Despite our improved understanding of neuroanaesthesia, there still remain many unresolved issues, which need to be discussed so as to reach a consensus, based on recent advances in the respective areas.

1. Controversies related to use of drugs in neuroanaesthesia:

Controversies regarding the provision of anaesthesia for intracranial neurosurgery remain, with no ideal technique identified\(^1\). Despite the theoretical benefits of intravenous agents, volatile agents remain popular. In a study comparing desflurane, isoflurane and sevoflurane in a porcine model of intracranial hypertension, at equipotent doses and normocapnia, cerebral blood flow (CBF) and intracranial pressure (ICP) were greatest with desflurane and least with sevoflurane\(^2\). The same authors also confirmed that sevoflurane also caused least vasodilation\(^3\). In two separate studies, isoflurane was seen to impair autoregulation, although reversible with hyperventilation, while autoregulation was virtually intact with sevoflurane 1 – 1.2 % at normocapnia\(^4,5\). Although large studies may be needed, sevoflurane appears to be the most suitable volatile agent for neuroanaesthesia practice.

Most discussions on neuroanaesthesia generally centre on the effects of drugs and therapeutic manoeuvres on cerebral metabolism (CMRO\(_2\)), cerebral blood flow (CBF) and intracranial pressure (ICP). Widely accepted anaesthetic goals in patients with intracranial pathology are to:

- Prevent a rise in ICP during induction and maintenance of anaesthesia.
- Achieve rapid and smooth induction and early and uneventful emergence from anaesthesia.
- Maintain an adequate cerebral perfusion pressure.
- Avoid interference with cerebral auto regulation.
- Have cerebral protective and anticonvulsant properties.

(a) Inhalational vs. intravenous anaesthesia: Inhalational anaesthesia with sevoflurane causes a dose dependent decrease in CMRO\(_2\) and regional cerebral blood flow. It allows a rapid control of the depth of anaesthesia and rapid recovery to facilitate early postoperative neurological examination. Carbon dioxide reactivity is preserved, as is autoregulation at normocapnia.
Propofol decreases ICP, CBF and CMRO₂ and causes least interference with autoregulation, some studies showing it to actually increase strength of autoregulation. It is increasingly being used for induction and maintenance of anaesthesia and its pharmacokinetics allows for rapid recovery and assessment. Propofol appears preferable (over all inhalational anaesthetics) in patients with raised ICP or complicated surgical access requiring maximal brain relaxation. Despite its stable cardiovascular profile etomidate has been shown to have detrimental effects on tissue oxygenation by causing a proportionally greater decrease in cerebral blood flow than metabolism and its use in neuroanaesthesia is declining. Thiopental is still commonly used for its anticonvulsant action and smooth induction characteristics and its relatively stable cardiovascular profile, helping to maintain cerebral perfusion pressure on induction. For shorter procedures however it may cause a delay in recovery and is not suitable for use in functional neurosurgery where patients are required to be responsive during and immediately after procedure.

Both inhalational and intravenous anaesthetics are neuro-protective. However, inhalational anaesthetics generally offer better protection as they reduce neuronal excitotoxicity by inhibiting the NMDA receptors as well as by activation of GABA-A receptors. On the other hand, the intravenous agents, eg; propofol, only enhance the GABA-A mediated inhibitory pathways and have no effect on NMDA receptors. Among inhalational, isoflurane offers better protection as it inhibits NMDA receptors more effectively than sevoflurane. However, sevoflurane is capable of inducing pre-conditioning in a dose dependent manner. In spite of this, some clinical studies comparing inhalational and intravenous anaesthetic regimens have failed to show any difference in outcome.⁶

Role of nitrous oxide in neurosurgery: The use of N₂O during intracranial surgery continues to be the subject of considerable controversy. Opponents of N₂O cite evidence of raised ICP, raised CBF, a rise in CMRO₂ and impaired autoregulation as valid reasons for condemning it. Although these effects seem to be largely reversed by opioids, benzodiazepines, barbiturates, propofol or an inhaled anaesthetic⁷ (Table 1), it is prudent to avoid the use of N₂O in the presence of air in the ventricles, during ventricular drainage, in situations with increased chances of venous air embolism and pneumocephalus, in patients with severely reduced intracranial compliance and in those requiring a high FiO₂.

