Review Article

# Research studies that have influenced practice of neuroanesthesiology in recent years: A literature review

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## ABSTRACT

Through evolving research, recent years have witnessed remarkable achievements in neuromonitoring and neuroanesthetic techniques, with a huge body of literature consisting of excellent studies in neuroanaesthesiology. However, little of this work appears to be directly important to clinical practice. Many controversies still exist in care of patients with neurologic injury. This review discusses studies of great clinical importance carried out in the last five years, which have the potential of influencing our current clinical practice and also attempts to define areas in need of further research. Relevant literature was obtained through multiple sources that included professional websites, medical journals and textbooks using key words "neuroanaesthesiology," "traumatic brain injury," "aneurysmal subarachnoid haemorrhage," "carotid artery disease," "brain protection," "glycemic management" and "neurocritical care." In head injured patients, administration of colloid and pre-hospital hypertonic saline resuscitation have not been found beneficial while use of multimodality monitoring, individualized optimal cerebral perfusion pressure therapy, tranexamic acid and decompressive craniectomy needs further evaluation. Studies are underway for establishing cerebroprotective potential of therapeutic hypothermia. Local anaesthesia provides better neurocognitive outcome in patients undergoing carotid endarterectomy compared with general anaesthesia. In patients with aneurysmal subarachnoid haemorrhage, induced hypertension alone is currently recommended for treating suspected cerebral vasospasm in place of triple H therapy. Till date, nimodipine is the only drug with proven efficacy in preventing cerebral vasospasm. In neurocritically ill patients, intensive insulin therapy results in substantial increase in hypoglycemic episodes and mortality rate, with current emphasis on minimizing glucose variability. Results of ongoing multicentric trials are likely to further improvise our practice.

**Key words:** Aneurysmal subarachnoid haemorrhage, brain protection, carotid artery disease, glycemic management, neuroanaesthesiology, neurocritical care, traumatic brain injury

## INTRODUCTION

Neuroanaesthesiology is a rapidly growing and evolving branch of medicine, which not only has evolved as a separate super-specialty, but has also witnessed remarkable achievements in neuroanesthetic techniques. All this may be accredited to better understanding of pathophysiological processes, advent of newer state of the art neuromonitoring techniques and high quality research carried out in various aspects of neuroanaesthesiology and neurocritical care. Despite all developments, controversies still exist. Majority of recently conducted multicentric trials provide equivocal results with little clinical significance.

In this review we discuss the strength and weakness of landmark studies, published between 2007 and 2012, on controversial topics in neuroanaesthesia along

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with a brief review of how their results influence our current practice or thinking.

An extensive literature search was performed through MEDLINE, PubMed, Google Scholar, science journals and textbooks to identify such studies using key words "neuroanaesthesiology," "traumatic brain injury," "aneurysmal subarachnoid haemorrhage," "carotid artery disease," "brain protection," "glycemic management" and "neurocritical care."

## TRAUMATIC BRAIN INJURY

### Fluid resuscitation

In patients with severe traumatic brain injury (TBI), aggressive fluid resuscitation is of utmost importance to prevent hypotension, subsequent mortality and secondary neurological injury.[1,2] The American guidelines for pre-hospital management of TBI advocates avoidance of hypotension (systolic blood pressure <90 mmHg in adults).[2] However, the ideal resuscitation fluid has always been a matter of debate – isotonic versus hypertonic fluids and colloid versus crystalloid.

#### *Hypertonic saline versus normal saline*

Currently, initial fluid resuscitation in traumatic patients begins in out-of-hospital settings and, despite lack of evidence, is considered standard of care. The major reason for pre-hospital hypotension after TBI is hypovolemia from blood loss and requires blood transfusion ideally. In its absence, isotonic fluid resuscitation is recommended;[2] however, the relatively large volumes of fluid required may exacerbate cerebral oedema. In comparison, hypertonic solutions (1.6% to 23.4% saline), either alone or combined with dextran, have potential of early restoration of intravascular volume with a smaller fluid volume,[3] improved cerebral perfusion with reduced intracranial pressure (ICP)[4] and a possible modulation of the inflammatory response.[5,6]

To determine whether an early out-of-hospital administration of hypertonic fluids would be able to improve long-term neurologic outcome, Bulger *et al.* conducted a multicentric randomized controlled trial (RCT) of fluid resuscitation among 1282 patients with severe TBI [Glasgow coma scale (GCS) score <8] without hypovolemia.[7] Patients were randomly distributed to receive a single 250 ml bolus of either 0.9% saline (NS), 7.5% hypertonic saline (HS) or HS/6% dextran-70 combination for initial fluid resuscitation. Authors observed that, compared with NS, HS resuscitation offered no benefit in terms of survival (74.3% with HS/dextran, 75.7% with HS and 75.1% with NS, $P$=0.88) or better neurological outcome. However, the lack of effect of hypertonic resuscitation was attributed to varied treatment protocols, dilutional effects of crystalloids and a short period of hyperosmolarity. Authors concluded that their study results does not preclude a benefit from HS as it was administered differently but, at present there appears to be no compelling reason to adopt a practice of hypertonic fluid resuscitation in patients with TBI in the out-of-hospital setting. Notably in this study, patients with the most fatal prognosis, ones with hemorrhagic shock, were excluded.

