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Review Article

Management of intracranial hypertension: Recent advances and future directions

Gentle S Shrestha[1], Saurabh Pradhan[2]

Abstract

Intracranial hypertension is a major cause of morbidity and mortality in critically ill patients. Great deal of research has been done with the goal to improve patient outcome, but the challenges are enormous. From basic managementlike sedation and analgesia, to higher tier therapies, there are mixed evidences, some indicating these interventions to be beneficial and some to be equivocal, but the paucity of high-quality trials limits strong recommendations. This review will try to analyze the extensive literature regarding management of raised intracranial pressure, with particular focus on recent advances and will also try to shed some light on future directions.

Keywords: *Brain herniation, intracranial hypertension,*

Introduction:

Intracranial hypertension (ICH) is a common complication associated with all neurological emergencies and intractable high intracranial pressure (ICP) is the leading cause of mortality in such patients.[1] The association between the severity of ICH and poor outcome is well recognized,[2] withdeath or disability averaging 60%or even higher.[3]

The cranium is a closed vault that protects its contents: the brain parenchyma, cerebrospinal fluid (CSF) and blood. However, it provides little room for expansion during disease states. The total intracranial volume is constant, and an increase in any one of the components is offset by an equal decrease in another, or else the pressure increases. This phenomenon has been described as the Monro- Kelly doctrine.[4]

Initial rises in ICP is usually compensated by a decrease in CSF and blood volumewhich are active in maintaining ICP up to 20-25mmHg. Further rise in volume causes a dramatic increase in ICP causing either a mechanical injury to brain tissue in the form of herniation (Fig. 1) or an ischaemic injury by decreasing the cerebral perfusion pressure (CPP).

1. Gentle S Shrestha, Lecturer, Department of Anaesthesiology, Tribhuvan University Teaching Hospital, Maharajgunj, Kathmandu, Nepal
2. Saurabh Pradhan, DM Critical Care Medicine Resident, Tribhuvan University Teaching Hospital, Maharajgunj, Kathmandu, Nepal

Corresponding Author:

Dr. Gentle S Shrestha
MBBS, MD, FACC, EDIC, MRCP (I), FCCP
Neuro-Intensivist & Anaesthesiologist
Email: gentlesunder@hotmail.com
Phone: +977-9841248584

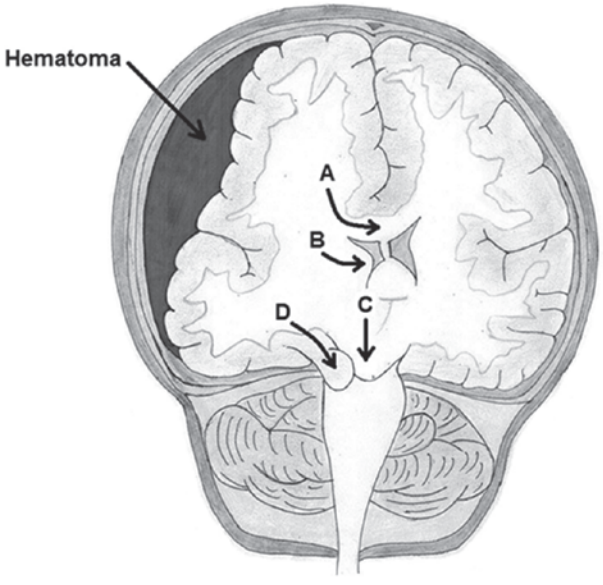

Fig.-1. Schematic representation of cerebral herniation syndromes.**(A)** subfalcine herniation; **(B)** Midline shift; **(C)** Central herniation and **(D)** Uncal herniation.

Therefore the main goal of lowering ICP is maintaining CPP and prevention of brain herniation. The definitive therapy for ICH is treatment of the primary cause of raised ICP. However, regardless of the cause, there are basic principles applicable to all patients with ICH and are employed to acutely reduce ICP before and after definitive measures take place. There are many methods that may be used in decreasing ICP and these treatment strategies have been stratified into tiers (Table 1).[5,6] These strategies will be briefly discussed below before reviewing the recent literature and reflecting on future prospects.