The detrimental effects of nitrous oxide are well documented.⁸ However, most of the studies can be directly extrapolated to clinical practice where other agents influence the effects of nitrous oxide. Interesting finding in a study on 700 patients was that the drugs used for induction and maintenance of anaesthesia, were not independent risk factors for intraoperative brain swelling. ICP at the start of surgery, degree of midline shift on computed tomographic scan, and the histological diagnosis of glioblastoma or metastasis were the risk factors.⁹

(b) Use of Opioids: The effect of opioids on ICP and CBF has always been controversial. Morphine does not have any direct cerebrovascular effect. However there are reports of adverse effects of fentanyl and its congeners on ICP and cerebral perfusion pressure (CPP). Sufentanil can cause a significant increase in ICP and a mild fall in mean arterial pressure (MAP) in head injured patients. The use of remifentanil can effect minor increases in CBF but usually causes no significant change in ICP during anaesthesia. It
may however have effects on systemic haemodynamics causing a dose dependent fall in MAP and CPP. Remifentanil has been associated with significant rises in ICP during the recovery period in animal models and sudden withdrawal of remifentanil may cause agitation and hypertension. Its use therefore needs to be tempered with strategies for dealing with such complications.

2. Related to sitting position:
Despite the well-recognized risks of the sitting position, a number of reports in the literature have shown a relatively low incidence of serious complications. The main indication for the sitting or semi-sitting position is surgery for tumours in the cerebello-pontine angle and in the posterior third ventricular region, its primary advantages lying in the optimized surgical access, improved surgical field and reduced tumour vascularity leading to ease and improved quality of surgery. The main disadvantages of this position are air embolism, haemodynamic instability and profound hypotension, tension pneumocephalus and quadriplegia. The incidence of complications may be greater with poor patient selection, inadequate monitoring and an inexperienced team making occasional use of the position. It may still have its place however in dedicated neurosurgical departments using it frequently. Where planned, the preoperative evaluation should include a search for echocardiographic evidence of a patent foramen ovale. The intra-operative monitoring should include precordial Doppler and if available, trans-oesophageal echocardiography.

3. Use of mild hypothermia:
Cerebral ischemia and hypoxia can occur in a variety of perioperative circumstances and controversy surrounds the role of hypothermia in cerebral protection. While hypothermia initially showed beneficial effects in survivors of cardiac arrest and hypoxic insults, its application was not favored in years to come. There is evidence from experimental models of the benefits of hypothermia in preventing secondary neuronal injury following a primary insult. The beneficial effects of hypothermia are thought to be due to a reduction in cerebral metabolism and an increase in the neuronal tolerance to hypoxia. However as moderate and severe hypothermia can be detrimental to outcome, only mild hypothermia of 2-3°C has found acceptance. Controversy lies in the fact that although the results of studies using hypothermia are conflicting, many neuroanaesthetists often use mild to moderate hypothermia and many intensivists still prefer hypothermia for 24 hours following head injury. The well designed National Acute Brain Injury Study (NABIS) trial concluded that mild hypothermia following head injury does not reduce mortality or brain dysfunction. According to the recently completed Intra-Operative Hypothermia for Aneurysm Surgery Trial (IHAST), consisting of 1000 patients randomized to undergo aneurysm clipping, intra-operative hypothermia was not beneficial. However studies done on head injured patients with severe intracranial hypertension (ICH) have clearly demonstrated a beneficial effect and mild hypothermia has been shown to reduce mortality and improve outcome when used in the immediate management of patients with cardiac arrest. Thus only in a few specific clinical situations is hypothermia able to provide any neuronal preservation.
Mild Hypothermia (MH) is often used as one of the options in the second-tire treatments for patients with severe traumatic brain injury (TBI). But there is still a lack of clinical evidence on its benefit although many experimental studies suggest clear neuroprotective effect on neurotrauma. A thorough review of the reliable literature with recent randomized clinical trials and past clinical experiences, commonly indicate that MH reduces intracranial pressure, but this does not necessarily improve the outcome of patients with TBI. The risks associated with MH directly influence on the outcomes. At present, clinical problems to be solved will be focused on several topics: appropriate selection of patients, optimum target temperature, time period of maintenance, methods of rewarming and counter measures of complications. The mortality and morbidity rates of severe TBI have remained high and every trial on neuroprotective agents has also resulted in failure. Among many trials, MH is one of the promising options among new neuroprotective modalities and further well organized randomized clinical trials will be needed.