Thus, current data do not support routine use of hypertonic fluid resuscitation in TBI patients. HS, however, may be considered as a treatment option in patients with severe TBI.[2]

#### *Colloid versus crystalloid*

Saline versus Albumin Fluid Evaluation (SAFE) study was the first large multicentric RCT of albumin versus NS fluid resuscitation in 6,997 patients admitted in multidisciplinary intensive care units (ICUs) and showed no difference in 28-day mortality. In post-hoc analysis of SAFE study subgroup with TBI ($n$=460), severe TBI patients treated with albumin had a 1.88 fold increased relative risk (RR) of death at 24 months compared with saline treated subjects ($P$<0.001), possibly because of exacerbation of cerebral edema by albumin.[8] Results of this study led to the recent recommendation by European Society of Intensive Care Medicine that colloids should not be used in patients with TBI.[9]

On-going Crystalloid versus Hydroxyethyl Starch Trial (CHEST trial) comparing NS fluid resuscitation with third generation hydroxyethyl starch 130/0.4 in 7000 ICU patients, including mild to moderate TBI patients, is expected to further clear the controversy of colloid versus crystalloid resuscitation in the critically ill.[10]

### Targeted approach for optimal cerebral perfusion pressure

The optimal management strategy for treatment of increased ICP has traditionally been either *cerebral perfusion pressure (CPP) targeted* (Rosner's concept) which advocates increasing blood pressure to augment cerebral blood flow (CBF) and CPP[11] or *ICP targeted* which focuses on aggressive reduction

of ICP as the primary target.[12] A specific and more common subcategory of ICP control involves a "*volume-targeted*" strategy (Lund's concept) based on physiological principles for brain volume regulation and improved microcirculation.[13] Both concepts have their own merits and demerits. However, in absence of well-controlled randomized comparative studies, no approach can be stated superior to other.

With the advent of advanced multimodal neuromonitoring, a more individualized and patient-specific approach for optimal CPP appears promising. Over years, there has been a paradigm shift in neuromonitoring in TBI patients-from global ICP and CPP monitoring to more localized brain tissue oxygen ($PbtO_2$) monitoring. Studies have been published from advanced neurosurgical centers comparing $PbtO_2$ based therapy with ICP/CPP based therapy in TBI.[14,15] However, as yet, there is no strong outcome evidence to support this approach likewise. Until further research, the current brain trauma foundation (BTF) guidelines of maintaining CPP within 50-70 mmHg (level III evidence) and ICP <20 mmHg (level II evidence) continues to be the gold standard treatment target.[16]

### Tranexamic acid in TBI

Antifibrinolytics reduce blood loss in patients undergoing surgery by inhibiting fibrinolysis and, hence, improve hemostasis. Clinical Randomization of an Antifibrinolytic in Significant Head Injury (CRASH-2 trial) evaluated the effect of tranexamic acid (TXA) in bleeding traumatic patients and found that an early administration within eight hours of injury is safe and effective in reducing all-cause mortality compared to placebo (RR=0.91, *P*=0.0035). As a consequence of trial results, TXA has been incorporated into trauma treatment protocols worldwide and has been included on the World Health Organization List of Essential Medicines.

To quantify the effect of TXA on intracranial haemorrhage, the CRASH-2 Intracranial Bleeding Study evaluated 270 adult patients with TBI out of 20,211 trauma patients recruited in the CRASH-2 trial.[17] There was a reduction in intracranial haemorrhage growth (–3.8 ml, *P*=0.33), ischemic lesions and mortality (11% vs 18%; *P*=0.06) in TXA allocated patients, but these results were statistically insignificant showing neither moderate benefits nor harmful effects of TXA in TBI patients. Results of ongoing CRASH-3 will reliably determine the effectiveness of early administration of TXA in TBI patients.[18]

### Decompressive craniectomy in patients with resistant intracranial hypertension

In a review of therapies for treatment of intracranial hypertension (ICH), Schreckinger *et al*., reported decompressive craniectomy (DC) as most effective method than mannitol, cerebrospinal fluid drainage, HS, hyperventilation, barbiturates or hypothermia.[19] DC, however, is also associated with serious medical complications, intracranial infection and a need for later cranioplasty.

In Decompressive Craniectomy in Diffuse Traumatic Brain Injury (DECRA) trial, early bifrontotemporoparietal DC was found to decrease ICP (14.4 mmHg vs. 19.1 mmHg, *P*<0.001) and the length of stay in ICU (13 vs. 18, *P*<0.001) but was associated with more unfavorable functional outcomes.[20] Fifty-one patients (70%) who underwent DC either died, were in a vegetative state or had severe disabilities 6 months after injury, compared with only 42 patients (51%) in the standard-care group (*P*=0.02).

This study has been criticized for the bias created by allowing compassionate use of DC in the standard-care group if, after 72 h, ICP could not otherwise be controlled. The currently on-going Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intra-Cranial Pressure (RESCUEicp study) will further determine the role of DC in managing resistant ICH.[21]

### Osmotherapy: Mannitol versus hypertonic saline

Hyperosmolar therapy remains the primary medical management strategy for ICH. Till now, mannitol has been considered as the gold standard hyperosmolar agent. However, HS has become a progressively more common alternative to mannitol, with current literature proving its relative superiority.

### Patients with TBI and stroke

When used in stable patients of TBI and stroke with ICH and intact cerebral autoregulation, single equiosmolar doses of 20% mannitol and 7.45% HS were found to exhibit comparable effectiveness in reducing ICP.[22] Investigators were of the opinion that factors such as serum sodium, systemic and brain haemodynamics should be considered while choosing the most appropriate osmotic compound.

