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Review Article

Current Therapy for Severe Head Injury : Controversy and Limitation

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Head injury is a worldwide leading cause of morbidity and mortality particularly among people who are under the age of 45.[1,2] Care of these patients consumes considerable resources and the expense is very high. Acute hospitalization that costs annually at least $40 billion in the United States is only a small fraction of the total expenditure and does not include rehabilitation and loss of productivity.[3]

Advances in our understanding of the neurophysiology of brain injury along with advances in neuroradiology in the past two decades have shown that prompt and intensive management leads to a significant improvement in outcome.[4-6] One of the major reasons for the increase number of patients making a good recovery has been the early recognition and more aggressive treatment of disorders that can lead to secondary brain injury.

However, the management of head injury has some limitation and in some aspects are subject to debate. In this article, the author would like to emphasize some managements which are important in hospital care of severe head-injury (SHI) patients.

Position of the Head

Head-of-bed elevation has been traditionally recommended in treating intracranial hypertension.[7-9] Nevertheless, several investigators have questioned its benefit. Durward et al found that 15 or 30 degrees of head elevation significantly reduced intracranial pressure (ICP) while maintaining cerebral perfusion pressure (CPP) and cardiac output but further elevation to 60 degree caused an increase in ICP and a significant decrease in CPP and cardiac output.[10] Rosner et al suggested that CPP is maximum when patients are in the horizontal position although this results in an increase intracranial pressure.[11] Felement et al indicated that head elevation to 30 degrees significantly reduced ICP without reducing CPP, cerebral blood flow (CBF), cerebral metabolic rate of oxygen $(CMRO)_2$ and cerebrovascular resistance (CVR).[12]

Recently, Schneider GH et al found no significant change in CPP and jugular bulb venous oxygen saturation (SjO_2) associated with head elevation of 15, 30 and 45 degrees. At 30 degrees, 92 per cent of reducible effect on ICP was also detected.[13]

Therefore, patient's head should be kept in a neutral plane with the body and maintained in an elevated position of 30 degrees. Turning the head sharply to the right or the left should be avoided due to kinking of jugular vein and raised consequently ICP.[14] However, patients in shock or those with an accompanying spinal cord injury should be managed in horizontal position.

Mechanism supporting ICP reduction by head of bed elevation are:

- Central venous pressure and jugular venous pressure markedly decline with head elevation which leads to a reduction in cerebral blood volume (CBV).
- Cerebrospinal fluid (CSF) was displaced into the spinal subarachnoid space.
- Reduce intraabdominal pressure on intrathoracic space thus ventilation was easier in head of bed elevation.

Ventilation

Controlled hyperventilation to obtain a $PaCO_2$ of 20-30 mmHg during the first few days after severe head injury is advocated in many papers on traumatic coma[8,15-18] The beneficial effects of prolonged hyperventilation are as follows.[19]

1. Decrease in ICP hypertension.
2. Respiratory alkalosis, neutralizing metabolic acidosis in extracellular tissue.
3. Normalization of regional cerebral blood flow pattern.
4. Normalization of cerebral autoregulation.
5. Inverse steal phenomenon.
6. Reduces energy consuming and exhausting respiratory work.
7. Reduction of CSF formation.

However, arguments have be made as follows.[19]

1. May causes cerebral oligemia in focal regions and watershed areas by its vasoconstrictive effect.
2. Decrease in diastolic filling and cardiac output.
3. Decrease in mean arterial blood pressure (MABP) and CPP.
4. Increase in central venous pressure (CVP) and cerebral venous pressure.
5. Water and salt retention by effects of 3,4 which induces a decreas in renal function.
6. Inhibition of oxygen delivery to tissues (Bohr effect).
7. The effect on CBF, CBV and ICP is of short duration.

