Review Article

Cellular and molecular mechanisms in perioperative hepatic protection: a review of current interventions

Zahra Talebi[1], Hassan Peyvandi[2*], Ali Dabbagh[1]

Abstract

Liver is one of the most important organs needing great concern during the perioperative period. There are a number of different mechanisms that interact with liver cells and might affect their integrity and cell live. Though these mechanisms are not all the same, there is a great common point: all affect the metabolic pathways of the liver. Ischemia, anesthetic drug effects and other perioperative insults may affect the liver. Disturbance in an organ's blood flow is an inherent part of diverse surgical procedures, which leads to lack of oxygen and nutrient supply. These ischemic periods can be particularly long in case of liver surgeries, such as resection of large hepatic tumors, management of hepatic trauma and liver transplant. Once the blood flow and oxygen supply are restored, the interruption of blood flow affects the oxygen dependent cells in liver, which require mitochondrial oxidative phosphorylation for their metabolism. Molecular mechanisms such as Redox status, ionic interchange disturbances as well as different mediators and cells like KC, SEC, dendritic cells, leukocytes, and lymphocytes, are involved in the process ultimately leading to cell death by apoptosis and necrosis. This review provides an overview on the cellular and molecular mechanisms involved in liver injuries, categorizing these mechanisms in 3 different classes: preoperative mechanisms, intraoperative mechanisms and postoperative mechanisms. Each of them are discussed in a different part of the manuscript.

Keywords: Cellular, Molecular, Hepatic, Organ Protection, Perioperative

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1. Anesthesiology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Clinical Research Development Center, Loghman Hakim Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Corresponding Author:
Hassan Peyvandi, MD, Associate Professor, Clinical Research Development Center, Loghman Hakim Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
E-mail: Hassan.peyvandi@gmail.com

Introduction

Disturbance in an organ's blood flow is an inherent part of diverse surgical procedures, which leads to lack of oxygen and nutrient supply. These ischemic periods can be particularly long in case of liver surgeries, such as resection of large hepatic tumors, management of hepatic trauma and liver transplant (1). Once the blood flow and oxygen supply are restored, the interruption of blood flow affects the oxygen dependent cells in liver, which require mitochondrial oxidative phosphorylation for their metabolism. Molecular mechanisms such as redox status, ionic interchange disturbances as well as different mediators and cells like KC, SEC, dendritic

