World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v16.i48.6098

World J Gastroenterol 2010 December 28; 16(48): 6098-6103
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

Rene Schmidt, MD, DESA, *Series Editor*

Current protective strategies in liver surgery

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Received: June 28, 2010 Revised: August 9, 2010
Accepted: August 16, 2010
Published online: December 28, 2010

Abstract

During liver resection surgery for cancer or liver transplantation, the liver is subject to ischaemia (reduction in blood flow) followed by reperfusion (restoration of blood flow), which results in liver injury [ischemia-reperfusion (IR) or IR injury]. Modulation of IR injury can be achieved in various ways. These include hypothermia, ischaemic preconditioning (IPC) (brief cycles of ischaemia followed by reperfusion of the organ before the prolonged period of ischaemia i.e. a conditioning response), ischaemic postconditioning (conditioning after the prolonged period of ischaemia but before the reperfusion), pharmacological agents to decrease IR injury, genetic modulation of IR injury, and machine perfusion (pulsatile perfusion). Hypothermia decreases the metabolic functions and the oxygen consumption of organs. Static cold storage in University of Wisconsin solution reduces IR injury and has prolonged organ storage and improved the function of transplanted grafts. There is currently no evidence for any clinical advantage in the use of alternate solutions for static cold storage. Although experimental data from animal models suggest that IPC, ischaemic postconditioning, various pharmacological agents, gene therapy, and machine perfusion decrease IR injury, none of these interventions can be recommended in clinical practice. This is because of the lack of randomized controlled trials assessing the safety and efficacy of ischaemic postconditioning, gene therapy, and machine perfusion. Randomized controlled trials and systematic reviews of randomized controlled trials assessing the safety and efficacy of IPC and various pharmacological agents have demonstrated biochemical or histological improvements but this has not translated to clinical benefit. Further well designed randomized controlled trials are necessary to assess the various new protective strategies in liver resection.

Key words: Liver; Hepatectomy; Liver transplantation; Ischemia-reperfusion injury; Hypothermia; Ischaemic preconditioning

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Gurusamy KS, Gonzalez HD, Davidson BR. Current protective strategies in liver surgery. *World J Gastroenterol* 2010; 16(48): 6098-6103 Available from: URL: http://www.wjgnet.com/1007-9327/full/v16/i48/6098.htm DOI: http://dx.doi.org/10.3748/wjg.v16.i48.6098

INTRODUCTION

Approximately 11 000 liver transplantations and an estimated 7000 to 10 000 liver resections are performed every year in US[1-3]. During liver resection and transplantation, the liver is subject to ischaemia (reduction in blood flow). A period of ischaemia is unavoidable in organ transplantation between the time the donor heart stops pumping blood through the circulation and the circulation to the organ is restored in the recipient. When the blood flow is restored (reperfusion), the liver is subjected to further injury. The damage caused by ischemia and then reperfusion in an organ is called ischemia-reperfusion injury (IR injury).

MECHANISM OF IR INJURY

The mechanisms involved in the production of the tissue damage by the IR injury are complex. Overviews of the mechanisms involved in liver IR injury have been described by various authors[4-6]. In simple terms, the sequence of ischaemia followed by reperfusion results in the activation of Kupffer cells (liver macrophages) and polymorphonucleocytes resulting in the production of reactive oxygen species (ROS), cytokines, and adhesion molecule activation leading to liver parenchymal damage.

PROTECTIVE STRATEGIES TO DECREASE LIVER IR INJURY

Modulation of IR injury can be achieved in various ways. These include hypothermia[7,8], ischaemic preconditioning (IPC)[9,10], ischaemic postconditioning[11], pharmacological agents to decrease IR injury[12,13], genetic modulation of IR injury[14], and machine perfusion[7,15]. Systematic reviews of well designed randomized controlled trials (with homogeneity) are currently considered the highest level of evidence to assess the effects of interventions[16]. A well designed randomized controlled trial is the next highest level of evidence[16]. The safety and effectiveness of the different interventions based on randomized controlled trials and systematic reviews of randomized controlled trials in humans is discussed under each of the methods.

Hypothermia

Hypothermia decreases the metabolic functions and the oxygen consumption of organs[17]. Although the organ can be preserved by warm perfusion, hypothermia has been used to decrease IR injury in the transplantation setting for several decades.

