Invited Comment

Intracranial hypertension in acute liver failure

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Introduction

The development of liver failure is a medical emergency requiring specialist assessment and care. The development of renal failure in the patient with hepatic failure is one of the few prognostic indicators of poor outcome. Its presence is associated with prolonged intensive care unit (ICU) stay, prolonged hospitalization and death [1,2]. The high incidence of renal failure with necessity for dialysis support requires the nephrologist to have an understanding of liver failure and its concomitant complications. Indeed the nephrologist may be called upon outside of a liver centre to provide advice and may be in a position to guide subsequent management and referral to an appropriate centre or within that centre may be asked to assist with investigation and management. An understanding of the causes and treatments of intracranial hypertension will better arm the nephrologist in the management of this syndrome.

Encephalopathy and intracranial hypertension: not the same thing

Encephalopathy is characterized by decreased consciousness level and is associated with the development of increased cerebral oedema, raised intracranial pressure (ICP) and reduced cerebral perfusion pressure (CPP) and its severity is graded (Table 1). Encephalopathy can arise without a rise in ICP, with a gradual rise, or with acute ‘surges’ in pressure. The more acute the encephalopathy then the more likely is a rise in ICP (hyperacute liver failure ~ 70%, subacute < 4%). The causes of swings or surges in intracranial pressure are multifactorial and most often relate to decreases in systemic blood pressure, hypovolaemia, increments in systemic vascular resistance and hypoxia.

Hepatic syndromes: the relationship with renal failure and intracranial hypertension

Approximately 30–75% of patients with fulminant hepatic failure (FHF) or subacute hepatic failure (encephalopathy within 8 weeks from development of jaundice) develop renal failure with a higher incidence following paracetamol poisoning [3]. Late onset hepatic failure (LOHF) (encephalopathy from 8 weeks to 6 months) carries a lower risk of renal failure but this increases with the duration of the hepatic failure. The development of renal failure can adversely affect the management of raised intracranial pressure. A suggested redefinition of the hepatic syndromes [4] improved the link between the defined syndrome and prognosis; hyperacute liver failure (encephalopathy within 7 days), acute liver failure (8–28 days) and subacute liver failure (5–12 weeks).

Aetiology of intracranial hypertension

Hyperammonaemic states are associated with cerebellar herniation (liver failure, Reye’s syndrome and idiopathic hyperammonaemia) [5]. Ammonia is detoxified to glutamine in the astrocyte and accumulation of astrocyte glutamine (known to occur in acute liver failure) is associated with increased intracellular osmolality and cerebral oedema. Inhibition of glutamine synthetase may prevent the development of cerebral oedema. Accumulation of aspartate is also associated with encephalopathy and N-methyl-D-aspartate (NMDA) antagonists are effective in reducing glutamine levels. A non-competitive NMDA receptor antagonist improved encephalopathy in rats with lower increases in glutamine levels [6] but did not reduce ICP or ammonia levels. The role of therapeutic

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hypothesis of hepatic encephalopathy.

Management of hepatic failure

Successful management depends upon the recovery of hepatic function or, in the case of irreversible hepatic disease, upon liver transplantation. FHF is associated with a high incidence of cerebral oedema and intracranial hypertension (60%) [7] whilst LOHF has a much lower incidence (9%) and routine monitoring of these patients is not usually necessary. FHF patients are at continual risk of hypoglycaemia, and regular glucose monitoring (at least hourly) should be undertaken with a 50% dextrose infusion initiated in any patient at risk. The primary treatment consists of avoidance of arterial hypotension, hypoxia and hypocapnia. Liver transplantation has dramatically improved survival rates (40–80%) [8–11] and patients who develop hepatic failure should be discussed with/ transferred to the regional liver transplant unit, preferably prior to the development of cerebral oedema. Patients with grade III–IV encephalopathy should be electively intubated and ventilated for transfer to a liver ICU unit. Cerebellar herniation is a serious risk for patients transferred in the later stages of encephalopathy.

Intracranial hypertension

Definition

Intracranial hypertension secondary to cerebral oedema reduces the cerebral perfusion pressure (Cerebral Perfusion Pressure (CPP) = Mean Arterial Pressure (MAP)−Intra-Cranial Pressure (ICP)) and if this falls below 50–60 mmHg hypoxic brain damage can result. It is therefore more important to maintain a viable cerebral perfusion pressure than to attain a particular value for ICP. Cerebral oedema is the leading cause of death (~50%) in FHF and occurs in up to 85% of patients with FHF.

Monitoring

Intracranial pressure monitoring is performed, once the patient is anaesthetized and ventilated, using subdural/subarachnoid catheters. The reported incidence of complications in an Italian study [12] of 542 patients with trauma or subarachnoid haemorrhage were ~2% for infection and <1% for cerebral parenchymal bleeding, with a mean catheter placement life of 104 h. Monitoring confers an advantage in acute liver failure in allowing early management of raised ICP on the ICU or during transplantation.