### During elective craniotomy

Equiosmolar solutions of 20% mannitol and 3% HS in patients undergoing craniotomy were found to be associated with similar brain relaxation scores

and cerebral arterio-venous oxygen and lactate difference.[23] Rozet *et al.* hence recommended HS as a safe alternative to mannitol for intraoperative brain debulking, especially in haemodynamically unstable patients. Results of recently published meta-analysis of RCT suggest HS to be comparatively effective than mannitol for the treatment of elevated ICP regardless of the concentration used, mode of administration (bolus or continuous drip) or origin of ICH.[4]

Thus, mannitol can be used as first-line agent in patients with evidence of pretreatment brain hypoperfusion, whereas HS can be recommended to treat patients with pretreatment hypovolemia or hyponatremia.

## BRAIN PROTECTION

Mild to moderate therapeutic hypothermia represents one of the most solidly evidence-based neuroprotective strategies currently available. Despite successful results in experimental studies, by far no anesthetic or non-anesthetic pharmacological agent has been convincingly shown to provide profound neuroprotection in humans.

### Hypothermia in TBI

National Acute Brain Injury Study: Hypothermia II trial (NABIS: H-II) does not confirm the utility of hypothermia as a primary neuroprotective strategy in patients with severe TBI.[24] However, subgroup analysis suggests that patients who underwent surgical removal of intracranial hematomas and had hypothermia had significantly fewer poor outcomes than patients who had normothermia ($P$=0.02), whereas in patients with diffuse injury, there was a trend toward worse outcomes with hypothermia ($P$=0.09). Hypothermia, therefore, warrants further evaluation to confirm benefit in specific TBI subgroups.

The Prophylactic Hypothermia to Lessen TBI (POLAR-RCT) trial and The Eurotherm-3235 trial are presently underway to assess the efficacy of therapeutic hypothermia in TBI. Pending their results, BTF guidelines provide level III evidence that prophylactic hypothermia is not significantly associated with decreased mortality.[16] Current recommendations are that therapeutic hypothermia should not be considered as standard of care for patients with severe TBI but may be beneficial when used by experienced clinicians within few hours after TBI for more than 48 hours (Class IIA evidence).[25]

### Hypothermia during aneurysmal subarachnoid haemorrhage surgery

After landmark IHAST trial, refuting the benefits of intraoperative hypothermia (target temperature, 33.0°C) as an effective neuroprotective modality among good-grade patients with aneurysmal subarachnoid haemorrhage (SAH),[26,27] no large study has yet been carried out for evaluating the efficacy of hypothermia in preventing postoperative neurological deficits. Based on clinical data, mild hypothermia may still have beneficial effects in patients with good-grade SAH.[28] The latest American Heart Association (AHA)/American Stroke Association (ASA) guidelines for management of aneurysmal SAH recommend induced hypothermia as a reasonable option in selected cases only [Class III, Level of Evidence (LOE)-B].[29]

### Use of intravenous inducing agents

In post-hoc analysis of IHAST data, administration of thiopental or etomidate was not found to have any clinically demonstrable effect on postoperative neurologic outcomes in patients undergoing temporary clipping.[30] According to AHA/ASA guidelines for management of aneurysmal SAH, at present there is insufficient data to recommend their routine use, apart from a few selected cases such as those with high risk of prolonged temporary clipping (Class IIb, *LOE*-C).[29]

### Primary treatment modality of aneurysmal subarachnoid haemorrhage

The International Subarachnoid Aneurysm Trial (ISAT) is the largest trial till date comparing clipping and coiling of ruptured intracranial aneurysms. Higher independent survival rate was observed in patients with small anterior circulation aneurysms of good neurological grade who underwent endovascular coiling than those undergoing neurosurgical clipping. Long-term follow up revealed an increased small risk of recurrent bleeding from coiled aneurysm compared with clipped aneurysm[31] and a greater incidence of clinically defined delayed cerebral ischemia (DCI) after neurosurgical clipping than after endovascular coiling.[32]

Results of ISAT have largely changed the management of intracranial aneurysms worldwide. Neuroanesthesiologists now face the challenge of managing critically ill aneurysmal SAH patients in the remote locations of neuroradiological suite more often. ISAT remains the most influential study in neurosurgery and, at the same time, the most controversial and criticized one for the recruitment

biases and operators' selection. In the multicentric Clarity GDC study, all patients of ruptured intracranial aneurysm underwent coiling as first-intention treatment by non-selected operators and the results were still very similar to ISAT.[33]

Current AHA/ASA guidelines recommend endovascular coiling in patients with ruptured aneurysms, which are judged technically amenable to both treatment modalities (Class I; *LOE*-B).[29]

## ANAESTHESIA FOR NEUROSURGICAL PROCEDURES

### General anaesthesia versus local anaesthesia

The General Anaesthesia versus Local Anaesthesia (GALA) for Carotid Surgery trial examined the use of general anaesthesia (GA) versus local anaesthesia (LA) in 3500 patients undergoing carotid endarterectomy (CEA) and found no significant difference between the two groups with regard to length of hospital stay, quality of life and major perioperative complications.[34] Investigators suggested that there is no reason to prefer one technique over another as routine and choice should be made on an individual basis. Similar conclusion was drawn in the Cochrane review of LA versus GA for CEA.[35] However, in a subgroup analysis of GALA study, performing CEA under LA was associated with significantly lower serum levels of neuro-biochemical marker of cerebral ischemia (S100ß; 0.06 µg/l vs. 0.087 µg/l, *P*=0.006) and better performance in neurocognitive tests.[36] Consequently, it appears that LA should be preferred over GA for better neurocognitive outcome if both techniques are feasible.

