

Perioperative ischaemia-induced liver injury and protection strategies: An expanding horizon for anaesthesiologists

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ABSTRACT

Liver resection is an effective modality of treatment in patients with primary liver tumour, metastases from colorectal cancers and selected benign hepatic diseases. Its aim is to resect the grossly visible tumour with clear margins and to ensure that the remnant liver mass has sufficient function which is adequate for survival. With the advent of better preoperative imaging, surgical techniques and perioperative management, there is an improvement in the outcome with decreased mortality. This decline in postoperative mortality after hepatic resection has encouraged surgeons for more radical liver resections, leaving behind smaller liver remnants in a bid to achieve curative surgeries. But despite advances in diagnostic, imaging and surgical techniques, postoperative liver dysfunction of varied severity including death due to liver failure is still a serious problem in such patients. Different surgical and non-surgical techniques like reducing perioperative blood loss and consequent decreased transfusions, vascular occlusion techniques (intermittent portal triad clamping and ischaemic preconditioning), administration of pharmacological agents (dextrose, intraoperative use of methylprednisolone, trimetazidine, ulinastatin and lignocaine) and inhaled anaesthetic agents (sevoflurane) and opioids (remifentanyl) have demonstrated the potential benefit and minimised the adverse effects of surgery. In this article, the authors reviewed the surgical and non-surgical measures that could be adopted to minimise the risk of postoperative liver failure following liver surgeries with special emphasis on ischaemic and pharmacological preconditioning which can be easily adapted clinically.

Key words: Ischaemia, liver resection, perioperative, protection

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INTRODUCTION

Liver resection is the most effective modality of treatment in patients with primary liver tumour, metastases from colorectal cancers and selected benign hepatic diseases.^[1,2] The aim of liver resection is to remove all macroscopic disease with clear margins on microscopy and to ensure that the remnant liver mass has sufficient function. The acceptable residual functioning volume is approximately one-third of the standard liver volume or the equivalent of a minimum of two segments.^[3]

During the last decade of the 20th century, morbidity

and mortality of major hepatic resection was reported to be from 20.1% to 32.0% and from 2.8% to 10.5%, respectively.^[4-7] In the present-day scenario, with the advent of better preoperative imaging, surgical techniques and perioperative management, there is an improvement in the perioperative outcome of liver resection and the mortality rates have decreased to 0-3.1%.^[8,9] This dipping postoperative mortality after hepatic resections has encouraged surgeons towards more radical liver resections, leaving behind smaller liver remnants in a bid to achieve curative surgeries.

In one of the largest study populations, regarding

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postoperative outcome of patients following hepatic resection, Jarnagin *et al.* showed that the cause of mortality is multifactorial in majority of cases, with an incidence of 3.1%.^[9] However, infection played a very prominent role (42%) in contributing to this mortality, with liver failure being responsible for 10.9% of the total.^[9]

The other risk factors for postoperative liver failure are old age (age >70 years), preoperative chemotherapy and steatosis, cirrhosis, fibrosis, hepatitis, intraoperative blood loss, ischaemia and obstructive cholestasis.^[10] Estimated blood loss (EBL), blood product transfusion and number of hepatic segments resected are all independent predictors of both postoperative morbidity and mortality.^[9,11] Blood and blood product transfusions are associated with adverse immunomodulatory side effects and poor long-term outcome in the form of increased incidences of tumour recurrences.^[12,13] In view of the detrimental influence of transfusions on long-term perioperative outcomes in patients following hepatic resection for colorectal metastases, it is essential that all possible measures to limit blood loss be adopted.

Although the cause of mortality is multifactorial, postoperative liver failure is implicated in 18-75% cases.^[7] Post-resection liver failure has been defined by the so-called “50-50” criteria, i.e. a prothrombin time of less than 50% (INR-1.7) and serum bilirubin greater than 50 µmL/L (2.9 mg/dL) at the fifth postoperative day. When these 50:50 criteria are met, the postoperative mortality rate observed is 59%, compared with 1.2% in patients not meeting this criteria.^[14]

Patients are being increasingly subjected to hepatectomies for definitive treatment for many benign and malignant diseases of liver. Postoperative liver dysfunction of varied severity including death due to postoperative liver failure is still a serious problem in such patients. This article deals with surgical and non-surgical measures that can be adopted to minimise the risk of postoperative liver failure following liver surgeries. Special emphasis has been laid on ischaemic and pharmacological preconditioning (PP) which can be easily adapted clinically.