4. Place of hyperventilation:

Hyperventilation decreases CBF, CBV and ICP in patients with unimpaired vascular reactivity to carbon dioxide. The effect is abolished in extreme hypotension. Yet its use remains controversial as there is evidence of its potential to cause cerebral ischaemia due to vasoconstriction.

The recent Cochrane Library Report, was unable to find experimental support for a positive or negative role of hyperventilation in acutely head injured patients. It is suggested that routine hyperventilation should be avoided and PaCO₂ be maintained above 4.0kPa except in patients who are facing the danger of herniation due to a critical rise in ICP. Even in these patients, hyperventilation is instituted as a rescue measure only when all other modalities are ineffective.

5. Place of induced hypotension:

Induced hypotension for global cerebral effect is no longer in use except for occasional patients with severe intra-operative haemorrhage due to vascular tumours or other vascular procedures. In the past, controlled hypotension for a brief period was often used in the later part of the surgical dissection and at the time of permanent clip placement during aneurysm surgery. In recent years, temporary clipping of the major feeding artery has been favoured over induced hypotension. Still, controversy centres on the safety of one method over the other. While systemic hypotension has the risk of global / focal cerebral ischaemia, temporary clipping for a longer period (limit of a safe duration remains ill-defined) may also result in ischaemia. The clip may occupy considerable space in the operating field and may disturb the dissection.

However, it is no longer used routinely because it may critically impair overall cerebral perfusion, especially in presence of hypovolemia, and has been associated with adverse outcome and a higher incidence of severe cerebral vasospasm.

6. Triple- H Therapy:

Hypervolaemia, hypertension and haemodilution (triple-H therapy) is the most consistently effective regimen available to prevent and treat ischaemic neurological deficits caused by cerebral vasospasm after subarachnoid haemorrhage. However few centres use the strict original protocol and there is no prospective randomised trial to demonstrate efficacy. The
rationale behind induced hypervolaemia and hypertension is that it increases the CBF, improving cerebral perfusion in ischaemic areas of the brain that have impaired autoregulation during cerebral vasospasm. At times hypervolaemia is insufficient to raise the blood pressure to the desired level, requiring vasopressors to induce hypertension. The possible complications of this are worsening of cerebral oedema, a rise in ICP, rebleeding into an infarcted area, pulmonary oedema, hyperdynamic circulation and congestive cardiac failure. Controversial concerns about triple-H therapy are in relation to the following:

[a] When to start triple-H therapy: The therapy is most successful if instituted early when the neurological deficits are mild and before the onset of infarction. However prophylactic treatment initiated before aneurysm clipping carries significant risk of rebleeding.

[b] Fluids for hypervolaemia: Hypervolaemia is generally achieved with infusions of a combination of colloids and crystalloids. Coagulation abnormalities have been reported in patients who have received hetastarch for hypervolaemia.

[c] Optimal MAP: During triple- H therapy the MAP is titrated to a level necessary to reverse the signs and symptoms of vasospasm or to a maximum systolic pressure of 160-200 mmHg in patients whose aneurysm has been clipped. The elevated blood pressure should be maintained until the vasospasm resolves, usually within 3-7 days.

[d] Haemodilution and oxygen carrying capacity: As the haematocrit and viscosity decrease, the cerebrovascular resistance also decreases and CBF increases. However, there is a concern of reduced oxygen carrying capacity following haemodilution. Experimental studies and clinical experience suggest that a haematocrit of 30-33% is optimal.

7. Perioperative fluids & related issues:

(a) Crystalloids vs. colloids in brain injured patients: Isotonic crystalloids, hypertonic crystalloids (hypertonic saline) and colloids are the preferred fluids for head injured patients. A comparative description of these three fluids is given below in Table 2.