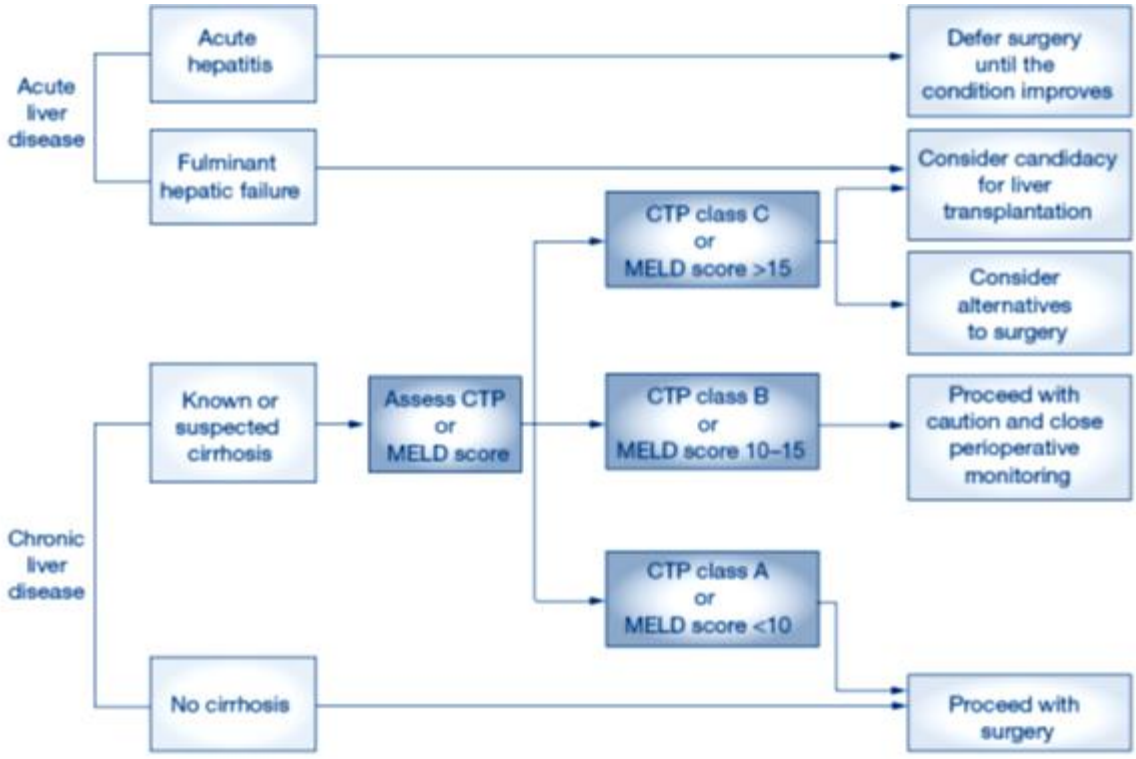

Figure 1. Proposed algorithm for the preoperative assessment of patients with liver disease (adapted from reference 12).

cells, leukocytes, and lymphocytes, are involved in the process ultimately leading to cell death by apoptosis and necrosis (2).

There are 2 major types of ischemic reperfusion liver injury: Warm IR injury occurs during prolonged surgical liver resection using clamping of the perfusion and is nearly inevitable in liver resection surgery, liver transplantation, and in blood transfusion for hemorrhagic shock (3). Cold IR injury, on the other hand, results from cold preservation of the donor organ followed by restoration of blood flow after implantation during liver transplantation (2). Tissue damage during an ischemic reperfusion injury occurs in two phases: The early phase which occurs within the first 2-6 hours after the blood supply has been re-established is presumably the consequence of the fast change in the redox state of the liver tissue. It is characterized by the release of reactive oxygen species (ROS) and production of inflammatory mediators (TNFα, chemokines) by hepatocytes, Kupffer cells (KCs), and sinusoidal endothelial cells (SECs). The late phase which occurs 6–48 h after reperfusion further advances the liver damage and is caused by the production of inflammatory cytokines and chemokines as a result of the infiltration of neutrophils and macrophages into the liver tissue (1–3).

Clinically, liver IR injury can lead to elevation in liver enzymes and biliary dysfunctions which can even lead to liver failure (4). Furthermore, many other remote organs seem to be influenced during the process of IR liver injury, including kidney, lung, gut, pancreas, adrenal and Myocardial injury (5), which further increases the mortality after perioperative liver failure (6). This articles aims to review the main strategies implemented to minimize perioperative hepatic cellular injury.

Pre-operative Considerations

Since the extent of perioperative liver IR injury mainly depends on the duration of ischemia and preexisting health conditions, a targeted perioperative liver protection is only possible by obtaining the detailed knowledge and thorough assessment of preoperative liver impairment (7). Liver has the ability to compensate for temporary insults and regenerate itself to a certain degree as a result of its dual blood supply from portal venous and hepatic

Table 1: Overview of preoperative management of liver disease complications (Adapted from reference 12).

Clinical manifestation	Management considerations
Nutritional status	Maintenance of an adequate protein intake (1–1.5 g/kg per day) Consider DR
Coagulopathy	Vitamin K supplementation (oral or parenteral) Fresh, frozen plasma transfusions Intravenous administration of cryoprecipitate Intravenous administration of recombinant factor VIIa Platelet transfusions
Ascites	Paracentesis with analysis of ascitic fluid for evidence of infection Dietary sodium restriction (<2 g daily) Oral diuretic therapy with spironolactone and/or furosemide Fluid restriction (if sodium concentration is <120 mmol/l) Avoidance of excessive saline administration Avoidance of NSAIDs
Renal dysfunction	Avoidance of nephrotoxic insult Albumin infusion (with paracentesis volumes >5 l)
Portosystemic encephalopathy	Correction of reversible metabolic factors Avoidance of sedatives and opioid narcotics, as far as possible Oral lactulose administration, titrated to ~3–4 bowel movements per day Administration of nonabsorbable antibiotics Decreased protein intake
Pulmonary hepatic vascular disorders	Supportive care Supplemental oxygen