In retrospective study, Gordon and Rossanda observed a reduction in mortality rate from 32.1 to 9.2 per cent in 51 patients by hyperventilation. However, hyperventilation treatment did not increase the patient with good outcome.[20] Nevertheless, in a randomized study on the effect of artificial hyperventilation in stroke patient have been discouraging without beneficial effect in recovery or outcome being demonstrable.[21]

Strong argument came recently by the randomized clinical trial study of Muizelaar et al from which concluded that prophylactic hyperventilation is deleterious in severely head-injured patients with motor scores of 4-5.[22]

However, due to its rapid effect of cerebral vasoconstriction and ICP reduction, acute hyperventilation can be life-saving procedure in patients with an expanding cerebral lesion and may also be a helpful tool in the management of acute increased ICP but the effect has a limited duration and should be used with caution.[19,23,24] In experimental study, CBF and ICP trend to return to baseline levels 6 hrs. or more after hyperventilation[24] Early hyperventilation in ICU may be harmful because in the first 6 hrs. after injury, high proportion of patients show cerebral ischemia by CBF and $AVDO_2$ measurement.[25] Meixensberger et al in the studies of tissue PO_2 in human brain cortex, stated that hyperventilation is capable of decreasing oxygen pressure to very low levels in the pathological group, indicating a risk for inducing ischemia.[26] Thus, hyperventilation should be intermittently used before causes of increased intracranial pressure (IICP) are established or in case of cerebral hyperemia ($LO1 < 0.08$ and $AVDO_2 < 4$ ml/dl). Prophylactic hyperventilation is not recommended.[27] In addition, the practice of rapid "bagging" in re-

sponse to IICP should be avoid due to profound hyperventilation. Manual preoxygenation in anticipation of endotrachial suction should be performed judiciously, not to cause deep hypocapnia.

Anticonvulsants

Seizures occur in 28 per cent of patients who undergo removal of an intracranial haematoma and are more common before surgery than after.[28] Seizures can increase cerebral blood flow which may precipitate a rise in intracranial pressure even in a pharmacologically paralyzed and mechanically ventilated patient.[29] If seizure activity is prolonged or cerebral blood flow is reduced from impaired autoregulation or elected intracranial hypertension, blood supply may not met the metabolic demands and ischemic neural injury can result.[30]

To prevent this, all SHI patients should receive antiseizure medication prophylactically in the form of phenytoin 20 mg per kg intravenously, as a loading dose as early as possible. Injection rate must not more than 50 mg/minute while monitoring the electrocardiogram and blood pressure. The maintenance dose should be 300 mg per day in adult.[15] Blood level should be maintained between 15 to 25 μg/ml.[31] The entire requirement may be taken as a single daily dose. The drugs should be tapered off gradually after one week of trauma.[32]

In case of high risk (early seizure, presence of intracranial hematoma and depressed fracture) the drugs should be continued for many months. There are no hard and fast rules for when to stop anticonvulsants.[28]

Fluid Restriction

There is no controlled studies to demonstrate the benefit of fluid restriction in the management of ICP and cerebral edema.[33,34] Some study suggested that hypovolemia may potentiate cerebral ischemia.[35] Fluid overload may also increase cerebral edema. From this limitation, fluid therapy in SHI patients should be managed precisely in order to avoid hypotonicity and to maintain adequate cardiovascular function. In patients with an isolated head injury, volume therapy guided by intake and output measurements will usually suffice. In case of multiple injury or high doses barbiturate treatment, central venous catheter pressure is essential. Routine application of pulmonary artery catheter is not recommended due to its limited benefit in SHI.[8]

Maintenance fluid should be isotonic solution. In need of achieving adequate vascular expansion without excessive increase in total body water, concentrated albumin or synthetic colloid is recommended.[9,36] In the study of cerebral ischemia, brain edema should not be aggravated if colloid agents are used as a volume expander.[37]