Table 1. A proposed treatment strategy with different tiers of intervention for management of raised ICP and their inherent pitfalls.

Tiers	Treatment	Pitfalls
1	Maintain airway, ventilation, circulation, head end elevation of at least 30°	Coughing, ventilator asynchrony, ventilator associated pneumonia
2	Sedation and analgesia, prevent fever, seizure prophylaxis	Hypotension
3	CSF drainage from ventricles	Ventriculostomy related infection
4	Hyperosmolar therapy	Negative fluid balance, acute kidney injury, hypernatremia
5	Hyperventilation	Excessive vasoconstriction and cerebral ischemia
6	Hypothermia	Fluid and electrolyte disturbance, infection
7	Metabolic suppression (barbiturates)	Hypotension, infection
8	Decopmressive craniectomy	Infection, poor Glasgow Outcome Scale

Management:

There are not many interventions that are helpful in lowering the tissue and CSF compartment apart from surgical removal of intracranial tissue or CSF drainage by ventriculostomy. Therefore most measures are centered on decreasing the cerebral blood volume (CBV) and the fluid portion of the tissue compartment.

CBV can be decreased by either enhancing venous drainage, or decreasing arterial blood flow. Venous engorgement though is the simplest to manage, is a frequently overlooked condition that can cause raised ICP. Such maneuvers that help in cerebral venous drainage include keeping the patient in head-up position, avoiding extremes of head rotation, avoiding circumferential neck pressure (eg. Philadelphia collars, endo-tracheal tube ties), and avoiding conditions increasing central venous pressure, i.e. positive end expiratory pressure, cardiac failure, tension pneumothorax, coughing and bucking.

Decreasing CBV relies on controlling various physiological variables that influence it. As cerebral blood flow is tightly coupled to cerebral metabolic rate of oxygen consumption ($CMRO_2$), factors that decrease $CMRO_2$ also decreases CBV. Sedation and analgesia in a patient with ICH exerts specific cerebral protective effects primarily by reducing $CMRO_2$, and secondarily by preventing arterial hypertension, and preventing coughing and bucking. Furthermore sedation/analgesia is also indicated for specific conditions like during targeted temperature management,[8] refractory status epilepticus[9] and paroxysmal sympathetic activity.[10]

Seizures, which can occur in 15-20% of patients with severe traumatic brain injury (TBI),[11] can be deleterious as it can cause extreme rises in $CMRO_2$. A randomized clinical trial (RCT) in the early 1990s, showed that phenytoin reduced the incidence of seizures during the first week after trauma, but not thereafter.[12] Based on this study, seizure prophylaxis for patients with severe TBIis recommended for the first 7 days after injury and treatment beyond 7 days should be reserved for patients who develop late seizures.[13]

Similarly, fever-induced cerebral vasodilation can increase CBF and ICP and has shown to worsen neurologic injury[14] with poor neurologic outcome.[15] Fever should be urgently controlled with cooling, antipyretics, and the cause of fever should be immediately sought and treated.Theoretically, $CMRO_2$ decreases by 6% to 7% per degree Celsius of temperature reduction and hypothermiacan also cause complete suppression of the EEG(at approximately 18 to 20° C).[16] However prophylactic induction of hypothermia lacksevidence and the recent Brain Trauma Foundation guidelines on severe traumatic brain injury does not recommended it.[13]

As brain volume is highly responsive to changes in water content, hyperosmolar agents help decrease ICP by effectively reducing brain water. The use of hyperosmolar agents to treat ICH can be traced back to the publication of Weed and McKibben[17] and currently hyperosmolar therapy is the preferred treatment for ICH,[18] yet a Class I evidence is still lacking.[19] Various substances, including urea, glycerol, sorbitol, mannitol and, more recently, hypertonic saline formulations, have been investigated. Urea, glycerol and sorbitol are not commonly used due to either moderate efficacy in decreasing ICP, due to their inherent side effects or due to low reflection coefficients raising the concern of their accumulation inside the brain.[20] Currently mannitol is recommended by both the Brain Trauma Foundation and the European Brain Injury Consortium as the osmotic drug of choice.[13,21,22] However, hypertonic saline (HTS) is also gaining popularity and it will be further discussed below.