arterial blood flow (7), hence the liver injury occur only be clinically evident after substantial damage. However, this reserve capacity is significantly reduced in patients with advanced liver disease, and these patients are more prone to develop an inappropriate response to surgical stress, coagulopathy and hepatic encephalopathy. Evaluation of general health and co-morbidities such as coagulopathy, renal function, volume and electrolyte status and cardiovascular function, is therefore essential in order to anticipate the patient's individual needs during and after the surgery (8).

Cardiovascular assessment

In patients with liver cirrhosis, the systemic circulation is hyperdynamic and significantly dysfunctional and impaired myocardial contractility lead to limited contractile reserve to meet perioperative hemodynamic challenges. Additionally, the response to potent vasoconstrictors, such as angiotensin II and vasopressin and epinephrine injection, is blunted due to down regulation of receptors. Thus, it is difficult to maintain adequate intraoperative end organ perfusion in these patients. Pre-operative echocardiography and either an exercise or pharmacological stress-test is needed to ensure patients safety during the surgery (8).

Pulmonary assessment

The hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH) and hepatic hydrothoraxare known to occur in chronic liver disease and should be evaluated before surgery to minimize the risk of hypoxia and right heart failure (9). The clinical features of HPS are present in about 15% of patients with chronic hepatic disease and may have adverse effects on maintaining the adequate perioperative liver perfusion and oxygenation (8).

POPH, is about 10 times less common than HPS and it is diagnosed based on pulmonary hemodynamic criteria acquired through right heart catheterization (8). Moderate and severe POPH can

Table 2: Child–Turcotte–Pugh score (Adapted from reference 12).

Component	Score		
	1 point	2 points	3 points
Total bilirubin concentration (μmol/l)c	<34	34–50	>50
Serum albumin concentration (g/l)*	>35	28–35	<28
International normalized ratio	<1.7	1.7–2.2	>2.2
Ascites	None	Controlled with medication	Treatment-refractory
Encephalopathy	None	Grade I–II (or controlled with medication)	Grade III–IV (or treatment-refractory)

* For patients with chronic cholestatic diseases, assign 1 point for a bilirubin concentration of up to 68 μmol/l, 2 points for a bilirubin concentration of 68–170 μmol/l, and 3 points for a bilirubin concentration >170μmol/l

substantially increase the risk associated with liver transplant (10). Screening for POPH is advised using transthoracic Doppler echocardiography and right heart catheterization (8).

Preoperative blood gas analyses can also help in understanding the underlying mechanism of hypoxia, since patients with intra-pulmonary shunting are likely to have no or very little response in PaO2 after 100% inspiration of Oxygen, whereas patients with ventilation– perfusion mismatching or dilated alveolar capillaries are more likely to have a normal response (PaO2>500 mmHg) (8).

Renal assessment

Patients with chronic liver disease are at risk for renal dysfunction with renal hypoperfusion due to hemodynamic abnormalities. The risk of developing dysfunction is increased by diuretics, nephrotoxic agents including non-steroidal anti-inflammatory drugs (NSAIDs), large-volume paracentesis performed without albumin supplementation, infections, and gastrointestinal bleeding. Another common condition in this patient population is Hepatorenal syndrome, which is caused by alterations in renal blood flow following splanchnic vasodilatation (9).

Renal function should be closely monitored before and after the surgery, and potential insults should be dealt with accordingly. It should be noted that due to hemodynamic changes serum creatinine levels often overestimate the glomerular filtration rate (GFR) in patients with cirrhosis. Vasoactive compounds, midodrine and terlipressin as well as intravenous albumin are used in treatment of circulatory problems and the resultant renal impairment in patients with cirrhosis and reduced interstitial volume (9).

Renal dysfunction can lead to hyponatremia which in severe cases (<125 mEq/l) must be addressed carefully to avoid central pontine myelinolysis (11).