## NEURO-MONITORING

### During carotid endarterectomy

Moritz *et al*. did a comparison of transcranial Doppler (TCD), near-infrared spectroscopy (NIRS), stump pressure (SP) measurement and somatosensory evoked potentials (SSEP) in patients undergoing CEA during regional anaesthesia to determine their accuracy in detecting cerebral ischemia.[37] Although TCD, NIRS and SP measurement provided equal sensitivity and specificity, TCD monitoring was least practical of all. Authors suggested use of SP or NIRS for detection of cerebral ischemia during carotid artery surgery. However, under GA, NIRS proved better than SP measurement as indicator for shunting during CEA.[38]

### Electrophysiological monitoring during spine surgery

Multimodality intraoperative monitoring of spinal cord sensory and motor function during surgical correction of adult spinal deformity is feasible and provides useful neurophysiological data with an overall sensitivity of 100% and a specificity of 84.3%.[39] Similarly, combined neurophysiological monitoring with electromyography and SSEP recording, and the selective use of motor evoked potential was found to be helpful for predicting and possibly preventing neurological injury during cervical spine surgery.[40]

### Hyperventilation versus normoventilation during anaesthesia for supratentorial craniotomy

In the multicentric randomized crossover trial of hyperventilation and normoventilation in patients undergoing craniotomy for supratentorial brain tumors by Gelb *et al.*, intraoperative hyperventilation ($PaCO_2$ 25 vs 37 mmHg) was found to be associated with reduced ICP (12 vs 16 mmHg, *P*<0.001) and 45% reduction (*P*=0.004) in surgeon-assessed brain bulk, independent of anesthetic used. The study results thus support the use of intraoperative hyperventilation as part of the neuroanesthetic technique.[41]

### Use of nitrous oxide in anesthetic gas mixture

Controversy regarding nitrous oxide use in the general neurosurgical population exists despite its successful use for over 160 years. The initial results of Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia (ENIGMA trial) led to questioning of the routine use of nitrous oxide in adult patients undergoing major surgery.[42] Myles *et al.* showed that in 2,050 patients undergoing non-cardiac surgery, avoidance of intraoperative nitrous oxide combined with supplementary oxygen decreases the incidence of major complications [odds ratio (OR) =0.71, *P*=0.003] and severe nausea and vomiting (OR=0.40, *P*<0.001) but does not significantly affect duration of hospital stay (7.0 vs. 7.1 days, *P*=0.06). On long-term follow up, increased risk of myocardial infarction (adjusted OR=1.59, *P*=0.04) was observed in patients exposed to nitrous oxide, but not of death or stroke.[43] This trial included 295 neurosurgical patients but did not provide specific information about them.

Till date, only two investigations have evaluated the effect of nitrous oxide on outcome in humans at risk for cerebral ischemia. When analyzing the entire IHAST population, nitrous oxide use was found benign with no consistent effect on development of postoperative delayed ischemic neurologic deficit (DIND) and long-term gross neurological outcome.[44] However, in subset of patients who underwent temporary clipping

and were thus likely to experience intraoperative cerebral ischemia, nitrous oxide use was found to be associated with an increased risk of developing DIND, but again with no evidence of detriment to neurologic outcome.[45]

A recent subgroup analysis of GALA trial patients given GA provides evidence that nitrous oxide use does not increase the risk of mortality, stroke and myocardial infarction.[46] However, the trial was underpowered to detect any difference between two groups and the authors emphasize the need for conducting future trials in patients who are vulnerable to nitrous oxide, like those who are malnourished or deficient in cobalamin or folate. Thus, apart from avoiding nitrous oxide in such vulnerable patients, in presence of pneumocephalus and during acute venous air embolism, there is at present no logical rationale to avoid nitrous oxide in neurosurgical patients.

## ANESTHETIC TECHNIQUES

An ideal neuroanesthetic technique provides optimal intracranial operating conditions, maintains cerebral haemodynamics to ensure adequate cerebral perfusion, provides some amount of neuroprotection and allows rapid recovery.

In a multicentric RCT comparing emergence after sevoflurane/remifentanil anaesthesia with propofol/remifentanil anaesthesia for supratentorial craniotomy (Gas Anaesthesia versus Intravenous Anaesthesia-GAIA Trial), Lauta *et al.* found no difference in the two anesthetic techniques in terms of time to reach adequate recovery.[47] Authors suggested that patient age and anesthetic duration seem to influence anesthetic emergence more than the choice of sevoflurane over propofol.

Recently, use of desflurane and dexmedetomidine has also been evaluated in neurosurgical patients in many single centre studies. Clinical efficacy and safety profile have promoted their inclusion in current neuroanaesthesiology drug armamentarium.[48-51]

### Glycemic control of neurosurgical patients

Both hyperglycemia as well as hypoglycemia have detrimental effects on brain with or at risk of ischemia. Pooled evidence from various studies[52] and a recently conducted multicentric Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR study) in adult ICU patients suggest that tight glycemic control [blood glucose concentration (BGC) – target range 80-110 mg/dl] increases the risk of hypoglycemia as compared to conventional therapy (with BGC – 180 mg/dl or less).[53] On the other hand, hyperglycemia (mean BGC >140 mg/dl or even a single episode of BGC >200 mg/dl) is known to be associated with worsened neurological outcome.[54]

Post-hoc analysis of IHAST data has shown that intraoperative hyperglycemia was associated with long-term changes in gross neurologic function in neurosurgical patients at risk for new onset intraoperative and postoperative cerebral ischemia.[55] Authors thus advocated rigid glucose control in patients with aneurysmal SAH who undergo clipping.