The typical dose of mannitol is 0.25–1.0 g/kg body weight, but doses from 0.18 to 2.5g/kg/dose have been reported[19] with higher doses having more effective and durable responses.[23-28] However at doses > 200g/d may cause acute renal failure (ARF).[29] Thus serum osmolarity, usually sampled approximately 40 min after an infusion, is often monitored during mannitol administration with a conventional upper limit of 320 mOsm/kg.[30] However, there is lack of evidence to support this threshold.[31] A more reliable marker of serum mannitol level may be the osmolar gap (OG), which is the

difference between the calculated serum osmolarity and the measured serum osmolarity. Retrospective analyses of ARF case series data suggests that ARF occurring with an OG < 55mOsmol/kg is exceedingly rare, with renal failure becoming more likely once OG exceeds 60–75 mOsmol/kg.[29,32]

Hypocapnia causes cerebral vasoconstriction andhyperventilation is commonly employed targeting $PaCO_2$of 30-35mmHg. CBF changes approximately by 3% for each millimeter of mercury change in $PaCO_2$ over the clinically important range of 20 to 60 mmHg.[16] Howeverits effect on ICP is time limited because the pH of the CSF rapidly equilibrates to the new $PaCO_2$ level. Furthermore due to decrease in CBF, there is a theoretical risk of brain ischaemia. For these reasons, the most effective use of hyperventilation is acutely to allow time for other more definitive treatments to be put into action[16] As per the current BTF guidelines, it should be avoided in the first 24 hours after TBI and if used, jugular venous oxygen saturation or brain tissue oxygen partial pressure should be monitored.

Barbiturate coma employed by administering high dose pentobarbital is considered an effective way of reducing ICP and is recommended to control elevated ICP refractory to maximum standardmedical and surgical treatment.[13] An RCT showed that instituting barbiturate coma resulted in a twofold greater chance of controlling ICP.[33] However, it should only be considered for patients with refractory ICH because of the serious complications associated with it such as hypotension, hypokalemia, respiratory complications, infectious complications, hepatic dysfunction, and renal dysfunction.[34] It also hinders frequent neurologic examination.[35] A number of therapeutic regimens usingpentobarbital have been applied. The EisenbergRCT[33] used the following protocol: loading dose 10 mg/kg over 30 min; 5 mg/kg everyhourfor 3 doses, followed bymaintenance dose of 1 mg/kg/h. Availablepharmacologic literature suggests a poor correlationamong serum level, therapeutic benefit and systemiccomplications. A more reliable form of monitoring may be to target theelectroencephalographic pattern of burst suppression.

For ICH refractory to medical therapy, surgical decompression is done by performing a craniectomy. Decompressive craniectomy(DC) is the removal of a large area of skull to increase the potential volume of the cranial cavity. The rationale of this therapy is that it allows tissue to expand outside the cranium, normalizing ICP and preventing secondary tissue damage in the form of ischemia or herniation.[36] There has always been much controversy regarding the indication and the outcome after surgery but it is still commonly performed to effectively control ICP.

Recent Advances:

Sedation and analgesia:

Currently propofol is the recommended drug for sedation in ICH.[13] However it may cause hypotension and rarely propofol infusion syndrome, a fatal condition associated with high infusion rates and prolonged periods of infusion.Midazolam may be preferred in hemodynamically unstable patients and is equally efficacious as propofol in reducing ICP[37] however it may confound clinical assessment by delaying awakening, and cause delirium and withdrawal symptoms.[38] Ketamine, though conventionally thought to increase ICP,[39] a recent systematic review found it to be safe in ICH.[40] Furthermore it was also associated with the lowest incidence of spreading depolarizations, a potentially modifiable secondary injury mechanism.[41]Dexmedetomidine, due to its rapid distribution and elimination properties, perhaps would be the ideal sedative agent, but is yet not recommended due to scarcity of data and considerably higher cost than other sedatives.[42] Volatile agents are also emerging as sedative agents in ICU. Isoflurane at 0.8% has been shown to significantly improve regional CBF with only a modest effect on ICP in patients with subarachoid haemorrhage (SAH).[43] However, the available data do not show whether isoflurane or other volatile agents can reverse large vessel vasospasm in SAH.[42] Sedatives should be adequately supplemented with analgesics. Opioidsare the primary analgesics but non-opioid analgesics such as paracetamol and gabapentin help minimize opioid use.[44]