Invasive cooling of the donor liver: Ischaemic injury to the liver begins when the donor heart stops pumping blood through the circulation. During the liver retrieval operation, current standard practice involves perfusion of the liver through the aorta with or without perfusion through the portal vein using cold solution[18]. There are no randomized controlled trials comparing hypothermic with normothermic perfusion of the donor organ. Currently, there is evidence from one randomized controlled trial that the incidence of primary graft non-function decreases when double perfusion (aortic and portal vein perfusion) is used compared with single perfusion (aorta alone perfusion) in marginal donors (sub-optimal donors)[18]. In the optimal donor, there is currently no evidence of difference in clinical outcomes between single perfusion and double perfusion[18]. Apart from this comparison of the donor perfusion technique, there is currently no evidence for any difference in the graft or patient survival between the different solutions used for donor perfusion or different pressures used for perfusion[19-21].

Surface cooling of donor liver: There is currently no evidence that surface cooling of the donor liver in addition to invasive cooling by aortic and portal vein perfusion improves liver transplant outcomes.

Static cold storage and storage solutions: After removal of the liver from the cadaver, the liver is stored for a few hours till it can be transplanted to the recipient. This is the time required for the transport of the liver from the retrieval site to the transplant site. During this time, preservation injury occurs. This is because of lack of adequate oxygenation of the tissues. The current standard method for preservation is static cold storage. There have been no randomized controlled trials comparing static cold storage with other methods of organ preservation during transport of the liver. However, static cold storage remains the standard against which all other organ preservation methods can be compared. The introduction of University of Wisconsin (UW) solution in 1988[22] increased the capability of long distance procurement and sharing and decreased the costs associated with long distance procurement by decreasing the preservation injury[23,24]. Although the efficacy of UW solution compared with other solutions available at that time (Collin's solution) was not assessed by randomized controlled trial, the evidence for the benefits of UW solution over Collin's solution was so overwhelming[23,24] that a randomized controlled trial would have been considered unethical. To date, UW solution has remained the gold standard solution against which all other solutions are compared[25]. There is no evidence from randomized controlled trials that any of the other solutions such as Celsior solution or histidine-tryptophan-ketoglutarate solution result in a better graft or patient survival than UW solution[26-30].

Hypothermia in liver resections: While hypothermia has been used as the standard method of decreasing IR injury in liver transplantation, the role of hypothermia as a method of decreasing IR injury in liver resection surgery has not been established. The only randomized controlled trial assessing the impact of in-situ hypothermia in liver resections failed to demonstrate any major clinical benefits of in-situ hypothermia[8].

IPC

IPC is the mechanism by which brief periods of ischaemia followed by reperfusion of the organ results in the ability of the organ to withstand a subsequent prolonged period of ischaemia[31]. Overviews of the mechanisms of IPC have been provided by various authors[5,6,32,33]. Adenosine and nitric oxide play a pivotal role in the IPC response.

IPC can be achieved by a local preconditioning stimulus (direct IPC)[9,10] or by a remote stimulus (remote IPC)[6,34,35]. Remote IPC (RIPC) is the mechanism by which IPC of one vascular bed (area supplied by one artery) protects another vascular bed (area supplied by another artery) from IR injury[35]. The mechanisms involved in RIPC have been reviewed previously[6,34]. Currently, both neural and humoral pathways are believed to be involved in RIPC.

There is experimental evidence that direct IPC and RIPC protects against liver IR injury in the animal model[36-38]. In humans, a systematic review of randomized controlled trials showed that direct IPC decreases the enzyme markers of liver parenchymal injury after liver resections performed under vascular control (i.e. temporary occlusion of blood vessels supplying the liver)[9]. However, this did not translate into any clinical benefit[9]. One randomized controlled trial of remote IPC demonstrated a similar finding i.e. a decrease in the enzyme markers of liver parenchymal injury after liver resections without demonstrating any clinical benefit[39]. There is no evidence for benefit from direct IPC in liver transplantation based on a systematic review of randomized controlled trials[10]. Currently, there are no published randomized controlled trials of RIPC in liver transplantation. Thus, routine IPC (direct IPC or remote IPC) cannot be recommended in either liver resection or transplantation.