Coagulation profile assessment

All coagulation factors, except von Willebrand's factor are produced in the liver. The impaired production of coagulation factors, along with alterations in vitamin K metabolism and absorption due to cholestasis, enhanced fibrinolytic activity and/or peripheral thrombocytopenia due to entrapment of platelets as a result of portal hypertension, leads to coagulopathy in advanced liver diseases (8,9). The coagulation profile should be assessed and corrected, depending on the surgical procedure with vitamin K supplementation and administration of fresh-frozen plasma (FFP), Cryoprecipitate to reduce the prothrombin time,diamino-8-D-arginine vasopressin (DDAVP) for prolonged bleeding time and platelet transfusion to correct the thrombocytopenia (8,9). Blood temperature should be maintained using warmed fluids or warm-air devices to ensure adequate function of coagulation cascade during surgery. Platelet function might be impaired despite a normal platelet count, which can affect neuraxial anesthesia (8).

Other factors

Other conditions that should be addressed before the surgery are as follows:

Ascites: ascites should be treated aggressively with diuretics and/or large-volume paracentesis with regards to renal function before surgery, as it can lead to wound dehiscence, abdominal wall herniation, and respiratory problems due to reduced lung expansion, and increase mortality (9).

Encephalopathy: Portosystemic encephalopathy at baseline can increases risk of postoperative encephalopathy and mortality rate in cirrhosis patients. Addressing the underlying cause of encephalopathy, whether it is electrolyte abnormalities, infection, gastrointestinal bleeding, or sedatives may help prevent or decrease encephalopathy. Hepatic encephalopathy can also be treated with administering lactulose or poorly absorbed antibiotics such as rifaximin (9).

Malnutrition: Severe malnutrition increases the need for emergency supplies of packed red blood cells, FFP, and cryoprecipitate and is believed to prolong postoperative stay. Therefore it should be addressed in the preoperative period with supplements accordingly, to meet increased energy expenditure after surgery and improve surgery outcomes (9).

Preoperative nutritional interventions (mainly fasting and dietary restrictions for periods longer than the night before surgery) have been suggested as a way to protect against certain types of stress, such as ischemia-reperfusion injury. Although sufficient data are available to support this theory, there is a need for more detailed studies to determine the best nutritional intervention for each patient, as protein restriction can have the same results without calorie restriction, and can be combined with carbohydrate rich drinks in patients to protect the organ without compromising patient's health. Some pharmacological interventions can mimic these effects, for example resveratrol, a natural polyphenol, can induce genomic changes similar to ones induced by DR. resveratrol can also alleviate liver injury induced by ischemia-reperfusion injury, through a meaningful increase in glutathione reductase, copper-zinc superoxide dismutase, and catalase activities (12). Table 1 demonstrates an overview of the preoperative considerations (Table 1).

Quantified risk assessment

In order to quantify the risk associated with surgery in patients with chronic liver disease, two risk stratification schemes have been introduced: The Child–Turcotte–Pugh (CTP) score in 1984 and, the model of end-stage liver disease (MELD) in 1999. The CTP score was originally designed by Child and Turcotte and Pugh et al. modified it by including prothrombin time in place of nutritional status for use in patients undergoing esophageal transactions. The score was originally used to assess risks in patients undergoing portosystemic shunting for variceal hemorrhage, but subsequent studies have shown its benefits to determine risks of surgery in patients with liver disease. This score is widely used to assess disease severity and predict perioperative morbidity and mortality in patients with cirrhosis. The score is calculated with components in Table 2, with class A=5–6 points, class B=7–9 points, and class C=10–15 points. CTP classes A, B, and C are associated with mortality of 10%, 30–31%, and 76–82%, respectively in patients with liver disease (8,9,13) (Table 2).

The clinical parameters used in CTP scoring system are subjective and the cut-off points for biochemical parameters are inconsistent, therefore alternative systems have been developed in order to increase the accuracy in estimating the severity of underlying hepatic dysfunction. The model of end-stage liver disease (MELD) was designed for this purpose in 1999. This score is calculated from the patient's serum creatinine (Crea), bilirubin (Bil), and international normalized ratio (INR) instead of subjective clinical parameters (8,13).