Daily interruption of sedative, though beneficial in most other circumstances, it is not easily applicable to patients with ICH. Withdrawal of sedation allows timely detection of warning neurological signs, but it also increases circulating levels of stress hormones, with slight but significant increase in ICP.[45] Furthermore a study showed that this strategy actually detected new neurological signs only in a very low number of wake-up tests.[46] Avoidance of sedative interruption in all patients at risk for ICH is therefore preferred, with gradual withdrawal, titrating the sedation dose to ICP targets.[42]

Hyperosmolar therapy:

Though mannitol is a time tested agent, it is associated with many complications. Hypotension with rapid administration (< 5min),[47,48] rebound increase in ICP,[47,49] volume overload and electrolyte imbalances which include hyponatremia[50] or hypernatremia[51] and early but transient decrease of serum bicarbonate and increases in serum potassium.[19] So,in search for an alternate therapy, in 1988 Worthley et al. first found that HTS reduced ICP in patients that were refractory to mannitol.[52] As sodium has a reflection coefficient of 1 (compared to 0.9 for mannitol), HTS theoretically has an excellent osmotic action. Apart from hyperosmolar effect, other mechanisms of ICP reduction have also been proposed. They include reduction of blood viscosity with subsequent improvement in CBF causing autoregulatory vasoconstriction, endothelial cell shrinkage and improvement in circulation, immune-modulatory role, and decreased production of CSF.[53-55]

Dosing and concentration of HTS to be used has not been clearly defined. Studies have reported its use in various formats (volume/ dose, ml/kg, mOsm/kg). andconcentrations have ranged from 3% to 23.5%. However it is the total osmolar load that is actually important, with effective and safe limits ranging from 200- 641 mOsm/dose.[19] HTS has been

used as continuous as well as bolus dosing titrated to serum osmolartiy and/ or serum sodium, but with no clear guidelines regarding the specific target.[19]

However it is not without complications. There is a risk of hyperosmolarity induced ARF, but it not been validated in studies.[56-58] Electrolyte abnormalities are common, with hypernatremia, along with transient hypokalemia and metabolic acidosis secondary to bicarbonate poor fluid administration.[59] Central pontinemyelinosisthough is a theoretical concern, animal studies as well as clinical studies[60-61] do not show a clear association.Administration of HTS also poses a risk of thrombophlebitis especially with higher concentrations and prolonged infusions.Transient therapy with hyperosmolar fluids, however, does not cause thrombophlebitis,[62-64] so emergency administration may not be delayed for central venous access. Like mannitol, it may also cause rebound ICH, but the evidences are also less convincing.[65-66]

Many studies have compared mannitol with HTS with most in favour of HTS. HTS seems to have a greater and longer lasting reduction of ICP than mannitol,[67] is even effective in decreasing ICP refractory to mannitol[68] and also has less failure rates.[69] These findings have been further verified by a meta-analysis by Mortazavi et al.,[70] which showed that HTS may be more effective in reducing ICP than mannitol with odds ratio of 0.36 (0.19-068; p=0.002). A Cochrane review[71] compared HTS with mannitol for brain relaxation during craniotomy and found that brain relaxation was inadequate in 42 of 197 patients in HTS group vs 68 of 190 patients in mannitol group with risk ratio for brain bulge or tense brain in HTS group being 0.60 (0.44-0.83). Furthermore, there may be specific advantages of HTS in patients with SAH as mannitol induced systemic hypotension, diuresis and hypovolemia can be deleterious in such patients.