Ischaemic postconditioning

As opposed to IPC where the conditioning stimulus is applied prior to the prolonged period of ischaemia, ischaemic postconditioning (IPost) involves the application of the conditioning stimulus (brief intermittent cycles of IR) after the prolonged period of ischaemia but prior to permanent reperfusion i.e. ischaemia followed by conditioning stimulus followed by permanent restoration of blood flow[11]. Overviews of the mechanisms of ischaemic postconditioning have been reviewed previously[40,41]. As with IPC, adenosine and nitric oxide play a pivotal role in ischaemic postconditioning. As in the case of IPC, ischaemic post-conditioning can also be achieved by a local postconditioning stimulus (direct IPost)[11,42-44] or by a remote postconditioning stimulus (RIPost)[45].

In animal models, there is experimental evidence that IPost protects against liver IR injury[42-44]. There are currently no randomized controlled trials of ischaemic postconditioning (direct or remote) in either liver resection or liver transplantation. So, routine ischaemic postconditioning (direct IPost or RIPost) cannot be currently recommended in either liver resection or liver transplantation.

Pharmacologic interventions to decrease IR injury

Various pharmacologic interventions have been attempted with an intention of decreasing IR injury. Considering that ROS and inflammatory mediators play significant roles in IR injury[4-6], pharmacological interventions to neutralise or modulate the pathways using antioxidants and steroids are a subject of significant research[13].

There is experimental evidence that some pharmacological interventions[46,47] protect against liver IR injury in the animal model. In humans, a systematic review of randomized controlled trials assessing the role of pharmacologic interventions in decreasing IR injury after liver resections showed that some interventions such as methyl prednisolone decrease the enzyme markers of liver parenchymal injury after liver resections but without demonstrating evidence of clinical benefit[13]. The role of numerous pharmacological interventions in decreasing IR injury in liver transplantation has been investigated[48-77]. None of the interventions have shown any benefit in graft or patient survival.

Genetic modulation of IR injury

As the molecular mechanisms of IR injury are increasingly understood, more research is being performed on the genetic modulation of the pathways in IR injury both for better understanding of the mechanisms involved in IR injury and for potential therapeutic applications[78]. Experimental evidence to demonstrate the potential role of genetic modulation of liver IR injury exists[14]. There are no randomized clinical trials assessing the impact of genetic modulation of IR injury in liver resections or liver transplantation.

Machine perfusion

Machine perfusion involves pulsatile perfusion of the liver using a machine as opposed to static cold storage. This can be performed by perfusing the liver with a hypothermic perfusate[79] or with a normothermic perfusate[80]. There is experimental evidence in animal models that machine perfusion protects against liver IR injury[80,81]. The safety and efficacy of machine perfusion compared to static cold storage to decrease liver IR injury is yet to be assessed in humans by randomized controlled trials.

DIFFERENCES IN RESULTS BETWEEN ANIMAL MODELS AND HUMAN TRIALS

As discussed above, there are major differences in the results of the role of the different interventions in decreasing liver IR injury between animal models and clinical results. Some possible reasons for this include the lack of fidelity of the model used (i.e. how truly are the results transferable from the model to humans)[82], the use of unvalidated surrogate outcomes, and the use of inadequate sample size in human trials.

FUTURE TRIALS

Future trials of adequate sample size and low risk of bias (low risk of prejudice towards the treatment arm or the control arm)[83] should be performed to decrease the random errors (arriving at wrong conclusions because of pure chance, usually due to inadequate sample size) and systematic errors (arriving at wrong conclusions because of prejudice towards the treatment or the control arm). Measurement of meaningful differences in clinical outcomes requires a large trial. Development and validation of composite outcomes and surrogate outcomes will enable evaluation of the interventions using a smaller sample size.

CONCLUSION

Currently, the only intervention that has shown to be beneficial in the protection of the liver during liver transplantation is hypothermia. In liver resection surgery, there is currently no established intervention targeted at modulating

IR injury that provides any major clinical benefit. However, many new therapies and targets are being discovered. Well designed randomized controlled trials are necessary to assess the new protective strategies in liver resection and liver transplantation.

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