Vascular Health and Risk Management

Review and recommendations on management of refractory raised intracranial pressure in aneurysmal subarachnoid hemorrhage

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Abstract: Intracranial hypertension is commonly encountered in poor-grade aneurysmal subarachnoid hemorrhage patients. Refractory raised intracranial pressure is associated with poor prognosis. The management of raised intracranial pressure is commonly referenced to experiences in traumatic brain injury. However, pathophysiologically, aneurysmal subarachnoid hemorrhage is different from traumatic brain injury. Currently, there is a paucity of consensus on the management of refractory raised intracranial pressure in spontaneous subarachnoid hemorrhage. We discuss in this paper the role of hyperosmolar agents, hypothermia, barbiturates, and decompressive craniectomy in managing raised intracranial pressure refractory to first-line treatment, in which preliminary data supported the use of hypertonic saline and secondary decompressive craniectomy. Future clinical trials should be carried out to delineate better their roles in management of raised intracranial pressure in aneurysmal subarachnoid hemorrhage patients.

Keywords: aneurysm, intracranial pressure, intracranial hypertension, subarachnoid hemorrhage

Introduction
Aneurysmal subarachnoid hemorrhage (aSAH) is associated with significant morbidity and mortality. An important prognosticator is the admission neurological status, which includes the Hunt and Hess grade and the World Federation of Neurosurgical Societies (WFNS) grade. Raised intracranial pressure is associated with poor-grade aSAH, which was thought to have a dismal outcome irrespective of aggressive management in the past. With advances in cerebral aneurysm treatment and neurointensive care, half of the poor-grade aSAH patients can attain a favorable outcome if intracranial pressure can be controlled to reduce secondary brain injury.

Management of raised intracranial pressure (ICP), or intracranial hypertension, has been extensively investigated and translated into clinical practice in traumatic brain injury (TBI). However, there is lack of consensus on the management of raised ICP in aSAH, especially when refractory to first-line treatment. High ICP in aSAH is associated with poor outcome. Ryttlefors et al and Heuer et al both observed that in aSAH patients, refractory raised ICP is associated with unfavorable neurological outcome. The authors suggested that a better understanding and more aggressive approach in treating raised ICP may improve prognosis.

Standard therapies in treating high ICP in aSAH are frequently adopted from experiences from TBI, including optimizing cerebral venous outflow, controlled
hyperventilation, sedation with analgesia, cerebrospinal fluid diversion, and surgical removal of space-occupying intracranial hematoma.\textsuperscript{16,17} Second-tier treatments include mannitol, hypertonic saline, therapeutic hypothermia, barbiturate coma, and decompressive craniectomy. We aimed to review the literature about the effectiveness of these “salvage therapies” for refractory raised ICP in aSAH.

Pathophysiology of raised intracranial pressure in aSAH

Intracranial hypertension after aSAH can be due to cerebral edema, intracranial hematoma, hydrocephalus, intraventricular hemorrhage, early brain injury, aneurysm reperfusion, aneurysm treatment, or delayed cerebral ischemia.\textsuperscript{15} Cerebral infarct can take place as a consequence following vasospasm or as a complication after endovascular coiling or microsurgical clipping of ruptured aneurysms, and could contribute to raised ICP. Cerebral vasospasm usually peaks 4–10 days after initial hemorrhage, and can lead to delayed global cerebral edema in 20% of patients and hence elevated ICP.\textsuperscript{18,19} The resulting vicious cycle of raised ICP leads to insufficient cerebral perfusion pressure, contributes significantly to morbidity and mortality in patients with aSAH.\textsuperscript{20-22} Delayed cerebral infarction can also lead to similar disastrous results.\textsuperscript{22}

Nagel et al studied the effect of intracranial hypertension following aSAH with cerebral microdialysis.\textsuperscript{23} In patients with aSAH and intracranial hypertension, cerebral metabolic levels were severely deranged compared to those in patients with normal ICP, and were reflected in high levels of markers of “cerebral crisis.” Of these, both the excitotoxic neurotransmitter glutamate and membrane-degradation marker glycerol in cerebral diacylate further deteriorated 5 days after ictus, possibly reflecting development of secondary brain damage. The authors also found that ICP more than 20 mmHg was a strong predictor of death and associated with unfavorable neurological outcome. In TBI, elevated ICP has consistently been associated with poor outcome. Marmarou et al\textsuperscript{16} observed that outcome after TBI was significantly worse among patients with ICP greater than 20 mmHg. This was confirmed in a recent systematic review on TBI, where mortality reaches 55.6% for those with ICP >40 mmHg, and refractory intracranial hypertension in TBI patients had an 88-time-higher chance of mortality.\textsuperscript{25} This ICP cutoff value from TBI treatment is also frequently used in managing aSAH. In contrast to TBI, decompen-

dation of ICP in aSAH patients could occur earlier with the appearance of delayed cerebral infarction.\textsuperscript{26} Cerebral edema and/or intraparenchymal hematoma in aSAH can also lead to increased ICP, and is a significant poor prognostic factor.\textsuperscript{27}