In a prospective RCT of intensive insulin therapy (IIT) compared with conventional therapy (BGC target <215 mg/dl) in 483 patients undergoing elective or emergency brain surgery, IIT resulted in increased risk of iatrogenic hypoglycemia ($P$<0.0001), but also reduced the infection rate (25.7% vs. 39.3%; $P$=0.0018) and shortened the ICU stay (6 vs. 8 days; $P$=0.0001).[56] Green *et al.* found no benefit of IIT over conventional treatment on functional outcome in critically ill stroke and TBI patients.[57] Authors suggested that IIT for glucose control cannot be recommended in critically ill neurological patients.

In a recent cerebral microdialysis study, Magnoni *et al.* demonstrated that linear relationship between systemic glucose and brain glucose is preserved in patients with TBI and identical blood glucose levels translate into lower cerebral glucose availability when cerebral oxidative metabolism was disturbed.[58] Hence, brain glucose in tissues with disturbed oxidative metabolism may decrease to dangerously low levels even with systemic glucose being in the lower limit of "normal range". Authors thus propose a new concept of improved tolerance towards hyperglycemia in patients with severe TBI and strongly recommend avoiding severe glycemic reductions.

Presently, the best practice seems to adopt a moderate range of target BGC 140-180 mg/dl. AHA/ASA guidelines also recommend avoiding intraoperative hyperglycemia (Class IIa, *LOE*-B), minimizing glucose variability and aggressive management of hypoglycemia (Class IIb, *LOE*-B).[29]

## INTENSIVE CARE MANAGEMENT ON NEUROSURGICAL PATIENTS

### Management of cerebral vasospasm after aneurysmal SAH

At present, many treatment options are available for preventing and treating cerebral vasospasm following aneurysmal SAH. However, only nimodipine has shown beneficial results till now (Class I; *LOE*-A).[29] Triple-H therapy, fasudil, transluminal balloon angioplasty, thrombolytics, endothelin receptor antagonists, magnesium, statins and miscellaneous therapies such as free radical scavengers and antifibrinolytics require further evaluation.[29,59]

#### *Triple-H therapy*

Several studies have described the effectiveness of triple-H therapy for preventing neurologic deficits due to cerebral vasospasm. However, it was unclear which components of the triple-H therapy are crucial for the treatment of cerebral hypoperfusion.

Muench *et al.* first performed an experimental study in five healthy porcine models and later applied the same protocol in ten patients with aneurysmal SAH to investigate the efficacy of catecholamine-induced arterial hypertension, hypervolemia/hemodilution and hypervolemic arterial hypertension on ICP, regional cerebral blood flow (rCBF) and $PbtO_2$.[60] In animals with intact autoregulation, neither induced hypertension nor hypervolemia had an effect on ICP, $PbtO_2$ or rCBF. However, in patients with SAH, triple-H therapy failed to improve rCBF more than hypertension alone (mean arterial pressure 143±10 mmHg) and was characterized by the drawback that the hypervolemia and hemodilution component reversed the effect of induced hypertension on $PbtO_2$.

A systematic review of studies exploring the effect of different components of triple-H therapy on cerebral perfusion in patients with aneurysmal SAH also concluded that although there is no good evidence in support of triple-H therapy or its individual components on increasing CBF in SAH patients, hypertension still seems to be more effective than either hypervolemia or hemodilution.[61]

Based on clinical data, AHA/ASA guidelines recommend maintaining euvolemia and normal circulating blood volume to prevent DCI and induced hypertension for patients with DCI unless blood pressure is elevated at baseline or cardiac status precludes it (Class I, LOE-B).[29]

#### *Stellate ganglion block*

Stellate ganglion block (SGB) has an established role in treating patients with sympathetic pain syndromes like post-herpetic neuralgia. With respect to its cerebral circulatory effects, SGB has been found to decrease cerebral vascular tone and hence cause a significant increase in CPP.[62] In a preliminary study by Jain *et al.* in 15 patients who underwent aneurysmal clipping and developed refractory cerebral vasospasm, SGB was found to be an effective treatment modality with reduced ipsilateral middle cerebral artery mean flow velocity (from 133.66 cm/s to 110.53 cm/s at 6 h and 121.62 cm/s at 24 h, $P<0.001$) and improved GCS.[63] Overall, neurological deficits improved in 11 patients.[56] Authors suggested that this promising therapeutic modality needs to be evaluated further in a large RCT as a single mode of therapy by comparing its efficacy with other treatment modalities for cerebral vasospasm.

### Sedation of neurocritical care patients

Dexmedetomidine-based sedation (either alone or as an adjunct to propofol infusion) has been safely used for both intubated and extubated neurocritical care patients. However, patients may require higher doses and prolonged duration of infusions to achieve desired levels of sedation with clinically insignificant haemodynamic effects. Bolus loading may be avoided to prevent potential adverse effects.[64,65]

## CONCLUSION

In the era of rapidly evolving science, it is imperative to keep ourselves abreast of the on-going research work and improvise our practice based on evidence-based results. Recent research in TBI patients favors HS for osmotherapy but not for pre-hospital fluid resuscitation. Colloids are no more recommended and the role of multimodality monitoring, therapeutic hypothermia, TXA and DC in this patient population needs further evaluation. For patients with aneurysmal SAH, there is sound evidence to prefer endovascular coiling over aneurysmal clipping, while routine use of intraoperative hypothermia and anesthetics as clinical effective neuroprotectants is not recommended. During CEA, loco-regional anaesthesia appears favorable over GA. Intraoperative hyperventilation has been accepted as a part of neuroanesthetic technique during elective craniotomies and use of nitrous oxide is no more condemned. IIT has given way to more liberal target blood glucose levels, stressing on avoidance of hypoglycemia. Therapeutic strategies for prevention

and treatment of cerebral vasospasm need further evaluation. Role of SGB in managing resistant cerebral vasospasm appears promising in future. Lessons from the many recent failed trials have led to an improved methodology of the currently on-going clinical trials and their results are expected to bring a breakthrough in modern neuroanaesthesiology practice.