Management

Elective ventilation allows protection of the airway from aspiration and treatment of hypoxaemia. Intracranial pressure can rise rapidly during intubation and the patient should be anaesthetized (high-risk patients given intravenous mannitol, vide infra) prior to the procedure. Once anaesthetized and ventilated, an intracranial pressure monitor can be placed to enable early treatment of any increase in intracranial pressure. Elective ventilation is used to control arterial CO₂ tension and prevent cerebral vasodilatation that can exacerbate intracranial hypertension. Hypocapnia is a particular risk for self-ventilating patients with the metabolic alkalosis often associated with hepatic failure. Hyperventilation has been used to control intracranial hypertension in liver patients because hypocapnia can reduce cerebral blood flow and therefore reduce the volume of the intracranial vasculature [13]. Although cerebral blood flow has been reported as high in hepatic encephalopathy, aggressive hyperventilation can produce severe cerebral vasocostriction that may be harmful. While hyperventilation may delay cerebellar herniation, a randomized-controlled trial of prolonged hyperventilation demonstrated no decrease in ICP or incidence of cerebral oedema. In trauma patients hyperventilation improves CPP due to a reduction in ICP, but does not improve cerebral oxygenation or outcome. Hyperventilation should only be used with caution in the treatment of intracranial hypertension and only for the emergency control of surges in ICP [14].

Moderate head up tilt can help reduce ICP [13] but positioning in excess of 20 degrees can paradoxically increase ICP by reducing CPP [15]. Similarly, care should be exercised to avoid jugular vein compression by incorrect positioning of endotracheal tube tapes.

Normovolaemia should be maintained. Fluid overload can occur with generalized and cerebral oedema, particularly in association with hypoalbuminaemia and renal failure. Hypovolaemia secondary to haemorrhage, overdiuresis, excessive ultrafiltration, paracentesis or sepsis can reduce MAP and CPP thereby worsening cerebral oedema. Similarly hypovolaemia can precipitate renal failure or hepato-splanchnic ischaemia. Adequate assessment of intravascular volume is aided by early utilization of central venous pressure.
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monitoring, and in ventilated patients requiring inotropic support, more invasive monitoring including pulmonary artery catheter and/or trans-oesophageal Doppler placement is desirable.

Dialysis ultrafiltration is required in order to remove excess fluid when oligoanuric renal failure develops. Large volumes of blood products (fresh frozen plasma, platelets, packed cells) and drugs (inotropes, antibiotics, electrolytes, N-acetylcysteine) are often required during the period on ICU both pre- and post-transplant. Enteral feeding, once commenced, can also contribute to volume loading and efforts should be made to use low volume low sodium low potassium feed. Enteral feeding is preferred to parenteral feeding.

Fluid overload, particularly with hypoalbuminaemia, can risk the development or worsening of pulmonary oedema.

Hypertonic mannitol reduces ICP and improves cerebral oxygenation through an increment in cerebral blood flow in fulminant liver failure [16]. Mannitol 1 g/kg in FHF has been demonstrated as improving survival in patients with normal renal function [17]. A dose of 0.5 g/kg is more frequently administered. One hundred millilitres 20% mannitol should be given rapidly and not repeated for at least an hour. Further episodes of intracranial hypertension can be treated similarly if it responds to treatment initially. Hypovolaemia can be produced from the resultant diuresis [18] and if the MAP and CPP fall, the ICP may paradoxically increase. Hyperosmolality (>320 mosmol/l) should be avoided by measuring plasma osmolality in patients treated with mannitol. Mannitol is contraindicated in anuric patients unless the resultant hypovolaemia is treated by continuous ultrafiltration during renal replacement therapy.

The administration of osmotic agents is one of the principal therapies to lower elevated ICP and thereby increase CPP [19,20]. Glycerol and sorbitol, in addition to renal filtration, are metabolized, mainly by the liver. The risk of these compounds accumulating in patients with renal insufficiency is low, but high in those with hepatic failure. Both compounds frequently lead to hyperglycaemia. Mannitol is almost exclusively renally filtered and possesses the slowest elimination from serum (half-life 2–4 h). The half-life of mannitol is markedly increased in renal failure, but it does not interfere with glucose metabolism. Entry into the cerebrospinal fluid (CSF) occurs and elimination of all osmotic agents from the CSF compartment is substantially slower than from serum. During the elimination phase, the CSF to serum osmotic gradient is temporarily reversed. This is one cause of the paradoxical rise of ICP above the pre-treatment level.