Hemodilution improves the rheology of blood by decreasing its viscosity, decreased cerebral vascular resistance and increased CBF.[38] Oxygen delivery increases until a hematocrit of about 33 per cent is reached.[39] Keep hematocrit at 30 to 35 per cent is one of the protocol in SHI treatment.[36, 40]

In treatment of cerebral ischemia, keeping hematocrit at 30 per cent by removing blood via venesection is not associated with reduced tissue oxygen or glucose utilization or with cerebrovascular complication.[41] Cerebral venous pressure was maintained between 8-12 cmH_2O or pulmonary wedge pressure below 20 mmHg. Fluid management in SHI should also maintain a pulmonary artery wedge pressure of 10-15 mmHg.[22]

Mannitol

Intravenous mannitol has been employed in the reduction of ICP for nearly 30 years. After bolus dose, mannitol initially augments intravascular volume, resulting in a transient increase in blood volume and systolic arterial blood pressure which decrease blood viscosity and improves CPP respectively.[12,43] When autoregulation is intact, hemodilution after mannitol infusion is thought to improve oxygen transport to the brain leading to vasoconstriction. Increase flow by decreased blood viscosity is balanced by vasoconstriction. CBF thus, remains unchanged but cerebral blood volume (CBV) is decreased, enhancing the osmotic dehydrating effect in ICP reduction. In cases of abolished autoregulation, CBF is increased and the decrease in ICP is much smaller,[42,44] but transient increase in ICP is not found even when administra-

tion of mannitol to patient with intracranial hypertension.[45]

It is suggested that withdrawal of water from the brain across the osmotic gradient may be greatest in normal brain.[15] But in vivo study using magnetic resonance imaging showed that water withdrawal is maximal in areas where blood-brain barrier is abnormal.[46]

The response to mannitol is rapid, ICP will be reduced after 2-5 min of fast infusion, peaking of reducing ICP is approximately 30-60 minutes and the effects last 4-6 hours.[15,47] A dose of 0.25-0.5 gm per kg is often effective and can be administered every 1-2 hours if need.[5] Smaller doses of mannitol also results in fewer side effects e.g. hypotension, electrolyte disturbance.[48]

When repeated doses of mannitol are required, it is important to ensure that baseline serum osmolality is not allowed to rise above 320 mOsm/L.[15] Above this point, ICP-reducing effect of mannitol will not obtained. Further administration of mannitol at this stage may precipitate systemic acidosis and renal failure.[49] Continuous infusions of mannitol are not recommended as they negate the immediate hemodynamic benefit of mannitol as described above and may lead to equilibration of mannitol across blood-brain barrier.

High-dose Barbiturate Therapy of Elevated Intracranial Pressure

Barbiturate induces metabolic depression, cerebral vasoconstriction and reduced blood volume, and hence reduces ICP.[8,50,51] Reduction of the $CMRO_2$ theoretically reduces the demand for basic substrates such as oxygen and glucose, thereby raising the ischemic threshold.[8] Despite dramatic theory, clinical utility in SHI has been a topic of recent debate due to its conflicting results.[50-53] Its seems that role of barbiturates in helping control increased ICP but the outcome of patients is still controversial. Prophylactic barbiturate therapy does not appear to be effective in SHI.[54] Most problems come from systemic hypotension and cardiac output reduction effects of barbiturate. In the presence of preexisting hypovolemia, systemic hypotension may be profound and may themselves impair CBF and brain function. Therefore, beneficial effects might be counter-balanced by the side-effects of therapy.[51] Inadequate doses of barbiturate or adequate doses for a short period is another explanation for the failure of therapy.[55]

Table 1 Dosage and Blood Level of Pentobarbital and Thiopentone.