Hyperosmolar agents

Hyperosmolar agents such as mannitol and hypertonic saline are commonly used empirically for ICP control. They induce an immediate reduction in ICP through changes in blood-fluid dynamics or rheology. Their osmotic properties then produce a reduction in brain-water content and a reduction in brain volume, in the presence of an intact blood–brain barrier, which in return reduces ICP within a rigid skull (the Monro–Kellie hypothesis).\textsuperscript{24} For TBI patients, guidelines from the Brain Trauma Foundation in 2007, in cooperation with three neurosurgical societies, suggested level II evidence for the effectiveness of mannitol at doses of 0.25–1 g/kg of body weight to reduce ICP.\textsuperscript{29} However mannitol is associated with systemic hypotension due to secondary effects from decreasing peripheral vascular resistance. Prolonged administration can result in diuresis and hypovolemia, bearing risk of further reducing perfusion to the brain by lowering the blood pressure.\textsuperscript{30} Hypovolemia and hypotension are at odds with the hypervolemic and hypertensive treatment of vasospasm.\textsuperscript{31} On the other hand, hypertonic saline improves rheology and exerts a positive inotropic effect, in addition to hemodilution and hyperosmolarity. The hypertensive, hypervolemic, and hemodilution effect is similar to triple-H therapy for prevention and treatment of vasospasm.\textsuperscript{32-37} The Brain Trauma Foundation guidelines state that no direction can be given regarding the use of hypertonic saline or the interval of administration of any hyperosmolar agent, yet suggested hypertonic saline may be superior to mannitol, with better hemodynamic parameters, which can be of benefit in aSAH. Case series have shown hypertonic saline is also effective in lowering ICP in SAH that was refractory to medical treatment.\textsuperscript{34} There is no clinical trial data looking particularly at the effect of mannitol in aSAH. Several trials have examined the safety and efficacy of using hypertonic saline in aSAH (Table 1).

A retrospective study by Suarez et al\textsuperscript{35} found no complication with hypertonic saline infusion. Tseng et al\textsuperscript{32} demonstrated that hypertonic saline can be effective in ICP reduction in poor-grade aSAH. Sixteen of the 17 treatment episodes showed improved perfusion to ischemic areas, with increased global cerebral perfusion pressure in all cases. Two prospective studies published in 2007 and 2010 confirmed the radiological improvement in cerebral perfusion and respectively clinical improvement. The degree of cerebral blood flow
Table 1 Summary of clinical trials of hypertonic saline in aneurysmal subarachnoid hemorrhage

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>Number of treatments</th>
<th>Dose</th>
<th>ICP reduction</th>
<th>Other outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suarez et al25</td>
<td>Retrospective</td>
<td>29</td>
<td>Continuous 3% NaCl acetate</td>
<td>Not studied</td>
<td>No effect on CBF velocities</td>
</tr>
<tr>
<td>Tseng et al22</td>
<td>Retrospective</td>
<td>17</td>
<td>23.4% NaCl boluses</td>
<td>74.7% at 60 minutes</td>
<td>Improvement of perfusion defects on xenon CT scans</td>
</tr>
<tr>
<td>Bentsen et al36</td>
<td>Prospective randomized, single-blind, placebo-controlled</td>
<td>22</td>
<td>7.2% NaCl in 6% hydroxyethyl starch boluses</td>
<td>37% compared with control at 64 minutes</td>
<td>Beneficial hemodynamic effects with increased cardiac index</td>
</tr>
<tr>
<td>Tseng et al23</td>
<td>Prospective</td>
<td>35</td>
<td>23.5% NaCl boluses</td>
<td>93.1% at 60 minutes</td>
<td>Improvement in CBF on xenon CT scans, and associated with improved outcome at discharge</td>
</tr>
<tr>
<td>Al-Rawi et al37</td>
<td>Prospective</td>
<td>44</td>
<td>23.5% NaCl boluses</td>
<td>67.4% at 30 minutes</td>
<td>Improvement in cerebral oxygenation on xenon CT scans and favorable outcome at 12 months</td>
</tr>
</tbody>
</table>

Abbreviations: ICP, intracranial pressure; CBF, cerebral blood flow; CT, computed tomography; NaCl, sodium chloride.

(CBF) enhancement following hypertonic saline therapy was associated with favorable outcome (modified Rankin scale score of 1–3) upon discharge. These investigators later also found that administering hypertonic saline to patients with poor-grade aSAH improved CBF and cerebral oxygenation, and was associated with favorable outcome at 12 months after intervention.37 The only available pilot randomized trial, by Bentsen et al,36 showed that hypertonic saline improved ICP control and increased cardiac index in poor-grade aSAH patients. However, it was only single-blinded, and consisted of only eleven patients each in the hypertonic saline group and normal saline group.