Despite a great number of studies favouring HTS, there are a number of points to consider. First of all, not all the studies compared equiosmolar concentration of the agents. Comparison of 500mOsm of mannitol with 1000mOsm of HTS is not worth to draw a conclusion on. A study by Jagannatha AT et al.,[72] however, did compare equiosmolar concentration of mannitol with HTS and found physiological advantages of HTS over mannitol (significantly less increase in ICP, greater slope of fall in ICP after a bolus dose) but it did not translate into long term benefit in terms of ICP control or mortality.Secondly, there is lack of good quality evidence. Most of the studies conducted were not RCTs, the meta-analysis and systemic reviews did not include any large scale trials and the studies have a lot of heterogeneity. Therefore, there is inadequate evidence to strongly support the use of HTS over mannitol. At present, awaiting the results of better designed trials, it would be prudent to individualize the choice of hyperosmolar agents considering various patient characteristics, with some predilection in favor of HTS.

Hypothermia:

There have been many trials that have studied the role of hypothermia in patients with TBI but the results have been variable. A meta-analysis performed by Harris OA et al.[73] in 2002 suggested that hypothermia was not beneficial in the management of TBI. In contrast, McIntyre LA et al.[74] in 2003 reported a systematic review which showed benefit of hypothermia in reducing mortality and poor neurological outcome, especially when hypothermia was used for more than 48 hours, with target temperature maintained between 32 and 33^{o}C for a duration of 24 hours and rewarming completed within 24 hours. Another meta-analysis published the same year found hypothermia to confer a marginal benefit in neurological outcome, but without clear evidence of lowering mortality rates in unselected TBI patients.[75]All studies however showed unequivocal increase in the risk of pneumonia. The latest Cochrane review published in 2009,[76] also found no evidence of benefit of hypothermia in the treatment of head injury. They also concluded that significant benefit was only found in low quality trials.

Despite a large number of meta-analyses, due to the paucity of high quality RCTs, a strong conclusion could not be made. Recently, a large multicenter RCT, EUROTHERM trial,[77] was conducted that recruited patients at 47 centers from 18 countries. In this study, Andrews and colleagues randomized patients with recent TBI and directly measured ICP refractory to tier one strategy control measures, to receive either therapeutic hypothermia for a minimum of 48 hours plus standard care, or standard care alone. After 5 years of enrollment that included a total 387 patients, they found that the two approaches were equivalent in reducing ICP, but the intervention group paradoxically had a statistically significant increase in the odds of poorfunctional outcome and mortality at 6 months.Observing the increasing harm to the hypothermia group, the trial was terminated prematurely.

There are some key issues to consider in the conduct of this trial. First of all, hypothermia was used as the tier 2 management. So the control group received tier 2 management as osmotherapy whereas the intervention group received osmotherapy only if hypothermia failed. This may confound the analysis as the control group would be more likely to get osmotherapy commenced earlier, which could be one reason for the unfavourable outcome in hypothermia group. Secondly, the researchers changed the inclusion criteria from within 72 hours of injury to 10 days, after a pilot-phase finding. If hypothermia were to prevent secondary brain injury, then validity of introducing it to a patient at day 8 or 9 with established cerebral oedema would be questionable. This would also increase the heterogeneity of their cohort. However this study is a well conducted study and does provide some strong evidence. Overall what can be interpreted from this trial is that introduction of hypothermia at stage 2 is probably more harmful and should be avoided.

Barbiturate coma:

There have been 3 major RCTs that have assessed the effect of barbiturate coma in patients with TBI. Schwartz et al.[78] published an RCT in 1984 that compared pentobarbital with mannitol for control of ICH. The analysis indicated that pentobarbital coma was not better than mannitol for the

treatment of ICH and may be harmful in patients without intracerebral hematoma. Ward JD et al.[79] also reported a similar result with no difference in outcome with and without pentobarbital, but with much significant incidence of side effects (hypotension), that could potentially worsen outcome. In contrast, Eisenberg et al., in a five-center study, found a 2:1 benefit for those treated with pentobarbital and when patients were stratified by pre-randomization cardiac complications, the advantage increased to 4:1. The results supported the use of high-dose pentobarbital as an effective adjunctive therapy in patients with severe TBI. A Cochrane review published in 2000, reported a pooled analysis from all three trials. They concluded that there is no evidence of effectiveness of barbiturate therapy in patients with acute severe head injury and that barbiturate therapy results in a fall in blood pressure in 1 in 4 treated patients, which will offset any ICP lowering effect on cerebral perfusion pressure.[80]

Decompressive craniectomy:

There are 3 important trials that have studied the effect of craniectomy in malignant middle cerebral artery infarction (MCA). In 2007, DESTINY trial[81]was the first randomized, prospective study that showed that hemicraniectomy significantly reduces mortality in large hemispheric stroke. However the trial failed to show significant results for its primary endpoint, which was functional outcome at 6 months based on modified Rankin scale.The same year, another multicenter, randomized trial, the DECIMAL Trial[82] was conducted in France involving patients between 18 and 55 years of age with malignant MCA infarction to compare functional outcomes with or without DC. After randomization of 38 patients, the data safety monitoring committee recommended stopping the trial because of slow recruitment. The study found significant reduction in mortality rate (52.8% absolute risk reduction) but a non-significant improvement in functional outcome at 6 and 12 months. Similarly in 2009, HAMLET trial,[83] a prospective multicenter trial conducted in Netherlands which included 64 patients, found an absolute risk reduction in mortality of 38%. The most recent meta-analysis of DECIMAL, DESTINY, and HAMLET, included all patients from the 3 trials. With surgical treatment, there was an absolute risk reduction for mortality of 49.9% (number needed to treat of 2). Surgery, however, did not lead to an improvement in percentage of survivors with good outcome (modified Rankin Score of 0 to 3).[83]

Subsequently in 2014, DESTINY II Trial,[84] was conducted, and in contrast to the older studies it showed some benefit from surgery. In a total 112 patients of 61 years of older with malignant MCA infarction, it compared early hemicraniectomy (within 48 hours) with conservative treatment.The study found that the proportion of patients who survived without severe disability was significantly less in the hemicraniectomy group (38% vs 18%; p=0.04) and the rate of survival also doubled as a result of surgery (70% vs 33%); the trial was stopped early because of such dramatic outcomes.

However there is still ongoing controversy regarding craniectomy in patients with diffuse TBI. In 2011, the Decompressive Craniectomy (DECRA) trial, which investigated in adults with severe TBIthough found the use of craniectomy, as compared with standard care, to decrease the mean ICP and the duration of both ventilatory support and the ICU stay, it was associated with a significantly worse functional outcome at 6 months, as measured by the score on the Extended Glasgow Outcome Scale.[85] However it may be inappropriate to draw conclusions as there were certain limitations of the study. Randomization was not proper as patients in the surgical arm appeared to have sustained a more severe primary TBI. Secondly DC was used as a second tier management with a very short duration of raised ICP (ICP threshold of >20 mm Hg for >15 minutes), which did not reflect clinical practice of surgical management only for intractable ICH. Also, there was a high crossover rate from the standard care arm to the surgical arm. Because of these problems, the DECRA trial may have failed to show benefit of surgery and has received a great deal of criticism.[86]

The RESCUEicp trial[103] is a multicenter study that has recently been published in 2016 and is intended to clarify the controversies associated with DECRA. It has recruited a much larger number of patients (400), the ICP threshold has been increased to 25 mmHg instead of 20 mmHg and the duration of refractory ICH before intervention has also been increased to 1 h instead of 15 minutes. Also it has allowed the researchers much flexibility regarding the surgical approach with the use of either unilateral or bilateral craniectomy as per the surgeon's discretion. According to this study, DC for refractory ICH after TBI resulted in reduction of mortality by 22% points but was associated with higher rates of vegetative state, lower severe disability, and upper severe disability than medical management. The rates of moderate disability and good recovery with surgery were similar to those with medical management.

ICP monitoring:

Diagnosing raised ICP is clinically difficult. Clinical features of ICH are impossible to elicit in comatose patients. Papilloedema is a late sign and is observer-dependent. CT scan was also found to be predictive of ICH in only 88%[87] and though MRI has a stronger correlation, it is costly, time consuming, cumbersome and carries the risks of transportation. Therefore direct monitoring of ICP is important.