## REFERENCES


1. Chesnut RM, Marshall SB, Piek J, Blunt BA, Klauber MR, Marshall LF. Early and late systemic hypotension as a frequent and fundamental source of cerebral ischemia following severe brain injury in the Traumatic Coma Data Bank. Acta Neurochir (Wien) 1993;59:121-5.
2. Badjatia N, Carney N, Crocco TJ, Fallat ME, Hennes HM, Jagoda AS, *et al*. Brain Trauma Foundation; BTF Centre for Guidelines Management. Guidelines for prehospital management of traumatic brain injury 2nd edition. Prehosp Emerg Care 2008;12:S1-52.
3. Vassar MJ, Perry CA, Holcroft JW. Prehospital resuscitation of hypotensive trauma patients with 7.5% NaCl versus 7.5% NaCl with added dextran: A controlled trial. J Trauma 1993;34:622-32.
4. Kamel H, Navi BB, Nakagawa K, Hemphill JC 3rd, Ko NU. Hypertonic saline versus mannitol for the treatment of elevated intracranial pressure: A meta-analysis of randomized clinical trials. Crit Care Med 2011;39:554-9.
5. Bulger EM, Cuschieri J, Warner K, Maier RV. Hypertonic resuscitation modulates the inflammatory response in patients with traumatic hemorrhagic shock. Ann Surg 2007;245:635-41.
6. Baker AJ, Rhind SG, Morrison LJ, Black S, Crnko NT, Shek PN, *et al*. Resuscitation with hypertonic saline-dextran reduces serum biomarker levels and correlates with outcome in severe traumatic brain injury patients. J Neurotrauma 2009;26:1227-40.
7. Bulger EM, May S, Brasel KJ, Schreiber M, Kerby JD, Tisherman SA, *et al*. Out-of-hospital hypertonic resuscitation following severe traumatic brain injury: A randomized controlled trial. JAMA 2010;30:1455-64.
8. SAFE Study Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group; Australian Red Cross Blood Service; George Institute for International Health, Myburgh J, Cooper DJ, Finfer S, Bellomo R, Norton R, *et al*. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med 2007;357:874-84.
9. Reinhart K, Perner A, Sprung CL, Jaeschke R, Schortgen F, Johan Groeneveld AB, *et al*. European Society of Intensive Care Medicine Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. Intensive Care Med 2012;38:368-83.
10. Crystalloid versus Hydroxyethyl Starch Trial (CHEST) Management Committee. The Crystalloid versus Hydroxyethyl Starch Trial: Protocol for a multi-centre randomised controlled trial of fluid resuscitation with 6% hydroxyethyl starch (130/0.4) compared to 0.9% sodium chloride (saline) in intensive care patients on mortality. Intensive Care Med 2011;37:816-23.
11. Rosner MJ, Rosner SD, Johnson AH. Cerebral perfusion pressure: Management protocol and clinical results. J Neurosurg 1995;83:949-62.
12. Bullock R, Chesnut RM, Clifton G, Ghajar J, Marion DW, Narayan RK, *et al*. Guidelines for the management of severe head injury. Eur J Emerg Med 1996;3:109-27.
13. Eker C, Asgeirsson B, Grande PO, Schalén W, Nordström CH. Improved outcome after severe head injury with a new therapy based on principles for brain volume regulation and improved microcirculation. Crit Care Med 1998;26:1881-6.
14. Martini RP, Deem S, Yanez ND, Chesnut RM, Weiss NS, Daniel S, *et al*. Management guided by brain tissue oxygen monitoring and outcome following severe traumatic brain injury. J Neurosurg 2009;111:644-9.
15. Spiotta AM, Stiefel MF, Gracias VH, Garuffe AM, Kofke WA, Maloney-Wilensky E, *et al*. Brain tissue oxygen-directed management and outcome in patients with severe traumatic brain injury. J Neurosurg 2010;113:571-80.
16. Brain Trauma Foundation; American Association of Neurological Surgeons; Congress of Neurological Surgeons. Guidelines for the management of severe traumatic brain injury. J Neurotrauma 2007;24:S1-106.
17. CRASH-2 Collaborators, Intracranial Bleeding Study. Effect of tranexamic acid in traumatic brain injury: A nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). BMJ 2011;343:d3795.
18. Dewan Y, Komolafe EO, Mejía-Mantilla JH, Perel P, Roberts I, Shakur H. CRASH-3-tranexamic acid for the treatment of significant traumatic brain injury: Study protocol for an international randomized, double-blind, placebo-controlled trial. Trials 2012;13:87.
19. Schreckinger M, Marion DW. Contemporary management of traumatic intracranial hypertension: Is there a role for therapeutic hypothermia? Neurocrit Care 2009;11:427-36.
20. Cooper DJ, Rosenfeld JV, Murray L, Arabi YM, Davies AR, D'Urso P, *et al*. Decompressive craniectomy in diffuse traumatic brain injury. N Engl J Med 2011;36:1493-502.
21. Hutchinson PJ, Kolias AG, Timofeev I, Corteen E, Czosnyka M, Menon DK, *et al*. Update on the RESCUEicp decompressive craniectomy trial. Crit Care 2011;15:312.
22. Francony G, Fauvage B, Falcon D, Canet C, Dilou H, Lavagne P, *et al*. Equimolar doses of mannitol and hypertonic saline in the treatment of increased intracranial pressure. Crit Care Med 2008;36:795-800.
23. Rozet I, Tontisirin N, Muangman S, Vavilala MS, Souter MJ, Lee LA, *et al*. Effect of equiosmolar solutions of mannitol versus hypertonic saline on intraoperative brain relaxation and electrolyte balance. Anaesthesiology 2007;107: 697-704.
24. Clifton GL, Valadka A, Zygun D, Coffey CS, Drever P, Fourwinds S, *et al*. Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): A randomised trial. Lancet Neurol 2011;10:131-9.
25. Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. Lancet 2008;371:1955-69.
26. Todd MM, Hindman BJ, Clarke WR, Torner JC. Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) Investigators. Mild intraoperative hypothermia during surgery for intracranial aneurysm. N Engl J Med 2005; 352:135-45.
27. Samra SK, Giordani B, Caveney AF, Clarke WR, Scott PA, Anderson S, *et al*. Recovery of cognitive function after surgery for Aneurysmal subarachnoid hemorrhage. Stroke 2007;38:1864-72.
28. Li LR, You C, Chaudhary B. Intraoperative mild hypothermia for postoperative neurological deficits in intracranial aneurysm patients. Cochrane Database Syst Rev 2012;2: CD008445.
29. Connolly ES Jr, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, *et al*. Guidelines for the management of aneurysmal subarachnoid hemorrhage: A guideline for healthcare professionals from the American Heart Association American Stroke Association. Stroke 2012;43:1711-37.
30. Hindman BJ, Bayman EO, Pfisterer WK, Torner JC, Todd MM; IHAST Investigators. No association between intraoperative hypothermia or supplemental protective drug and neurologic