MELD score = (9.6 × ln [creatinine mg/dl]) + (3.8 × ln[bilirubin mg/dl]) + (11.2 × ln [INR]) + 6.4. The MELD score has been used in patients with cirrhosis, variceal bleeding or acute alcoholic hepatitis (14–16). A modified version of this model is adopted by the United Network for Organ Sharing (as of February 2002) to select patients for liver transplantation (15) (Figure 1)

Anesthetic Considerations

Volatile agents

It seems that all volatile anesthetics have the potential to harm the liver. The mechanism for this adverse effect is mainly immunologic; biotransformation of these agents by cytochrome P450 Specific results in trifluroacetylated proteins which can trigger an immune response in genetically susceptible individuals in the form of specific IgG

antibodies. The reaction of these antibodies with cell surface antigens of hepatocytes, increases incidence of antibody-dependent cell-mediated toxicity in these cells (17, 18). Halothane and enflurane are the main inhaled anesthetics that are most frequently associated with postoperative liver damage with this mechanism. The incidence of enflurane-induced hepatotoxicity appears to be less than halothane (19). Since 15–40% of Halothane and about 2.5 % of enflurane are metabolized in liver by cytochrome P450, it can be assumed that there is a cross-sensitization between enflurane and halothane and enflurane may not be the causative agent in the reported hepatotoxicity (20) .

There have been reports of different grades of hepatotoxicity with isoflurane which supposedly involves a similar mechanism, although the biotransformation of this agent is minimal (0.2%). On the other hand, isoflurane and sevoflurane can have a hepato-protective effect too (21). These agents induce an upregulation of hemoxygenase-1 (HO-1), which catalyzes the conversion of hem to biliverdin IX, free iron and carbon monoxide and ultimately leads to vasodilation of hepatic vascular bed (7).

Desflurane is metabolized by cytochrome p450 system to a small but variable extent (about 0.02%) which can potentially form immunogenic complexes, with several cases reported in the literature (22–24). However, preserves a better hepatic blood flow compared to earlier generations of volatile anesthetics such as halothane and enflurane. It is also associated with better outcomes in maintenance of anesthesia for liver transplantation comparison with total IV anesthesia (25).

Sevoflurane is the newest form of halogenated anesthetics. Its biotransformation is minimal and does not lead to the formation of reactive trifluroacetylated proteins; therefore it is unlikely to cause severe postoperative hepatic injury and can be considered as a perfect anesthetic for patients with previous exposure to other halogenated anesthetics or hepatic disease. Pretreatment with Sevoflurane can be used as a hepatoprotective strategy due to its vasodilation effect on hepatic vascular bed (19)

In Recent years, Xenon has gained much attention as an anesthetic gas with nearly all the ideal features. Xenon anesthesia has been shown to produce “the highest regional blood flow in the brain, liver, kidney and intestine” which is the goal in patients undergoing liver surgeries (26)

Intraoperative Considerations

Surgical measures

Portal triad clamping was the earliest method reported to reduce blood loss during liver resection. The maneuver is easily applicable in different situations (except for lesions in the hepatic veins or inferior vena cava and in patients with right heart failure and pulmonary hypertension), is considered effective and it is well tolerated in the majority of patients, however some complications including significant increase in mean arterial pressure and systemic vascular resistance, reduction of cardiac index, splanchnic congestion and bacterial translocation from the gut has been associated with PTC in the literature. Intermittent application of PTC and ischemic preconditioning was later introduced to improve outcomes in liver surgeries. Intermittent PTC may increase the total blood loss compared to continuous PTC, but it can reduce the incidence of postoperative liver failure, particularly in the presence of cirrhosis. In ischemic preconditioning, an increased tolerance to prolonged ischemia is induced in the liver by exposure to short periods of liver ischemia prior to transection with PTC, either surgically or by administration of chemical compounds. A meta-analysis on this technique has not shown any significant difference in mortality, blood loss or liver failure, although length of intensive care unit and hospital stay have been improved significantly (27,28). The liver can tolerate some episodes of warm ischemia, but especially in case of patients with preexisting liver damage due to chemotherapy or cirrhosis, it is vulnerable to anoxic conditions. Although several studies demonstrated ≤90 mininutes of complete PTC to be safe in normal livers, many surgeons choose to not clamp the inflow continuously for >45 minutes to prevent concern occult liver damage. In cases of complex liver surgeries with prolonged clamping time, ischemic preconditioning may be preferred (29).