SURGICAL MEASURES

Continuous portal triad clamping

One of the commonly used and described techniques is Pringle’s manoeuvre.^[15] This involves portal triad

clamping during the resection stage. This manoeuvre decreases the blood loss, but renders the liver susceptible to warm ischaemia and reperfusion injury which may lead to severe liver dysfunction and liver failure. In the presence of fibrosis or steatosis, Pringle’s manoeuvre is tolerated poorly by the liver.^[16] Though early studies reported significantly reduced blood loss with portal triad clamping,^[17,18] more recent studies have not confirmed this finding.^[19,20] Rise in liver enzymes in patients who underwent liver resection with portal triad clamping was more than in patients who underwent resection without portal triad clamping.^[19] No significant difference in terms of postoperative liver functions and morbidity was observed in the study between these two groups.^[19] In view of the above-mentioned facts, it is prudent to avoid continuous portal triad clamping during liver resection.

Intermittent clamping

In this technique, repeated portal triad clamping (PTC) is done with intermittent short periods of reperfusion. Initially the duration of ischaemia inflicted was 15 min, followed by reperfusion for 5 min.^[21,22] Safe upper time limit of Intermittent clamping (IC) was considered to be 120 min,^[23] but IC time exceeding 120 min for more complex tumour resection is now performed safely.^[24] Belghiti *et al.* showed that although IC resulted in significantly higher blood loss, postoperative rise in bilirubin and serum transaminases was significantly lower compared to continuous portal triad clamping in patients with chronic liver diseases.^[21] On the contrary, Capussotti *et al.* failed to show any significant difference between the two groups in terms of intraoperative blood loss, postoperative liver function tests and morbidity in cirrhotics.^[22] Rahbari *et al.*^[25] performed a meta-analysis on the effect of portal triad clamping on outcome after hepatic resection and found no difference between intermittent PTC and no PTC in terms of overall postoperative morbidity and mortality, cardiopulmonary and hepatic morbidity, blood loss, transfusion rate and alanine aminotransferase (AST) level. However, they did not include the randomised controlled trial done by Man *et al.* which showed significant decrease in blood loss by portal triad clamping.^[18]

Cochrane review in this regard concluded that intermittent vascular occlusion is safe in liver resection but does not decrease morbidity.^[26] Ischaemic preconditioning (IP) before continuous portal triad clamping may be of clinical benefit in reducing intensive therapy and hospital stay.^[26] The current recommendation is that among the different methods of

vascular occlusion, IC appears to be better tolerated. This is especially true in patients with chronic liver disease. In cases of complex liver resection, where the clamping time could be prolonged, IC may be preferred.^[20]

Preconditioning

It refers to a phenomenon in which tissues are rendered resistant to the deleterious effects of ischaemia reperfusion (IR) either by previous exposure to brief periods of vascular occlusion (IP) or by the administration of certain chemical agents (PP).^[27] Preconditioning causes induction of organ stress to elicit the enhancement of the endogenous defence systems, thus making the organ more tolerant to a subsequent IR injury.

Ischaemic preconditioning

The concept of IP in liver had been extrapolated from the observed beneficial effects in heart wherein it was shown conclusively that a short period of ischaemia followed by short reperfusion renders the myocardium protected against the subsequent prolonged period of ischaemia. For IP of the liver, the protocol followed is to inflict 10 min of ischaemia, followed by 10 min of reperfusion before more prolonged ischaemia.^[28] Clavien *et al.* showed a twofold reduction in postoperative transaminase level along with reduction in the number of apoptotic cells.^[29] Patients with mild to moderate steatosis, who would otherwise be less tolerant to ischaemia and reperfusion injury, were found to have an increased protection, and they tolerated occlusion period of up to 40 min.^[29] These findings were corroborated in another study conducted later.^[30] Subsequently, it was reported that compared to continuous inflow clamping, IP results in better cardiovascular stability with decreased inotropic requirement.^[17]