Brain Trauma foundation guidelines gives level II recommendation that ICP should be monitored in all salvageable patients with a severe traumatic brain injury (GCS 3-8) with an abnormal CT scan (hematomas, contusions, swelling, herniation or compressed basal cisterns).[88]ICP monitoring is also indicated in patients with severe TBI with a normal CT scan if two or more of the following features are noted at admission: age over 40 years, unilateral or bilateral motor posturing, or systolic blood pressure < 90mmHg.[88] Indications for ICP monitoring are less established for other neurological emergencies. Currently invasive monitoring of ICP using a ventricular catheter remains the gold standard.[89] However catheters can be placed

subdurally, intraparenchymally and in the subarachnoid space as well.

Cerebral perfusion measuring techniques include brain tissue oxygen monitoring, laser Doppler flowmetry, and thermal diffusion. Such advanced monitoring techniques may be considered to reduce mortality and improve long-term outcomes.[13]Though these methods are relatively robust for long-term monitoring of cerebral circulation, they are not without complications. Their invasive nature and their risk of infection, haemorrhage and catheter malfunction or malposition makes these methods only suitable for critically ill patients.[7]

This had led to search for non-invasive techniques that could possibly be a reliable surrogate for monitoring ICP directly. The choice often depends upon the clinical need and a balance between availability, accuracy, and practicality.[7] There is a potential role of these techniques of ICP monitoring in patients who need monitoring but invasive technique is not immediately available or may be contraindicated.[87] Two techniques that necessitate special mention are transcranial Doppler (TCD) and ultrasound guided optic nerve sheath diameter (ONSD) measurement.

TCD uses low frequency pulsed Doppler (2 MHz) through the acoustic windows of the skull to insonate the basal cerebral arteries generating the velocity-time waveform of CBF. As ICP increases, diastolic flow velocity is further reduced compared to systolic flow velocity leading to sharpening of systolic peak, loss of Windkessel effect and increased pulsality index.[90] There are many studies that have correlated TCD derived PI with invasively measured ICP but the best correlation ($r = 0.94$; $p < 0.001$) was reported by Bellner et al.[91] who proposed an equation ICP = 10.972 X PI – 1.284. In one study early use of TCD could predict poor outcome in those with an abnormal TCD.[92] However TCD is user dependent with a minimum of 25-50 supervised scan recommended.[93] Furthermore, there may be inadequate temporal window in 10-15% individuals.[94]

Measurement of ONSD is rapidly gaining popularity as it is quick, easily available and has a short learning curve. As the optic nerve sheath is continuous with dura mater, and subarachnoid compartment of optic nerve communicates with that of brain, any increase in ICP causes expansion of ONSD.[95-96] Measurement made 3 mm behind the globe is most optimal.[97] Inter-individual variation makes cut-off value hard to define and have ranged from 4.8-6.0mm with a sensitivity of 36-90% and specificity of 38-100%.[98] A systematic review and metanalysis[99] of trials published in 2011, reported a sensitivity of 0.90 (95% CI 0.80-0.95) and a specificity of 0.85 (95% CI 0.73-0.93) with area under ROC curve of 0.94 (95% CI 0.91-0.96). However the meta-analysis had inadequate power due to small number of patients included. Another point to note is that ONSD may vary and there is need to explore the normal range for each population. In a recently published study by the author, Shrestha GS, median ONSD was found to be 4.1mm (95% CI 3.1-4.6mm) in healthy Nepalese adults.[100]

At the moment, none of the non-invasive techniques are accurate and established enough to substitute invasive ICP measurement. Considering the limited availability, associated complications, contraindications and absence of established indications for invasive ICP monitoring in may scenarios, non-invasive monitoring can be valuable as a screening method for raised ICP. TCD and ONSD measurement are especially promising and may be useful in selected settings including the resource-challenged environments.[101]

Though ICP monitoring is considered standard of care for severe TBI, the efficacy of monitoring on outcome had not been tested until recently. The BEST: TRIP trial[102] was a multicenter, controlled trial in which 324 patients 13 years of age or older who had severe TBI and were being treated in ICUs in Bolivia or Ecuador were randomly assigned to one of two specific protocols: guidelines-based management in which a protocol for monitoring intra-parenchymal intracranial pressure was used or a protocol in which treatment was based on imaging and clinical examination. They found no difference in composite measure of survival time, impaired consciousness and functional status at 3 months and 6 months and neuro-psychological status at 6 months. This trial concluded that care focused on maintaining monitored intracranial pressure at 20 mm Hg or less was not shown to be superior to care based on imaging and clinical examination.