Stricter vascular isolation of the liver provides better control of hemorrhage, but it also increases the ischemic injury in the organ, congestion of the viscera and cardiac stress. Total inflow and outflow occlusion

of the liver is used in "Total hepatic vascular exclusion". This technique which can be combined with aortic clamping and hypothermic perfusion of the liver is intolerable for some patients due to an unexpected fall in cardiac output and is therefore commonly reserved for resections involving the inferior vena cava or hepatic veins. In Hemihepatic vascular clamping (HHVC), the vascular isolation is reduced and therefore ischemia to the liver remnant and splanchnic congestion is minimized but the risk for bleeding from the re-perfused remnant is higher (27).

Hemodynamic measures

As mentioned before, patients with chronic liver disease require a more restrict control of arterial blood pressure, since they are at a greater risk of ischemic and reperfusion injury due to their is impaired functional reserve capacity .

A low central venous pressure (CVP) between 2 and 5 mmHg should be maintained in order to reduce intraoperative blood loss due to hepatic vein distention. Fluid replacement should be considered afterwards to compensate the reduced organ perfusion and volume reserve.

Several vasoconstrictive agents have been used to maintain macrohemodynamic variables and tissue oxygenation. These agents increase oxygen consumption in the organ as well which may have adverse effects on overall nutritional blood supply (8).

Epinephrine and norepinephrine, dopamine, dobutamine and dopexamine all improve mean arterial pressure and cardiac output. In patients with sepsis, however, epinephrine had the potential to impair splanchnic circulation with its effect differing with the degree of underlying sepsis. In these patients, dopexamine could not increase splanchnic blood flow selectively, and did not improve surgery outcomes and organ dysfunction in major abdominal surgery. The reports on dopamine are controversial, and it has been suggested that its effects on splanchnic blood flow may be dependent on basal splanchnic perfusion (8). A cross-over study compared epinephrine with a combination of dobutamine and norepinephrine in septic shock patients. Results demonstrated improvement in splanchnic blood flow and oxygen uptake in the group using the combination of dobutamine and norepinephrine (30). There are several reports of dobutamine hepatoprotective effects with mechanisms similar to isoflurane (31). In a sepsis model in rats, dobutamine pretreatment Improved Survival, Liver Function, and Hepatic Microcirculation (32).

Vasopressin has shown to restore blood pressure rapidly in septic shock but its effects on splanchnic and hepatic blood flow are controversial (8). In a recent study on human subjects in hepatic surgery, vasopressin increased cardiac output, stroke volume, MAP and CVP. Systemic vascular resistance, heart rate and portal venous pressure remained unchanged, and HVP increased slightly. Vasopressin infusion also reduced portal and hepato-splanchnic blood flow (33). Dexmedetomidine, a selective α 2 adrenoceptor agonist, has the unique ability to induce sedation and analgesia at the same time, without increasing the risk of respiratory depression. DEX can reduce sympathetic drive, which makes it a more appropriate choice for analgesia in patients who are at risk of tachycardia and hypertension. According to pre-clinical data, DEX also has profound organo-protective effects in cerebral, cardiac, renal, hepatic and gastrointestinal ischemia-reperfusion injury but further clinical trials are needed to warrant its use in practice (34).

Phosphodiesterase inhibitors showed promising results in septic patients where an increase in hepatosplanchnic oxygen consumption, lidocaine metabolism and a decreased release of hepatic tumor necrosis factor alpha (TNF-α), was seen with enoximone treatment (8). Preoperative olprinone also showed improvement in systemic and hepatic circulation in a swine partial hepatectomy model (35). Pentoxyphilline, which is used in intermittent claudication, is also a phosphodiesterase inhibitor. Furthermore, it inhibits inflammatory cytokines such as TNF-αand protects the liver against ischemia and reperfusion injury (36).