IP versus IC

The study conducted by Azoulay *et al.* has, however, failed to show any beneficial effects of IP over continuous clamping in terms of rise in serum transaminase level or postoperative morbidity.^[31] The Cochrane analysis also did not find any statistically significant difference in the mortality, liver failure, intraoperative blood loss or haemodynamic changes by IP.^[32] Nevertheless, the length of intensive care unit stay and hospital stay were reduced in the IP group.^[31] When IP was compared to patients who underwent resections with IC, the efficacy of both these liver protection strategies was reported to be comparable.^[33] In the IP group, intraoperative blood

loss and transfusion requirement were less and there was a decreased transection time.^[33] It was documented that patients older than 65 years were less protected by IP. However, IC remained protective even beyond the age of 65 years. Therefore IC can be applied in patients more than 65 year of age and with steatosis.^[33] Another study found that the two strategies were comparable as long as the ischaemia time was less than or equal to 40 min. The markers of apoptosis were, however, increased in the IP group if the ischaemia time exceeded 40 min.^[34] The current recommendation regarding IP is that, if done before continuous portal triad clamping, it reduces reperfusion injury after warm ischaemia, particularly in steatotic patients (level A).^[20] Clinically, IP and IC are equally effective, but in cases of complex liver resection, where the clamping time could be long, IC must be preferred (level A).^[20]

Remote ischaemia preconditioning

Experimental studies had shown good results of RIPC on liver protection. In this technique, one of the lower limbs is subjected to 3 cycles of ischaemia and reperfusion of 10 min each, before liver resection. RIPC before IP of liver showed significant improvement in aminotransferases levels, mean arterial pressure, hepatic blood flow and peripheral oxygen saturation. But RIPC needs further evaluation before being included in the clinical practice.^[35]

Hepatic blood inflow occlusion and/or hemihepatic vascular occlusion

In this surgical technique, blood loss is minimised during hepatectomy by occluding hepatic blood flow with or without hemihepatic artery control.^[36] Hemihepatic vascular occlusion has the advantage that blood supply to the normal half of the liver is retained, thus minimising ischaemic damage and consequently improving the outcomes of the surgery.^[36] This technique requires complicated dissection of the hepatic artery and portal vein to enable occlusion of the hepatic vascular inflow to the half of the liver containing the lesion. Pringle manoeuvre is associated with lower postoperative levels of ALT and aspartate aminotransferase (AST) than with hepatic vascular inflow occlusion with or without hemihepatic artery control at first and seventh postoperative days. However, the levels of serum total bilirubin were higher and the incidence of complications was higher in the group with Pringle manoeuvre. There was no difference in reference to the mentioned parameters between the groups with or without hemihepatic artery control.^[36]

Hence, it has been suggested that hepatic blood inflow occlusion without hemihepatic artery control is a safe, convenient and feasible method for hepatic resections, especially in cases where the liver is complicated by preoperative diseases like cirrhosis, hepatitis, etc.^[36]

Segmental sparing surgeries

A better understanding of hepatic anatomy and increasing application of anatomically based resections are perhaps the most important factors in the marked improvement in postoperative outcome after hepatectomy.^[9] Multivariate analysis has demonstrated that estimated blood loss and the number of hepatic segments resected are independent predictors of both the morbidity and mortality.^[9]

Hepatic vascular exclusion

Hepatic vascular exclusion (HVE) has been proposed to decrease blood loss during liver resection; however, it failed to demonstrate any benefit regarding outcome of patients undergoing hepatic resection compared to portal triad clamping alone.^[37]

NON-SURGICAL MEASURES

Pharmacological preconditioning

Pharmacological preconditioning (PP) refers to the use of pharmacological agents including inhaled anaesthetics, prior to the ischaemic insult to the liver during hepatic surgeries, to attenuate the effects of liver injury. PP induces a stress response which protects liver against ischaemia–reperfusion injury. Many such agents have been tried for PP.

Doxorubicin

Doxorubicin protects against warm ischaemia–reperfusion injury in a rat model.^[38] But the toxicity of doxorubicin limits its clinical utility.