Most of these studies did not take into account the refractoriness of raised ICP. Pathophysiologically, the demonstrated effects of hypertonic saline in lowering ICP and improving cerebral perfusion could potentially improve clinical outcome in refractory ICP in aSAH.

Recommendation

While mannitol and hypertonic saline have been shown to reduce ICP in TBI patients, such effect on clinical outcome is lacking in aSAH. Hypertonic saline may improve CBF and outcome. Further randomized placebo-controlled clinical trials should be conducted for hypertonic saline in aSAH patients based on these encouraging initial data.

Hypothermia

Therapeutic hypothermia is generally defined as a body temperature in the range of about 33°C–35°C.38,39 Peterson et al analyzed 1339 TBI patients who received hypothermia as treatment in eight randomized controlled trials, and found that reduction in risk of mortality was greatest and favorable neurologic outcomes much more common when hypothermia was maintained for more than 2 days.40 Prophylactic hypothermia is associated with better outcome when compared with normothermic controls in TBI patients, according to the guidelines by the Brain Trauma Foundation.41 On the other hand, hypothermia is associated with electrolyte imbalance and significant risks of infection, including pneumonia, which can further increase when combined with barbiturates.42 Although mild hypothermia in rat SAH models has been shown to reduce brain edema,43 clinical benefits remained unclear in ICP control and outcome in aSAH.

Zhao et al38 and Li et al39 conducted systemic reviews on intraoperative hypothermia for microsurgical clipping of ruptured cerebral aneurysms in aSAH patients, which included the same three well-conducted randomized controlled trials with a total of 1158 participants.44–46 Li et al concluded that this treatment did not show statistically significant benefit in reduction in mortality and clinical outcome,45 which concurred with the conclusions of Zhao et al that there was no statistical difference in clinical outcome for intraoperative hypothermia over normothermia.38 Both groups concluded there was no difference in perioperative, intraoperative, and postoperative adverse events in between the mild-hypothermia and normothermia groups.

There are a few clinical studies on the effect of systemic hypothermia in aSAH. Inamasu and Ichikizaki47 treated eleven patients with poor-grade aSAH and intracranial hypertension refractory to mannitol with hypothermia for 3 days. Although ICP control was able to be achieved...
in nine patients, eight patients died and three patients were severely disabled or in a persistent vegetative state.

A cohort of 100 consecutive patients with refractory intracranial hypertension following aSAH were treated with prolonged mild hypothermia for a mean duration of 7 days, and 35.6% achieved good outcome at 1 year. However, 93% of the participants suffered from at least one clinically significant side effect, including electrolyte disorders, pneumonia, thrombocytopenia, and septic shock syndrome. Six patients died as a result of respiratory or multiorgan failure.

Recommendation
Reports from the literature suggested that systemic hypothermia was feasible for aSAH patients. However, there is no evidence that systemic hypothermia for refractory raised ICP can improve clinical outcome in aSAH patients.

Barbiturate coma
Barbiturates primarily exert their sedative and anesthetic effects by potentiating the action of gamma-aminobutyric acid (GABA) at the GABA<sub>A</sub> receptor. Barbiturates suppress cerebral metabolism, causing reduction in the cerebral metabolic rate of oxygen consumption, reduction in CBF, and decrease in cerebral blood volume and ICP. Both pentobarbitone and thiopentone can significantly reduce acute and chronic intracranial hypertension. Earlier case series suggested patients with refractory vasospasm complicating aSAH can have good recovery with barbiturate coma compared with historical controls.

However, barbiturates are associated with adverse effects, including cardiorespiratory depression, a prolonged duration of postinfusion clinical unresponsiveness, impaired white cell function, hypokalemia, and hepatic and renal dysfunction. It was demonstrated that blood-pressure reduction is significant, and might therefore adversely affect cerebral perfusion pressure and outcome. A systemic review in 2012 including seven randomized controlled trials and 341 patients concluded that there was no evidence that barbiturate therapy improves outcome in TBI patients. Hypotension was observed in 25% of patients, which is antagonistic to the beneficial effects of ICP control. The hypotensive effect could even be harmful in aSAH, exacerbating vasospasm and delayed cerebral infarction. One should be reminded that induced hypertension, associated with higher CBF, can reverse ischemic neurological deficits in approximately two-thirds of patients with vasospasm after aSAH.

Recommendation
With the lack of evidence to support an overall beneficial effect of barbiturate coma in patients with aSAH and the known side-effects, barbiturate coma should not be routinely administered for aSAH patients with refractory raised ICP.