	Pentobarbital	Thiopentone
Bolus dose	5-10 mg/kg	5 mg/kg very slow infusion
Maintenance dose	1-3 mg/kg/hr	50-200 mg/hr.
Maximum blood level	5 mg%	18 mg%
Therapeutic blood level	3-5 mg%	2-18 mg% (average 8 mg%)

Because of its risk, barbiturate therapy should be, therefore, employed only when all other methods have failed. Arterial pressure, ICP and central venous pressure monitoring are mandatory. Two barbiturates, pentobarbital and thiopentone, are used clinically as described in Table 1.[5,55-58]

Barbiturate can be administered in the form of intermittent boluses or as a continuous infusion. Clinically, reduction of the ICP below 20 is the end point. Care must be taken not to reduce the CPP below 70 mmHg. Blood level of barbiturate should be checked at least once a day. If ICP has remained below end-point for 48 hours, the dose may be tapered gradually. Abrupt discontinuation may result in acute deterioration 8 to 10 hours later.[59] A continuous infusion can be reduced by 25 per cent each day. Recurrent IICP may require reinstitution of barbiturate.

Sedation in SHI

Pain and nociceptive stimuli such as endotracheal tube suction or chest physiotherapy may induce increased ICP in SHI patients. Hypnotic, opiates and muscular relaxant are usually administered by the intensive care protocol of SHI management to provide good mechanical ventilation and avoiding fighting against ventilator and concomitant IICP.[52] Pavulon is the most widely used as muscle relaxant. Benzodiazepine have been generally used for sedation. Midazolam is now claimed to be widely

used agent in ICU.[52] It has limited systemic side effects and the duration of action is shorter than that of diazepam, allowing for a reasonable recovery time following prolonged infusion. Abrupt reversal from benzodiazepine sedation in SHI should be avoid due to induction of increased ICP. However, bolus doses of midazolam (0.15 mg/kg) should be given with great caution in patents with severe head injury, especially when control ICP is less than 18 mmHg. Because an increase in ICP was observed in this group of patients.[60]

Treatment of Cerebral Ischemia

Cerebral ischemia refers to the inadequate delivery of oxygen to the brain whether due to decreased arterial oxygen content, decreased cerebral blood flow (CBF), increased metabolic requirements or impaired tissue uptake.[61] It has long been recognized as a potential cause of secondary injury after brain trauma. Despite substantial improvement in modern trauma care, ischemic brain damage is still common in fatal non-missile head injury.[62] Cardiac arrest, respiratory abnormalities, epilepsy, reduced regional or global CBF, hypoxemia or vasospasm are the most frequent causative factors producing cerebral ischemia. Montoring of cerebral ischemia will be useful in improving patient management and outcome.

The cerebral arterio-venous oxygen content difference ($AVDO_2$) has been introduced in clinical practice as an estimation of CBF to cerebral metabolic rate of oxygen ($CMRO_2$) coupling ($CMRO_2 = AVDO_2 \times CBF$). $AVDO_2$ was calculated by multiplying the difference between arterial oxygen saturation (SaO_2) and jugular bulb venous oxygen saturation (SjO_2) by daily hemoglobin concentration and 1.34, divided by 100. Global cerebral hyperemia and ischemia were defined as $AVDO_2$ level of less than 4 ml/dl, ($SjO_2 > 75\%$) and more than 9 ml/dl ($SjO_2 < 40\%$), respectively.[63] However $AVDO_2$ can be misleading in the presence of ischemia. Many factors can influence cerebral $AVDO_2$.[64] Nevertheless, the correlation between CBF and $AVDO_2$ in severe head injury is generally poor. Alternative approach was suggested by Robertson et al in their study, $AVDO_2$ and arteriovenous difference of lactate content (AVDL) was studied together with global CBF measurement and the lactate-oxygen index ($LOI = AVDL/AVDO_2$) was calculated. Patients with an ischemia/infarction pattern typically had $LOI > 0.08$. In non-ischemic patients, defined as $LOI < 0.08$, could be defined as having hyperemia with $AVDO_2 < 1.3$ μmol/ml and compensated hypoperfusion with $AVDO_2 > 3.0$ μmol/ml. Patients who were in barbiturate coma were not included in Robertson's study due to the marked effect of barbiturate on cerebral metabolism.[65]