Volatile anaesthetic agents

Isoflurane and sevoflurane had been studied recently to evaluate their protective effects on the liver. Isoflurane and sevoflurane have been found to attenuate the myocardial mechanical dysfunction and limit ultrastructural abnormality on reperfusion after ischaemia in the cardiac myocytes.^[39,40] In an experimental study on rats, isoflurane pretreatment was done prior to induction of ischaemia (1 h) and reperfusion (1 h).^[41] Isoflurane pretreatment resulted in decreased plasma levels of liver enzymes like AST, ALT and alpha glutathione S-transferase (α -GST), and increased hepatic heme-oxygenase-1 messenger RNA, (HO-1mRNA), heme-oxygenase-1 (HO-1) protein

and HO enzyme activity. Histological analysis of the rat livers revealed reduction of necrotic areas, particularly in the periventricular region, the predominant site of isoflurane-induced HO-1 expression. Sinusoidal congestion, which is otherwise seen after ischaemia–reperfusion, was also inhibited by isoflurane.^[41] This study provides the first evidence that pretreatment with the nontoxic and clinically approved anaesthetic agents like isoflurane induces IP, and thereby protects rat livers from subsequent ischaemia–reperfusion injury.^[41]

Sevoflurane pretreatment has also been found to significantly reduce elevation of liver enzymes after liver resection with inflow clamping.^[42] Interestingly, the protective effects of sevoflurane pretreatment were more pronounced in patients with steatosis.^[42] The authors also reported that the expression of inducible nitric oxide synthase (iNOS) significantly increased compared with the baseline value in sevoflurane preconditioning group, which points to a possible protective role of nitric oxide (NO) in PP. This provides a new and easily applicable therapeutic option to protect the liver.^[42]

Propofol

Propofol had been found to be protective to liver in case of IR injury as a result of gut ischaemia–reperfusion.^[43] It may offer advantages by inhibiting lipid peroxidation and inflammatory cytokine production in an animal model of gut ischaemia–reperfusion-induced liver injury.^[43]

Verapamil

The role of verapamil (a slow calcium channel entry blocker) was studied in rats in the mediation of IR liver injury.^[44] This study demonstrated that verapamil, once administered before an ischaemic insult, had a beneficial effect during the 90-min period of warm liver ischaemia in the *in vivo* rat liver followed through the 21-day reperfusion period. But verapamil did not demonstrate the protective effects when administered after inducing ischaemia or during early reperfusion period.^[43]

Lignocaine

Lignocaine has also been found to have a protective effect on liver from IR injury in an experimental study.^[45] Pretreatment with lignocaine injected into the hepatoduodenal ligament prior to IR provides effective protection against subsequent IR injury to the liver, as evidenced by reduced levels of ALT and AST after the IR injury.^[45] (The hepatoduodenal ligament is the portion of the lesser omentum extending between the porta hepatis of the liver and the superior part of the duodenum.

It contains hepatic artery proper, hepatic portal vein and common bile duct. Collectively, these structures are known as the portal triad.) The protection offered by pretreatment with lignocaine is comparable to that offered by IP.^[45] Lignocaine blocks hepatic nerves when injected into hepatoduodenal ligament. Blocking the hepatic nerves improves hepatic blood flow, decreases neutrophil infiltration and reduces hepatic necrosis after IR.^[46] Lignocaine also has membrane-stabilising effects, thus inhibiting release of lysosomal enzymes and superoxide anions from neutrophils.^[46] Liver perfusion with lignocaine has been seen to increase the survival rate after transplantation.^[46]

Adenosine

Ischaemia results in considerable microscopic changes in the liver architecture. The release of transaminases is associated with a decrease in the normal expression of endothelial nitric oxide synthases (eNOS). Adenosine prevents this downregulation of eNOS, and thus offers protection from IR.^[27]

Ozone

Ozone therapy has also been evaluated in experimental study to see if it confers any protection from hepatic IR injury. During hepatic ischaemia, adenosine triphosphate (ATP) degradation leads to accumulation of adenosine and xanthine.^[47] Adenosine accumulation is beneficial, but xanthine accumulation is deleterious as it leads to formation of reactive oxygen species (ROS) due to activation of xanthine oxidase.^[47] Ozone pretreatment confers protection against hepatic IR injury by allowing accumulation of adenosine and by blocking xanthine and xanthine oxidase pathway for ROS generation. Ozone treatment, however, needs special equipments, and is therefore difficult to use in clinical practice.^[47] Ozone and IP share similar biochemical mechanisms of protection for preconditioning, but histologically ozone offered more effective protection than IP.^[48]