Levosimendan, has also been shown to hepatoprotective effects on hepatocytes (37). A study compared the effects of levosimendan and dobutamine on hepatic blood flow of the patients with low cardiac output in cardiac surgery, and the results suggested that levosimendan can improve hepatic blood flow as a selective liver vasodilator through the

hepatic artery and also the portal vain, while dobutamine has no vasodilating effect on the hepatic artery and only enhances the portal venous blood flow (38). Levosimendan can exert protection against ischemic liver damage through mechanisms related to NO production and mitochondrial KATP channel function (39) and significantly improve liver redox homeostasis (40)

Pharmacologic Interventions

Pharmacological preconditioning

As mentioned before, Pharmacological agents such as inhaled anesthetics can be used in preconditioning. PP induces a stress response which protects liver against IR injury.

Some of the agents used for PP are as follows:

Nitric oxide: NO has demonstrated a decrease in IR liver injury by reducing apoptosis in hepatic cells, alleviating oxidative stress and leukocyte adhesion, and also increasing the capillary blood flow, and improving mitochondrial function (41).

Doxorubicin: Doxorubicin preconditioning can induce ischemic tolerance and IR injury protection in rats abdomen island (42) , But its associated liver toxicity limits its clinical use.

Volatile anesthetic agents: Isoflurane and sevoflurane have been found helpful in prevention of IR liver injury, through previously discussed mechanisms.

Propofol: Propofol have some advantages in prevention of IR liver injury, by reducing lipid peroxidation, the number of apoptotic cells and activation of Caspase-3 in hepatic L02 cells, but the results are somewhat controversial (43,44).

Verapamil has hepatoprotective effects in warm liver ischemia when administered before an ischemic insult in rat models, but no protective effect was seen with administration after induction of ischemia or during the early reperfusion period (44).

Lignocaine: Injection of Lignocaine into hepatoduodenal ligament improves hepatic blood circulation, decreases neutrophil infiltration and ultimately reduces hepatic necrosis blocking hepatic nerves. Its membrane‑stabilizing effects, further inhibits the neutrophil function. Liver perfusion with lignocaine has been seen to increase the survival and reduce liver enzymes after liver surgeries (29).

Adenosine: Adenosine prevents down regulation of eNOS during IR liver injury and therefore has hepatoprotective effects (29).

Ozone: Xantine and adenosine are accumulated in the cell as a result of adenosine triphosphate (ATP) degradation after IR liver injury. Ozone therapy blocks xanthine and xanthine oxidase pathways, thus inhibits ROS formation and its associated hepatic injury during hepatic IR process (29). Ozone treatment and surgical preconditioning have similar biochemical effects but ozone seems to be more beneficial in the histological aspects (45).

Remifentanil: Preconditioning with remifentanil reduces liver injury in IR both in vivo and in vitro through Inducible NOS which exhausts reactive oxygen species and therefore diminishes the inflammatory response (46).

Glucocorticoids: Over the last decade, randomized controlled trials (RCTs) has shown that preoperative administration of glucocorticoids in patients undergoing liver resection can have beneficial effects on biomarkers of systemic inflammation, including IL-6, IL-10, TNF-α, C reactive protein (CRP), liver function tests such as AST, ALT, prothrombin time (PT) and total bilirubin, with no increased risk for infection or negative effects on liver regeneration (47).

Trimetazidine: trimetazidine is an anti-angina medication with both cytoprotective and antioxidant abilities which can preserve energy metabolism in cells exposed to hypoxia or ischemia. It has been shown to reduce cytolysis and increase liver ATP content with vascular clamping during hepatic IR injury and reduce hospital stay in human subjects (48).

Glucose: Administrating high concentrations of glucose 24 h prior to surgery has shown an increase in hepatic ATP content due to higher hepatic glycogen storage (29).

Iron and Thyroid hormone: A combination ofiron and T_3 was used in a study to suppressed ischemia–reperfusion injury in rat livers. The combination was able to attenuate the oxidative stress, Nrf2 and NF-kB activation, and upregulations in glutamate-cysteine ligase-c and haptoglobin (49).