It is recognized that in brain areas with an intact blood brain barrier (BBB), osmotic pressure is the primary determinant of movement of water across capillary membranes into or out of the brain. Areas with total disruption of the BBB become indifferent to the osmotic pressure gradient. In these areas water movement into the brain becomes a function of the hydrostatic pressure gradient between the capillaries and the brain. Controversy arises in the role of the osmotic pressure gradient in brain areas with partial disruption of the BBB. In these patients, it is safer to infuse fluids that will increase the plasma osmotic (and oncotic) pressure than hypotonic crystalloids. Although no single intravenous solution is best suited for the neurosurgical patient who is at risk for intracranial hypertension, the use of isoosmolar crystalloids is widely accepted and can be justified on scientific basis.16

(b) Hypertonic saline, mannitol and steroids: In recent years hypertonic saline (HS) has been under investigation for its potential to decrease cerebral oedema and ICP and improve regional CBF. The other benefits claimed are faster expansion of intravascular volume (with small volumes), increased cardiac output and pulmonary gas exchange,
reversal of immuno-modulation caused by hypotension, and decreased CSF production. The acute beneficial effect of HS is well established, with reports of improved survival of brain injured hypotensive patients after resuscitation with HS. Most studies in patients with head injury or brain tumours have reported a reduction in ICP and some even a reduction in lateral displacement of the brain after using HS, yet these benefits are not seen in patients with other conditions, e.g., vasospasm after SAH. On the other hand other studies claim that the HS is no more effective than normal saline, even in head injured patients. HS therapy is also associated with adverse effects e.g., sudden hypotension, hypernatraemia, altered consciousness and seizures. The overall results of HS related studies are inconsistent and further clinical trials are needed to define its role.

Although controversy still exists, mannitol is commonly believed to be a useful osmotic diuretic, which reduces the ICP effectively and improves cerebral perfusion and surgical access in patients with intracranial hypertension. Mannitol can reduce blood viscosity and hematocrit in higher doses (2g kg\(^{-1}\)) and can cause a rebound rise in ICP. The usual required dose is approximately 0.50 – 1.0 g kg\(^{-1}\) infused over 15-30 minutes. Many studies have compared the effect of 20% mannitol with hypertonic saline in neurosurgical patients with variable results.

Steroids are very effective in reducing ICP in cerebral tumours and infective intracranial lesions. Trials on the early use of high dose methylprednisolone in traumatic spinal cord injury have demonstrated significant benefits, though the efficacy has been questioned particularly in patients with penetrating trauma of the cord. Most studies examining the role of steroids in head injury have shown no substantial benefit with respect to clinical outcome and / or decreasing ICP. The Brain Trauma Foundation does not recommend the use of steroids for improving outcome or reducing ICP in patients with severe head injury. However, a meta-analysis of 13 trials indicated a marginal pooled risk reduction of 1.8% in patients who received steroids. This prompted a multicentre controlled study- the CRASH (Corticosteroid Randomization after Severe Head Injury) study on the role of methyl prednisolone in acute head injury. Though this international trial was designed to recruit 20,000 patients, it had to be stopped after only studying a total of 10,008 patients until May 2004, as the data monitoring committee found an increased risk of early death in the steroid group.

8. Glycemic control in neuro-intensive care:
As strict control of blood glucose level by intensive insulin therapy has been found to be associated with better outcome in all critically ill patients including surgical patients, it applies equally to neurosurgical and neurotrauma patients as well. However, in a recent large international randomized trial on 6104 general ICU patients, the investigators reported lesser mortality in conventional glucose control (≤180 mg % with mean of 144 mg%) group than those in the intensive control (80-110 mg %) group, mostly due to higher incidence of hypoglycaemic episodes. But, we need to exercise caution in extrapolating this into neurointensive, especially, neurosurgical and head injury patients as they behave mostly like surgical ICU patients. Moreover, as the adverse metabolic and cerebral ischaemic effects of high blood glucose levels are very well documented, it appears obvious that blood glucose should be vigorously checked and maintained at 5-6.5mmol l\(^{-1}\) (90-120 mg %), especially, in those who are at the risk of tissue and / or brain hypoxia. On the other hand, all efforts must be made to avoid episodes of hypoglycaemia as well.
A consensus statement of the American Association of Clinical Endocrinologists and the American Diabetes Association has recommended a revision of the glucose targets. In critically ill patients, starting active treatment is recommended at a threshold of >180 mg/dl (>10.0 mmol/l), preferably with IV insulin therapy, and maintain the glucose level between 140 and 180 mg/dl (7.8 and 10.0 mmol/l). Greater benefit may be obtained at the lower end of this range. Glucose concentrations <110 mg/dl (<6 mmol/l) are not recommended. However, these goals should be flexible and individualized to the particular patient and the clinical circumstances. Persistently elevated readings indicate that the treatment regimen must be adjusted or changed and should alert the treating physician of the need to explore the possible reasons for hyperglycemia.