Hypertonic saline decreases ICP and cerebral water content in experimental models of traumatic brain injury. Hypertonic saline (7.5%) solutions alone or in combination with 6% hydroxyethyl starch for the treatment of intracranial hypertension have been described in traumatic brain injured patients with normal renal function as therapy for resistant intracranial hypertension [21,22]. Administration lowered ICP by 44% and improved CPP by 38% to above 70 mmHg at 30 min without affecting arterial blood pressure or blood gases. Plasma sodium normalized within 30 min. The ICP lowering effect appears to be due to dehydration of brain tissue, as cerebral blood volume remains largely unaffected. A retrospective study of 23.4% saline for resistant increased ICP [23] (again in non-liver failure patients) suggests that intravenous bolus administration reduces ICP and augments CPP. This reduction can be maintained for several hours while other therapeutic measures are being considered. However, hypertonic saline therapy is untested in hepatic failure where salt and water overload and renal failure are common and is currently not to be recommended.

Barbiturates have not been demonstrated as effective in safely reducing ICP in head trauma [24] nor FHF. The hypotensive effect of barbiturate therapy will offset any ICP with lowering of CPP a particular problem.

Steroid therapy for intracranial hypertension is ineffective in hepatic failure [25].

Indomethacin: A single case report described low dose indomethacin [26] normalizing intracranial pressure in acute liver failure and is of interest but not supported by controlled studies. In addition, the use of non-steroidals in patients with acute renal failure and at high risk of gastro-intestinal bleeding may be hazardous.

Prostacyclin has been used predominantly as a circuit anticoagulant in patients with liver failure. Prostacyclin (PGE1) may be associated with reduced haemorrhage compared to heparin [27], a reduction in post-transplant acute renal failure [28] and improved early graft function [29] but has been associated with increased ICP and decreased CPP [30]. The reduction in CPP is probably secondary to its vasodilatory properties.

Continuous renal replacement therapy (CRRT) has been advocated as providing advantages over intermittent dialysis in liver failure on the ICU [31]. Improved haemodynamic stability has been demonstrated in the early period after initiation of dialysis with CRRT compared to intermittent dialysis [32,33] but no difference in MAP was demonstrated beyond 15 min from the start of dialysis between the two modalities. However, a greater increase in ICP was seen in intermittent dialysis than for CRRT and this may be important in unstable patients with a raised ICP. CRRT should therefore be associated with a reduced exposure to the early hypotension and raised ICP if the circuits survive >24–48 h.

Cooling the core body temperature using polar blankets and intra-gastric cooling in traumatic brain injured patients successfully reduced ICP and increased CPP [34]. More recently the use of cooling to produce hypothermia has been advocated for the treatment of severe intracranial hypertension in hepatic failure [35]. Cooling to sub-normal temperatures can reduce ICP where other methods have failed [36], but without subsequent liver transplantation the
mortality is 100%. Cerebral blood flow decreased by more than half with a corresponding increase in cerebral perfusion pressure from 45 mmHg to 70 mmHg. The reduction in ICP was quite rapid and is therefore probably achieved through a reduction in cerebral vascular volume and not through a reduction in brain water. The temperature of the brain falls more slowly than the circulating blood and more mild hypothermia may also be of benefit [37]. Arterial ammonia and cerebral uptake of ammonia are significantly reduced with cooling [36].

Conclusion

Cerebral oedema is the most common cause of death in FHF and, if not controlled by repeated mannitol infusions and ultrafiltration, death ensues in the majority (90%) within 12 h [38]. Patients who develop intracranial hypertension pre-transplant are more likely to develop further episodes during transplantation, hepatic dissection or reperfusion [39]. During transplantation the anhepatic phase is associated with a reduction in ICP. Moderate hypothermia has been demonstrated as a possible therapeutic manoeuvre to reduce ICP when conventional therapy fails. Although this can act as a holding procedure to allow an extra few hours for procurement of a donor organ, re-warming without transplantation is universally fatal.

The future

The introduction of bioartificial livers has been reported as a bridge to liver transplantation but its use in FHF is experimental. In pigs with FHF induced by 70% hepatectomy, portocaval shunt and 1 h of hepatic ischaemia, the use of a bioartificial liver was associated with a reduction in ICP and improvement in survival (to 15 days) compared to controls [40]. Additions to the evidence base in the use of NMDA antagonists, therapeutic hypothermia and bio-artificial liver support are eagerly awaited.

The present

The mainstay of therapy for patients with liver failure and at risk of intracranial hypertension remains supportive, with early transfer to a liver transplant ICU and appropriate selection of patients for liver transplantation. Increases in ICP are treated and/or prevented through the use of multimodality monitoring, elective ventilation, continuous ultrafiltration using CRRT when renal failure is present, and intravenous mannitol. Short periods of hyperventilation can be used for the emergency control of surges in ICP. Recovery from hepatic dysfunction prior to the development of protracted intracranial hypertension and irreversible neurological damage remains the hope in the remainder of these patients.

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