Antioxidants and other pharmacological

agents: as oxidative stress and inflammatory pathways play a major role in IR liver injury, different antioxidants and anti-inflammatory agents including vitamins C and E, N-acetyl cysteine (50), statins (51), S-adenosyl methionine (48), melatonin (52) and several herbal extracts such as Silymarin in Milk thistle (53,54), grape skin component resveratrol and green tea extracts (55), cannabinoids (56) and Ginsenoside Rg1, the major effective component of ginseng (57), has been suggested to attenuate ischemic reperfusion liver injury. However it is usually difficult to predict their efficacy in the clinical use due to lack of information about their exact mechanism of action.

Novel Strategies

Different approaches are being pursued in experimental models to minimize preoperative hepatic injury, with promising results but limited clinical data. Some of these are as follows:

Antioxidants targeting mitochondrial stress: Edaravone is an antioxidant drug specifically designed to reduce the effects of ischemia reperfusion by inhibiting MPT (Mitochondrial permeability transition) channel formation in mitochondria. It has shown to be highly effective in protecting against both warm and cold hepatic IR injury in rodents and larger mammals (55).

Cytoprotective Strategies: A number of pharmacological interventions has been proposed in this category, including Calcium channel blockade (CCB) , low-dose therapeutic use of carbon monoxide (CO) as a cytoprotective, vasoactive and anti-inflammatory drug, Emricasan as a pan-caspase inhibitor (caspase enzymes are involved in the cell apoptosis process) and Glycine as a cytoprotective agent working by reducing the oxidative stress of proteolysis (48).

Preservation Solutions: Carolina rinse solution (CRS) and AQIX RS-I© has been introduced to prevent reperfusion injury in endothelial cells, but clinical data on their use is insufficient (48).

Prostaglandins have been extensively evaluated for IR hepatic protection, with controversial results. A recent study on prostaglandin I2, found it clinically beneficial in reducing hepatic injury biomarkers in liver transplant surgery. Other immunologic drugs such as TNF-α inhibitors, Platelet-activating factor (PAF) antagonists, adaptive Immune System suppressors such as tacrolimus and everolimus (58) and Innate Immune System suppressors such as eculizumab (an anti-C5 antibody) and Gadolinium chloride (an inactivator of Kupffer cells) has also been suggested in experimental models (48).

Gene therapy strategies: These strategies target redox sensitive pathways in mitochondria with an emphasis on intracellular nuclear factor kappa B (NFκB) and activator protein-1 (AP-1). The results from animal models were promising but there is a long way remaining to their use in clinical practice (29).

Postoperative Care

For Patients with underlying liver disease mortality rates are up to 10 fold higher in post-operative period of liver surgeries (8). Signs of hepatic decompensation, including encephalopathy, coagulopathy, ascites, worsening jaundice and renal dysfunction, should be monitored in patients with underlying liver disease so that the treatment can be initiated immediately.

Liver depletion of glycogen and decreased gluconeogenesis can lead to hypoglycemia in these patients; therefore serum glucose levels should be monitored.

Intravascular volume should be maintained carefully to ensure adequate perfusion in kidney and liver, whilst minimizing the risk for hepatic congestion which can lead to edema, ascites, and wound dehiscence (59). Due to increased cardiac output and splanchnic blood flow which persists for at least 3 days after liver resection surgery, patients often experience mild-to-moderate pulmonary edema and transient ascites (60). Therefore close monitoring is advised for early detection of complications in all patients undergoing major liver resection and patients with significant preoperative liver damage

Conclusion

Surgical techniques and perioperative care has progressed significantly in recent years and liver surgery has become dramatically safer, with a mortality rate lower than 1% in patients with normal

preoperative liver function (61), however ischemic reperfusion injury of the liver still remains a problem. Appropriate protective strategies, surgical or pharmacological, should be considered in every step of the way, before, during and after the surgery, with regards to patients needs to minimize this injury and improve surgery outcomes.

Although countless studies are published every year with focus on minimization of the IR liver injury with promising effects in vitro or on animal models, clinical data is still limited in this matter and conducting large randomized clinical trials can help facilitate the transition of these numerous preventive measures in to the clinical setting and fill in the gaps toward a more personalized treatment plan for each patient.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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