9. Non-anaesthetic drugs and brain protection:

Among many non-anaesthetic drugs investigated for their cerebro-protective property, three deserve specific mention.

(a)**Nimodipine**- is widely used for the prophylactic treatment of cerebral vasospasm. It is reported to improve outcome without changing mortality in non-traumatic subarachnoid haemorrhage (SAH) patients. In contrast, it fails to improve outcome in stroke patients.

(b)**Magnesium**- has shown neuroprotective effects in animals with traumatic and ischaemic injuries when given within 24 hrs of injury. Work is being done on its use in head injury and subarachnoid haemorrhage although there is no evidence as yet for its efficacy. It is ineffective as a neuroprotectant in stroke.

(c)**Remacemide**- a NMDA receptor antagonist that is reported to improve some neuropsychological tests after cardiac surgery.

Many other drugs have been tried mostly in animals. Some, such as dexmedetomidine, dexamabinol and tirilazad mesylate have already received FDA approval for clinical use, some others such as substance P antagonists are in various stages of human trials. Most of these are NMDA receptor antagonists and antioxidants.

10. Other Controversial Issues:

(a)**Pain management**: It has traditionally been thought that patients experience only minimal postoperative pain after craniotomy but a number of studies have disproved this, making the issue of pain management and opiate use in neurosurgical patients a continual topic of debate.

(b)**Monitoring**: Less invasive monitoring strategies have recently gained some acceptance in neurosurgical practice. It has been shown that because of hazards and complication of invasive monitoring, non-invasive monitors that are equally sensitive, safe and easy to learn are preferred.

(c)**Carotid endarterectomy**: Another debate is on the superiority of regional anaesthesia or general anaesthesia in the management of CEA. An awake patient is the best monitor for CEA. There are reports of reduction in intraoperative shunting and perioperative stroke and the duration of hospital stay after regional anaesthesia than general anaesthesia for CEA. Local anaesthesia also offers clinical and cost advantages over general anaesthesia. However, an uncooperative patient may require general anaesthesia, which requires optimal cerebral monitoring.
(d) **Are new tools needed?** Currently available newer monitoring tools are cost-intensive and not yet fully accepted as the standard of care. These include bispectral index (BIS) monitoring and evoked potentials (EPs). There is an increasing trend to do more minimally invasive procedures in place of traditional craniotomies to minimize surgical trauma, and to do “awake” procedures, particularly for functional neurosurgery. Many of these procedures are done under monitored anaesthesia care (MAC) with patients remaining awake or under minimal sedation. In addition techniques such as transcranial Doppler ultrasonography, jugular bulb oximetry, near infra red spectroscopy and laser Doppler flowmetry have been introduced as tools to monitor cerebral blood flow and oxygenation. Transcranial Doppler in particular is useful in the critical care setting to determine whether autoregulation is intact and therefore whether a cerebral perfusion pressure-driven protocol is appropriate. These tools have their limitations in clinical practice but have been instrumental in improving our understanding of cerebral pathophysiology and in challenging some of the older concepts of care.

(e) **Awareness during Anaesthesia:** Knowledge of cerebral electrophysiology has prompted the development of monitors of depth of anaesthesia such as bispectral index (BIS) and spectral entropy. Though questions have been raised on the consistency of their performance, and a recent study found no difference between BIS and end tidal anaesthetic agent concentration monitoring in preventing awareness during anaesthesia, for the moment, they have brought in some measure of objectivity in the quantification of the depth of hypnosis.

(f) **Anaesthetics, Neurogenesis and Neurological Dysfunction:** Anaesthetics have a potential to cause neurological dysfunction, which may take the form of postoperative neurocognitive dysfunction in the elderly, learning disabilities of the neonates exposed to anaesthetics in utero or early after birth, and precipitation or exacerbation of Alzheimer's in susceptible individuals. Majority of this information comes from rodent experiments, the clinical relevance of which remains largely unexplored. There are a few clinical publications which are either retrospective analyses or case-control studies. The drugs that have been predominantly implicated in the causation of neurological dysfunction are bezodiazepines and ketamine, though evidence exists with other agents also including barbiturates, propofol, halothane, isoflurane, and sevoflurane.