Decompressive craniectomy
Decompressive surgery for refractory intracranial hypertension is directed towards improving cerebral perfusion, preventing ischemic damage, and avoiding brain herniation. The rationale for decompressive surgery is based on the Monro-Kellie doctrine. Accordingly, intracranial volume should remain constant, and volumetric compensations should be achieved by shifts in cerebrospinal fluid, CBF, or brain herniation. Decompressive craniectomy removes part of the rigid skull so the intracranial volume can expand through the skull and dural defect, and hence ICP can be lowered. Its effectiveness in reducing ICP in severe TBI was demonstrated in different studies, and is increasingly utilized for refractory ICP control. Although Sahuquillo and Arikan did a systematic review and failed to find a significant association with better neurological outcome for decompressive craniectomy in TBI patients, favorable outcomes may be expected in selected patients with decompressive craniectomy for salvaging high ICP after maximizing medical treatment. It is thus reasonable to believe the procedure would play a similar role in ICP control in aSAH, and hence improve clinical outcome. Similar to TBI, decompressive craniectomy for aSAH can also be performed as primary prophylaxis apart from secondary salvage purposes. Prophylactic decompression or primary decompressive craniectomy is defined as any surgical decompression performed in patients undergoing craniectomy primarily for the evacuation of any type of intradural lesion. The aim of prophylactic craniectomy is not to control refractory ICP, but to avoid expected postsurgical increase in ICP.

Fisher and Ojemann suggested that rapid increase in ICP can result in a “feed-forward” cycle of brain injury, causing a vicious cycle of cerebral anoxia and edema. Decompressive craniectomy helped in breaking this cycle. Jaeger et al reported that following decompressive craniectomy for medically intractable ICP elevation in three patients with diffuse cerebral edema secondary to aneurysmal SAH, cerebral tissue oxygenation improved. Similar improvement in cerebral tissue oxygenation was also reported by Stiefel et al. It was also found that neurogenic hypotension due to brain-stem compression was relieved after decompressive craniectomy,
possibly due to a restoration of normal basal sympathetic vascular tone.\textsuperscript{64}

The presence of intracranial hematoma in aSAH was associated with a worse prognosis.\textsuperscript{65} Buschmann et al treated 38 patients with aSAH by using decompressive craniectomy for intractable raised ICP and found 52.6% favorable outcomes (Glasgow Outcome Scale 4–5) after 12 months.\textsuperscript{66} Among those in whom secondary decompressive craniectomy was performed, 72.7% patients attained favorable outcome in those without infarct, whereas only 16.7% had a favorable outcome in the group with delayed infarct and refractory intracranial hypertension. Similarly, among the 79 aSAH patients where Güresir et al performed 16 decompressive craniectomy, for raised ICP secondary to brain edema without infarction or rebleeding.\textsuperscript{67} At 6 months, 37.5% had a good outcome (modified Rankin Scale 1–3), compared to an overall 26.6% in all craniectomy patients. This suggested that patients with progressive cerebral edema without radiological signs of infarction may benefit most from secondary decompressive craniectomy in aSAH.

Schirmer et al found that for intractable intracranial hypertension in aSAH, the long-term outcome was better for patients who underwent secondary decompressive craniectomy within the first 48 hours of aSAH.\textsuperscript{68} With its potential role in improving outcome, prophylactic decompressive craniectomy was reported in eight patients with poor-grade aSAH with large sylvian hematomas.\textsuperscript{69} Five out of the eight patients enjoyed excellent or good outcome at 1 year, suggesting the potential beneficial effect on rapid control of ICP may translate into good outcome. Another retrospective study also had similar findings: prophylactic decompressive craniectomy in patients led to more than half of them enjoying a favorable outcome among those presenting with WFNS grade IV aSAH together with large intracerebral or sylvian hematomas.\textsuperscript{70}

Complications of decompressive craniectomy can include infection, development of subdural hygroma, and syndrome of the trephined in the later phase of recovery, characterized by new cognitive, neurological, or psychological deficits.\textsuperscript{71–74} Decompressive hemicraniectomy was associated with postoperative hydrocephalus, and it was postulated that the cerebrospinal fluid-flow dynamic was disturbed after part of the skull vault was removed.\textsuperscript{75,76}

**Recommendation**

Although there is a lack of randomized controlled trials on the efficacy of decompressive craniectomy, it could be considered for refractory raised ICP in aSAH patients when medical treatment has been exhausted, as preliminary evidence suggests that decompressive craniectomy can reduce mortality and improve clinical outcome. Further clinical trials are required to investigate the timing, indications, and the balance between the beneficial and detrimental effects.

**Conclusion**

Raised ICP refractory to standard treatment in aSAH can lead to poor outcome and mortality. Preliminary data supported the use of hypertonic saline and secondary decompressive craniectomy, but further randomized trials should be conducted.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**