Remifentanyl

Remifentanyl has been recently evaluated and found to be effective in attenuating the effect of hepatic ischaemia and reperfusion injury. The probable mechanisms involve iNOS (not through opioid receptors) which mediates the preconditioning effect by exhausting ROS by consuming them for NO synthesis and attenuating the inflammatory response.^[49]

Methylprednisolone

Methylprednisolone, a corticosteroid well known for

its anti-inflammatory potential, has also been studied in the prevention of hepatic IR injury. Preoperative administration of methylprednisolone has been shown to significantly lower the postoperative serum ALT, AST, total bilirubin, and inflammatory cytokines levels.^[50] There is modulation of inflammatory response leading to reduced incidence of postoperative complication as well as maintenance of coagulant-anticoagulant homeostasis.^[50] The randomised trial conducted by Pulitanò *et al.* has also confirmed the above findings.^[51]

Trimetazidine

It is an anti-angina medication which preserve the energy metabolism in cells exposed to hypoxia or ischaemia and selectively inhibits the fatty acid beta-oxidation enzyme 3-keto-acyl-CoA dehydrogenase (3-KAT).^[52] Trimetazidine pretreatment in liver resection with vascular clamping has been documented to reduce cytolysis, increase liver ATP content and limit the increase of reduced and oxidised glutathione in the plasma during reperfusion. These findings suggest a possible role of trimetazidine in the prevention of hepatic IR injury.^[53]

Glucose

Selzner *et al.* demonstrated that ageing liver poorly tolerates IR injury due to mitochondrial dysfunction and decreased intrahepatic energy content which can be reversed with glucose administration prior to ischaemic insult in experimental model.^[54] This was later studied in humans by Tang *et al.*^[55] They administered high concentration of glucose 24 h prior to surgery to increase the hepatic glycogen storage before IR. They found that in the group with glucose infusion there was significantly higher hepatic ATP content and beneficial effect of high concentration of glucose infusion in complex liver surgery with vascular occlusion.^[55]

Antioxidants and other pharmacological agents

Vitamins C and E have been studied in hepatic IR injury and found to have a possible role in the prevention of oxidative stress of hepatic IR injury.^[56,57] In a systemic review of the available literature on various pharmacological strategies for liver protection under vascular occlusion, Abu-Amara *et al.* reported that methylprednisolone, trimetazidine, dextrose and ulinastatin (a protease inhibitor) may have protective roles against IR injury in liver resection, but they concluded that these therapies cannot be recommended for routine use.^[58] In the absence of an established mechanism of action of ROS scavengers, it is difficult to predict their potential efficacy and

success in the clinical use.^[59]

Gene therapy strategies

Gene therapy targeting common mitochondrial redox sensitive pathways involving intracellular nuclear factor kappa B (NFκB) and activator protein-1 (AP-1) has succeeded in reducing IR liver injuries in animal model.^[60] Gene therapy strategies are in their initial phases. A lot needs to be done before they can be introduced into clinical practice.^[46]

CONCLUSION

Reduced perioperative blood loss and consequent decreased transfusions improves patient survival after liver resection. Among the methods of vascular occlusion, both intermittent portal triad clamping and IP seem to be safe and equally effective during liver surgery. For complex and prolonged surgical resection of liver, IC appears to be more effective. IC is also beneficial in patients who are above the age of 65 years and in cases of steatosis. IP may be employed before continuous clamping as it decreases intensive care and hospital stay of patients. The administration of pharmacological agents, particularly preoperative use of dextrose, intraoperative use of methylprednisolone, trimetazidine, ulinastatin and lignocaine seems to be beneficial to protect the liver from ischaemia-induced injury. Anaesthetic agents (sevoflurane) and opioids (remifentanyl) may have the potential of liver protection by increasing the expression of inducible nitric oxide, but this need to be investigated further.

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