The mechanism of anaesthetic-induced neurotoxicity remains unexplained. During normal CNS development, neurons are produced in excess and as much as 50%–70% of these neurons and progenitor cells undergo apoptosis. General anaesthetics seem to inhibit the synaptic transmission mediated through gamma aminobutyrate (GABA) and/or N-methylaspartate (NMDA) receptors. Because GABA-and NMDA-mediated neuronal activity is essential for mammalian brain development, exposure to general anaesthetics could potentially interfere with normal brain maturation.

(g) **Anticoagulation in a head-injured patient:** Head injury occurring in patients already receiving anticoagulants is known to have added hazards. In a retrospective study the case fatality was 50% compared with 20% in a group not receiving anticoagulants. The question of thromboembolism prophylaxis in neurosurgical patients is difficult: these patients are commonly immobile for long periods and are prone to deep vein thrombosis, yet haemorrhage into the operation site is more dangerous than in other forms of surgery.
where heparin prophylaxis is advocated. Constantini et al.,\textsuperscript{34} reported no excess risk from perioperative low-molecular-weight heparin, in a randomized comparison with 0.9% saline, in patients having brain surgery. However, these studies were conducted on elective neurosurgery. In emergency work, Norwood and colleagues\textsuperscript{35} gave enoxaparin, 30 mg 12-hourly, to 177 patients admitted with blunt injury and with documented intracranial haemorrhage. Progression of intracranial haemorrhage, on CT, was seen in 4% and the authors concluded that enoxaparin could be used for prophylaxis if started 24 hours or more after the acute admission.

Controversy will always exist around what represents best practice in any field of anaesthesia. With continued advances in our understanding assisted by large scale controlled studies and using newer techniques of monitoring it is hoped, we will come to rely more on evidence rather than tradition in neuroanaesthetic management.

References:


Table–1: Cerebral effects of N₂O alone or N₂O with commonly used anaesthetics.

<table>
<thead>
<tr>
<th></th>
<th>N₂O alone</th>
<th>N₂O with isoflurane</th>
<th>N₂O with propofol</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP</td>
<td>↑</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>CBF</td>
<td>↑</td>
<td>Variable</td>
<td>No effect</td>
</tr>
<tr>
<td>CMRO₂</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Auto-regulation</td>
<td>Impaired</td>
<td>Variable</td>
<td>No effect</td>
</tr>
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</table>

Table – 2: A comparative description of fluids used in head injured patients

<table>
<thead>
<tr>
<th>Property</th>
<th>Isotonic saline</th>
<th>Hypertonic saline</th>
<th>Colloids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume required</td>
<td>3 times the suspected blood loss</td>
<td>Smaller volume</td>
<td>Equal to suspected blood loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 2ml/kg body wt.</td>
<td></td>
</tr>
<tr>
<td>Haemodynamic effects</td>
<td>Satisfactory but slower response</td>
<td>Very prompt rise in cardiac output, MAP and tissue perfusion</td>
<td>Satisfaction and faster than crystalloids</td>
</tr>
<tr>
<td>- Duration of effects</td>
<td>- Short lived</td>
<td>- Short lived unless combined with colloid</td>
<td>- Longer duration</td>
</tr>
<tr>
<td>Hypersensitivity response</td>
<td>Nil</td>
<td>Nil</td>
<td>±</td>
</tr>
<tr>
<td>Grouping &amp; cross matching</td>
<td>No effect</td>
<td>No effect</td>
<td>May interfere</td>
</tr>
<tr>
<td>Inflammatory response to trauma</td>
<td>No change</td>
<td>May cause inhibition</td>
<td>No change</td>
</tr>
<tr>
<td>Effect on MAP &amp; CPP</td>
<td>May ↑ MAP &amp; CPP</td>
<td>↑ MAP &amp; improves CPP</td>
<td>↑ MAP &amp; may improve CPP</td>
</tr>
<tr>
<td>Effect on ICP</td>
<td>Variable</td>
<td>↓↓</td>
<td>↓</td>
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</tbody>
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