outcomes in patients undergoing temporary clipping during cerebral aneurysm surgery: Findings from the Intraoperative Hypothermia for Aneurysm Surgery Trial. Anaesthesiology 2010;112:86-101.
31. Molyneux AJ, Kerr RS, Birks J, Ramzi N, Yarnold J, Sneade M, *et al*. Risk of recurrent subarachnoid haemorrhage, death, or dependence and standardised mortality ratios after clipping or coiling of an intracranial aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): Long-term follow-up. Lancet Neurol 2009;8:427-33.
32. Dorhout Mees SM, Kerr RS, Rinkel GJ, Algra A, Molyneux AJ. Occurrence and impact of delayed cerebral ischemia after coiling and after clipping in the International Subarachnoid Aneurysm Trial (ISAT). J Neurol 2012;259:679-83.
33. Cognard C, Pierot L, Anxionnat R, Ricolfi F; Clarity Study Group. Results of embolization used as the first treatment choice in a consecutive nonselected population of ruptured aneurysms: Clinical results of the Clarity GDC study. Neurosurgery 2011;69:837-41.
34. GALA Trial Collaborative Group; Lewis SC, Warlow CP, Bodenham AR. General anaesthesia versus local anaesthesia for carotid surgery (GALA): A multicentre, randomised controlled trial. Lancet 2008;372:2132-42.
35. Rerkasem K, Rothwell PM. Local versus general anaesthesia for carotid endarterectomy. Cochrane Database Syst Rev 2008;CD000126.
36. Weber CF, Friedl H, Hueppe M, Hintereder G, Schmitz-Rixen T. Impact of general versus local anaesthesia on early postoperative cognitive dysfunction following carotid endarterectomy: GALA Study Subgroup Analysis. World J Surg 2009;33:1526-32.
37. Moritz S, Kasprzak P, Arlt M, Taeger K, Metz C. Accuracy of cerebral monitoring in detecting cerebral ischemia during carotid endarterectomy: A comparison of transcranial Doppler sonography, near-infrared spectroscopy, stump pressure, and somatosensory evoked potentials. Anaesthesiology 2007;107:563-9.
38. Tambakis CL, Papadopoulos G, Sergentanis TN, Lagos N, Arnaoutoglou E, Labropoulos N, *et al*. Cerebral oximetry and stump pressure as indicators for shunting during carotid endarterectomy: Comparative evaluation. Vascular 2011;19:187-94.
39. Quraishi NA, Lewis SJ, Kelleher MO, Sarjeant R, Rampersaud YR, Fehlings MG. Intraoperative multimodality monitoring in adult spinal deformity: Analysis of a prospective series of one hundred two cases with independent evaluation. Spine (Phila Pa 1976) 2009;34:1504-12.
40. Kelleher MO, Tan G, Sarjeant R, Fehlings MG. Predictive value of intraoperative neurophysiological monitoring during cervical spine surgery: A prospective analysis of 1055 consecutive patients. J Neurosurg Spine 2008; 8:215-21.
41. Gelb AW, Craen RA, Rao GS, Reddy KR, Megyesi J, Mohanty B, *et al*. Does hyperventilation improve operating condition during supratentorial craniotomy? A multicenter randomized crossover trial. Anaesth Analg 2008; 106:585-94.
42. Myles PS, Leslie K, Chan MT, Forbes A, Paech MJ, Peyton P, *et al*. Avoidance of nitrous oxide for patients undergoing major surgery: A randomized controlled trial. Anaesthesiology 2007;107:221-31.
43. Leslie K, Myles PS, Chan MT, Forbes A, Paech MJ, Peyton P, *et al*. Nitrous oxide and long-term morbidity and mortality in the ENIGMA trial. Anaesth Analg 2011;112:387-93.
44. McGregor DG, Lanier WL, Pasternak JJ, Rusy DA, Hogan K, Samra S, *et al*.; Intraoperative Hypothermia for Aneurysm Surgery Trial Investigators. Effect of nitrous oxide on neurologic and neuropsychological function after intracranial aneurysm surgery. Anaesthesiology 2008;108:568-79.
45. Pasternak JJ, McGregor DG, Lanier WL, Schroeder DR, Rusy DA, Hindman B, *et al*.; IHAST Investigators. Effect of nitrous oxide use on long-term neurologic and neuropsychological outcome in patients who received temporary proximal artery occlusion during cerebral aneurysm clipping surgery. Anaesthesiology 2009;110:563-73.
46. Sanders RD, Graham C, Lewis SC, Bodenham A, Gough MJ, Warlow C; *et al*. Nitrous oxide exposure does not seem to be associated with increased mortality, stroke, and myocardial infarction: A non-randomized subgroup analysis of the General Anaesthesia compared with Local Anaesthesia for carotid surgery (GALA) trial. Br J Anaesth 2012; 109:361-7.
