy is auspicable, taking in consideration that there is a need to individuate patients where high chances of deterioration can support a prompt surgery, including DC. The equipoise of effectiveness of both techniques for that specific subsetting of patients can allow an ethical correct research.

Cisternostomy requires a well-trained experience of skull base approaches and surgery within the basal cisterns. This must urge more centers to increase the surgical skill of their staff neurosurgeons, and it requires the training as early as possible for neurosurgical residents in stan-

dard skull base surgery techniques. This must be justified by the workload of the single center, and it is not always technically feasible for treating only a small TBI subset of patients.

Conclusions

Best medical and surgical management in TBI are still the subject of extensive discussions, mostly due to the difficulty of conducting adequate prospective randomized clinical trials. Several reasons underlie this difficulty, going from sample size to local ethical barriers, and without randomization we face an evident selection bias that hinders generalization of results. Furthermore, especially in high income countries, we face both the epidemiological shift from young victims of devastating RTIs towards falls in the elderly and the peculiarity of the legislation related to the patient in coma to be included in clinical studies.

Since the current paucity of evidence does not allow the adoption of defined guidelines, the reported recommendations have to be extensively discussed in each professional context, as to pre-evaluate local pitfalls that might invariably occur and maximize adherence when clinically coherent. Local protocols for daily practice guidance are strongly recommended.

The effect of DC to reduce mortality and prolonged high ICP dose, to minimize days in the ICU and hospital is well reported. Unfortunately, so many variables depending on patients, surgical strategy and neurointensivist management are connected with the unclear impact on outcome of TBI patients underwent DC.

Although there is substantial evidence that multimodality neuromonitoring-guided therapy results in improvements in cerebral physiology, high-quality evidence that this translates into beneficial effects on clinical outcomes remains inconclusive. Despite the benefits of multimodality neuromonitoring after TBI, the use of individualized therapeutic interventions and adoption of monitoring strategies has yet to be proven to improve outcome. Much progress has recently been done regarding the technology behind the monitoring field. Computational analysis and integration of data are essential prerequisites, although many systems have been designed around the needs of individual institutions.

An important challenge is presented when one or more variables remain normal in the face of derangements in another. It is clear that the information derived from automatically generated data cannot, and should not, substitute clinical judgement, rather it should be integrated in order to assist the clinician in obtaining a clearer picture regarding the patient's brain state. For example, ICP can be increased for both pathological (brain ischemia, mass lesions etc.) and physiological (the patient is awakening) conditions. In this case monitoring parameters can help distinguish between one state and the other.

Neuromonitoring can only modulate patient outcome if a monitor-detected change in physiology prompts timely and appropriate therapeutic intervention to reverse an abnormality that is itself an integral determinant of outcome. Furthermore, thresholds for intervention and optimal therapeutic interventions in response to changes in monitored variables remain undefined in many circumstances. Incorporating patient demographics and brain imaging with multimodality neuromonitoring strategies might better optimize individualized treatment decisions.

Study design and conduct are clearly of crucial importance in this regard. One must bear in mind that TBI does not represent a single pathophysiologic entity but a complicated and heterogeneous set of disease processes with substantial temporal and regional heterogeneity.

It remains to be seen whether indications for neuromonitoring after TBI can demonstrate whether monitor-guided interventions lead to improved outcomes for this category of brain injured patients.

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