Hypertensive, hypervolemia and hemodilution therapy has been used to treat ischemic complication of vasospasm in subarachnoid hemorrhage patients with promising result.[66] Many authors have felt that abnormality of autoregulation was prominent in SHI and induction of systemic hypertension will potentiate brain edema and further raise ICP. However, some studies suggested that low blood pressure or CPP would trigger cerebral vasodilatation and lead to IICP. Consequently, induced arterial hypertension has been proposed in the treatment of uncontrollable intracranial hypertension or in the protocol to maintain above CPP threshold.[36,67] Global cerebral ischemia was also improved by raising CPP from the threshold CPP.[25] The tolerance of intracranial mass lesion was better in the presence of adequate

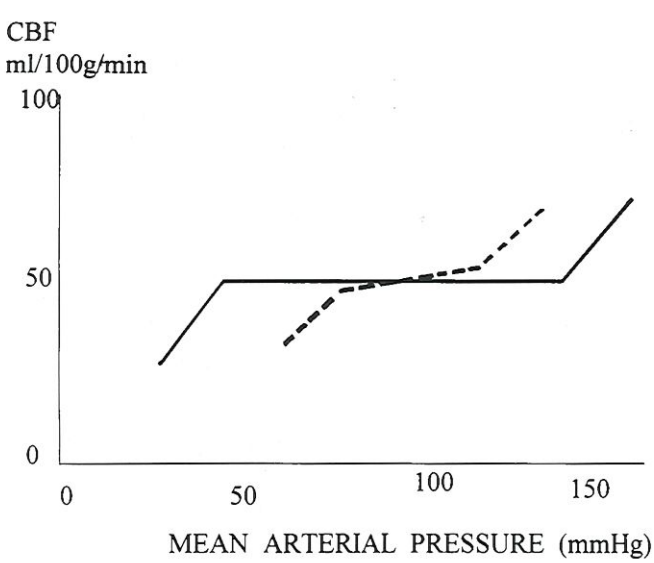

Fig. 1 Solid line shows normal cerebral autoregulation. In acute head injury, the autoregulatory curve may be altered as illustrated by the dotted line.

CPP.[68]

In patients with SHI, autoregulation curve way be altered. The lower limit of autoregulation may be shifted upward and the upper limit may be shifted downward (Figure 1).[69] Arterial hypertension, therefore, should be adequate to sustain tissue viability but not sufficiently high to aggravate hyperemia and intracranial hypertension. We extrapolates from Figure 1 that induced hypertension should not exceed 110 mmHg of mean ABP in case of IICP or evidence of having ischemia by LOI or SjO_2. Muizelaar reported a case in which the CBF was improved from 15ml/100g/min to 30 ml/100g/min by raising CPP up to 104 mmHg. In this case, close observation is needed by using multimodality monitoring system including CBF study.[25]

Recent study was emphasized on jugular venous oxygen saturation as a measure of cerebral oxygenation either by intermittent or continuous monitoring.[70-73] Normal value was reported in between 54 and 75 per cent.[74] In the absence of anemia or a sudden increase in FIO_2, increase in SjO_2 over 75 per cent (global cerebral oxygen extraction ratio, OER = SaO_2 - SjO_2/ SaO_2, below or equal 22%) suggests luxury perfusion (although areas of regional ischemia or infarction may be present) and reduction of SjO_2 below 54 per cent (OER > 43%) indicates relative hypoperfusion while below 40 per cent (OER > 57%) global cerebral ischemia is likely and will be associated with an increased of LOI.[70] Some defined a SjO_2 between 50 and 55 per cent as critical, below 50 per cent as pathological (insufficiency of cerebral oxygenation).[71,72] A poor outcome was strongly associated with the occurrence of jugular venous desaturation (SjO_2 < 50%).[73]

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