47. Lauta E, Abbinante C, Del Gaudio A, Aloj F, Fanelli M, de Vivo P, *et al*. Emergence times are similar with sevoflurane and total intravenous anaesthesia: Results of a multicenter RCT of patients scheduled for elective supratentorial craniotomy. J Neurosurg Anaesthesiol 2010;22:110-8.
48. Magni G, Rosa IL, Melillo G, Savio A, Rosa G. A comparison between sevoflurane and desflurane anaesthesia in patients undergoing craniotomy for supratentorial intracranial surgery. Anaesth Analg 2009;109:567-71.
49. Bekker A, Sturaitis M, Bloom M, Moric M, Golfinos J, Parker E, *et al*. The effect of dexmedetomidine on perioperative hemodynamics in patients undergoing craniotomy. Anaesth Analg 2008;107:1340-7.
50. Souter MJ, Rozet I, Ojemann JG, Souter KJ, Holmes MD, Lee L. Dexmedetomidine sedation during awake craniotomy for seizure resection: Effects on electrocorticography. J Neurosurg Anaesthesiol 2007;19:38-44.
51. McCutcheon CA, Orme RM, Scott DA, Davies MJ, McGlade DP. A comparison of dexmedetomidine versus conventional therapy for sedation and hemodynamic control during carotid endarterectomy performed under regional anaesthesia. Anaesth Analg 2006;102:668-75.
52. Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: A meta-analysis. JAMA 2008;300:933-44.
53. NICE-SUGAR Study Investigators; Finfer S, Chittock DR, Su SY, Blair D, Foster D, *et al*. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283-97.
54. Kruyt ND, Biessels GJ, de Haan RJ, Vermeulen M, Rinkel GJ, Coert B. Hyperglycemia and clinical outcome in aneurysmal subarachnoid hemorrhage: A meta-analysis. Stroke 2009;40:e424-30.
55. Pasternak JJ, McGregor DG, Schroeder DR, Lanier WL, Shi Q, Hindman BJ, *et al*. IHAST Investigators. Hyperglycemia in patients undergoing cerebral aneurysm surgery: Its association with long-term gross neurologic and neuropsychological function. Mayo Clin Proc 2008;83:406-17.
56. Bilotta F, Caramia R, Paoloni FP, Delfini R, Rosa G. Safety and efficacy of intensive insulin therapy in neurosurgical patients. Anaesthesiology 2009;110:611-9.
57. Green DM, O'Phelan KH, Bassin SL, Chang CW, Stern TS, Asai SM. Intensive versus conventional insulin therapy in critically ill neurologic patients. Neurocrit Care 2010;13:299-306.
58. Magnoni S, Tedesco C, Carbonara M, Pluderi M, Colombo A, Stocchetti N. Relationship between systemic glucose and cerebral glucose is preserved in patients with severe traumatic brain injury, but glucose delivery to the brain may become limited when oxidative metabolism is impaired: Implications for glycemic control. Crit Care Med 2012;40:1785-91.
59. Castanares-Zapatero D, Hantson P. Pharmacological treatment of delayed cerebral ischemia and vasospasm in subarachnoid haemorrhage. Ann Intensive Care 2011;1:12.
60. Muench E, Horn P, Bauhuf C, Roth H, Philipps M, Hermann P, *et al*. Effects of hypervolemia and hypertension on regional cerebral blood flow, intracranial pressure, and brain tissue oxygenation after subarachnoid hemorrhage. Crit Care Med

2007;35:1844-51.
61. Dankbaar JW, Slooter AJ, Rinkel GJ, Schaaf IC. Effect of different components of triple-H therapy on cerebral perfusion in patients with aneurysmal subarachnoid haemorrhage: A systematic review. Crit Care 2010;14:R23.
62. Gupta MM, Bithal PK, Dash HH, Chaturvedi A, Mahajan RP. Effects of stellate ganglion block on cerebral haemodynamics as assessed by transcranial Doppler ultrasonography. Br J Anaesth 2005;95:669-73.
63. Jain V, Rath GP, Dash HH, Bithal PK, Chouhan RS, Suri A. Stellate ganglion block for treatment of cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage-A preliminary study. J Anaesthesiol Clin Pharmacol 2011;27:516-21.
64. Grof TM, Bledsoe KA. Evaluating the Use of Dexmedetomidine in Neurocritical Care Patients. Neurocrit Care 2010;12: 356-61.
65. Yokota H, Yokoyama K, Noguchi H, Nishioka T, Umegaki O. Komatsu H. Post-operative dexmedetomidine-based sedation after uneventful intracranial surgery for unruptured cerebral aneurysm: Comparison with propofol-based sedation. Neurocrit Care 2011;14:182-7.

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