Future Directions:

Management of ICH has evolved through all these years. Numerous studies including good quality RCTs have had major impact in changing our practice regarding patient safety and outcome. However many queries remain unanswered.For the various interventions for lowering ICP, the optimal position in the ladder, in the tiered approach remains uncertain.

More studies are needed to identify certain subsets of patients who might respond favorably to analgesic-sedative and/or barbiturate treatment, and to identify alternative agents, drug combinations, and dosing regimens. More research should come up to foster the findings of current studies of the novel sedative-anesthetic dexmedetomidine and its effects in patients with severe TBI. They should attempt to identify subsets of patients who might respond favorably or unfavorably to barbiturate treatment. For example, the effects of barbiturate-mediated ICP control on the quality of survival after severe TBI remain, for the most part is unknown. Finally, additional studies examining the comparative clinical efficacy of different barbiturates or combinations of barbiturates are warranted.

The debate between mannitol and HTS continues. As already discussed, the evidence of relative benefit of HTS over mannitol, found by existing studies, is inadequate to recommend one agent over the other. This needs to be confirmed with largerRCTs. The dosing and concentration of HTS that is the most beneficial is yet undetermined. Studies are required to find out the optimal dosing and concentration for HTS as well as efficacy of prolonged infusions in relation to outcome.

There are still gaps in understanding whether hypothermia may be beneficial or harmful. Though the EUROTHERM trial tried to answer this question, the various drawbacks that have already been discussed limits applicability of this intervention. What needs to be determined is whether hypothermia is effective as a third or higher tier management rather than as a second tier. There are also more specific objectives that need to be clarified like that has been done with using hypothermia after cardiac arrest. The timing of initiation, the duration of intervention and the temperature to be targeted need to be determined. Furthermore the applicability of hypothermia has mainly been tested in TBI; further studies are required to see whether its effects can be generalized to all patients with neurological emergencies.

There is also paucity of high-quality evidence regarding the best surgical strategy for patients with acute SDH, which has been associated with high rates of mortality and poor neurological recovery. Only some retrospective studies[104-105]favour primary DC over craniotomy to confer a better outcome. High-quality studies are required to prove the effectiveness of primary DC in these patients. On this background, the RESCUE-ASDH is being conducted as an intention-to-treat multicenter trial that is going to evaluate the clinical and cost-effectivess of primary DC versus craniotomy in patients with acute SDH.[106] It may provide some insight to the role of DC in this subset of population.

Most of the studies that have been done in neurological emergencies are based on a threshold ICP as a target of intervention. However, it must be understood that the pathophysiology of ICH is much more complex, and targeting a numerical threshold may be an oversimplification.The BEST: TRIP trial has already shown that monitoring of ICP is not enough to improve outcome. This has led to the concept of multimodal monitoring; that ICP may be better managed when considered in the setting of individual intracranial compliance, cerebral autoregulation, and measurement of indices of CBF and brain metabolism.[107] There are emerging evidences showing that, maintaining CPP within the range of individual autoregulation may improve outcome rather than targeting a generalized range of 50-70mmHg.[108] More refined monitoring of autoregulatory efficiency is now possible through calculation of derived indices such as the pressure reactivity index.[109]The BOOST 2 trial is a prospective RCTthat intends to evaluate the impact of brain tissue oxygen monitoring in addition to control of ICP on outcome. It has already completed enrollment and it is currently undergoing analysis. Further confirmation of the usefulness of non-invasive techniques, such as ONSD and TCD may mark an important advancement in the care of patients with ICH.

Ultimately,no doubt, the future is to individualize the care for each patient. There is no one-size-fits-all and probably this approach can be attributable to the disappointing results of many well designed trials. Multimodal monitoring may help provide a better insight into the pathophysiological process which may help set individual targets. However, the addition of multiple monitoring tools to clinical studies would add further complexity to trial design and data analysis.[110]Despite the obstacles, the medical community has undergone great advances in this field. A few more dedicated high-quality trials may pave a clearer road towards better patient care and outcome that we do and will always long for.

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