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REVIEW ARTICLE

Clamping techniques and protecting strategies in liver surgery

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Abstract

The use of vascular occlusion during liver resection is still a matter of debate. The aim of this review was to assess the advantages and disadvantages of portal triad occlusion as a protective strategy during elective liver resection and liver transplantation. Newer strategies such as pharmacological preconditioning are also discussed. A systematic literature search was conducted to detect randomized controlled trials assessing the effectiveness and safety of portal triad clamping, ischaemic preconditioning and pharmacological preconditioning during liver surgery. Vascular clamping cannot be systematically recommended. When used, portal triad clamping is associated with a tendency towards reduced blood loss and blood transfusion without having an impact on morbidity. Intermittent clamping appears to be better tolerated than continuous clamping, especially in patients with chronic liver disease. Ischaemic preconditioning before continuous portal triad clamping reduces reperfusion injury after warm ischaemia, particularly in steatotic patients. Ischaemic preconditioning has unclear effects in transplantation and there is currently no evidence to support or refute the use of ischaemic preconditioning in the donor. There are emerging alternative conditioning strategies, including the use of volatile anaesthetics, which may provide new and easily applicable therapeutic options to protect the liver.

Keywords

liver surgery, liver transplantation, vascular clamping, ischaemic preconditioning

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Introduction

Over the past two decades, liver resection has increasingly been performed worldwide because of improved post-operative outcomes and evidence that this approach offers the only chance of cure in many patients.[1–4] Technical innovations have mainly focused on minimizing bleeding during transection of the hepatic parenchyma[5,6] as excessive haemorrhage and the need for blood transfusion are associated with increased post-operative morbidity and mortality,[7] as well as reduced long-term outcome.[7–9] Portal triad clamping (Pringle manoeuver) has been used since the early 20th century[10] to prevent bleeding during parenchyma transection.[11–14] The concomitant use of low central venous pressure (CVP) anaesthesia further minimizes blood loss by preventing retrograde bleeding from the hepatic veins.[15,16]

However, the Pringle manoeuver causes ischaemic injury to the remaining liver with a risk of poor post-operative outcome.[12,17] Diseased livers with steatosis or fibrosis poorly tolerate reperfusion injury and can develop liver failure even after short periods of ischaemia.[18] Various methods have been attempted to decrease the reperfusion injury associated with prolonged duration of vascular occlusion including intermittent clamping, ischaemic preconditioning and more recently pharmacological preconditioning. Intermittent clamping consists of repeated periods of clamping followed by short periods of reperfusion.[19–21] However, the benefits of intermittent clamping are debatable, as it may lead to multiple reperfusion events with potentially repetitive hepatocellular damage, bleeding during reperfusion episodes and a prolonged operating time. Ischaemic preconditioning consists of a brief period of ischaemia and reperfusion applied prior to the prolonged ischaemic insult (10 min of ischaemia and 10 min of reperfusion).[22,23] Finally, pharmacological preconditioning with a volatile anaesthetic is a new approach in liver surgery. It has been shown in a rat model[24] and in a clinical study[25] that the application

of isoflurane before induction of hepatic ischaemia protected the liver from ischaemia/reperfusion injury.

The aim of the review was to assess the advantages and disadvantages of hepatic vascular occlusion as a protective strategy during elective liver resection and liver transplantation. New strategies such as pharmacological preconditioning will also be discussed.

Methodology

An electronic search of Medline was undertaken to identify comparative randomized controlled trials (RCT) and meta-analyses regarding the subject. The terms 'vascular occlusion', 'portal trial clamping', 'liver resection' and 'liver transplantation' were used in various combinations. The search terms were identified in the title, abstract, or medical subject heading (MeSH). With a few exceptions, only original articles published in English until October 2008 were selected for further analysis. Manual cross-referencing was also used to find further relevant articles. All articles were classified according to their level of evidence. The classification proposed by the Oxford Centre for Evidence-based Medicine was used to rank each publication and to give the grade of recommendation (A, B, C, D) based on the available literature for each topic.[26]

Portal triad clamping vs. no clamping

There were four RCT comparing clamping vs. no clamping during elective liver resection (Table 1).[20,23,27,28] Three of them compared intermittent clamping with no clamping, whereas Chouker *et al.*[23] included patients with continuous clamping. According to the first three RCT,[23,27,28] portal triad clamping was associated with less intra-operative blood loss, a shorter resection time and a higher level of post-operative transaminases. However, Capussotti *et al.*[20] did not confirm these results as no significant difference was shown between patients with or without clamping, even in patients with a chronic diseased liver. The Cochrane meta-analysis published in 2007,[29] based on these RCT, revealed decreased blood loss with vascular clamping but this difference was not statistically significant. It confirmed a significant higher peak of transaminases at post-operative days 1 and 2 associated with vascular clamping. However, there was no significant difference in terms of post-operative liver function and morbidity between patients with or without vascular clamping. The recent meta-analysis by Rahbari *et al.*[30] did not show any difference in blood loss and post-operative morbidity in patients undergoing a liver resection with or without portal triad clamping. However, for methodological reasons, this meta-analysis did not include the same RCT than the previous one. Although early studies reported significantly reduced blood loss with portal triad clamping, more recent studies have not confirmed this finding. This could be because of technical advances in hepatic surgery that now permit resection with limited blood loss, even without hepatic inflow occlusion.

Table 1 Randomized controlled trials comparing portal triad clamping and no clamping

Author	Year	No patients	No clamping vs.
Man *et al.*[27]	1997	93	Intermittent clamping
Man *et al.*[28]	2003	40	Intermittent clamping
Chouker *et al.*[23]	2004	75	Intermittent ($n = 25$) and continuous ($n = 25$)
Capussotti *et al.*[20]	2006	126	Intermittent clamping

Portal triad clamping: continuous vs. intermittent

Two RCTs compared continuous and intermittent portal trial clamping in patients who underwent liver resection (Table 2).[19,31] In both studies, intermittent clamping consisted of repeated periods of 15 min of ischaemia followed by 5-min reperfusion episodes. In the trial by Capussotti *et al.*[31] all patients suffered from liver cirrhosis. Belghiti *et al.*[19] demonstrated that blood loss during liver resection was significantly higher in the intermittent clamping group. Post-operative transaminase levels were significantly higher in the continuous portal triad clamping group than in intermittent portal triad clamping group when livers with chronic liver disease were included. Post-operative bilirubin levels were also significantly higher in the continuous portal triad clamping group than in the intermittent portal triad clamping group when cirrhotic livers were included in the analysis. Thus it appears that livers with chronic disease do not tolerate continuous vascular clamping as well as normal livers. It must be noted that the other trial which included only cirrhotic livers did not find any significant difference in terms of blood loss, post-operative liver function tests and post-operative morbidity.[31] The Cochrane meta-analysis pooled the patients from the last two RCTs.[29] Although blood loss during transection was significantly less in the continuous clamping group compared with the intermittent clamping group, there was no significant difference in the total operative blood loss and transfusion between both groups. Considering that intermittent portal triad clamping does not increase the total blood loss, the operating time and the predisposition of the cirrhotic and steatotic livers

Table 2 Randomized controlled trials comparing intermittent and continuous portal triad clamping

Author	Year	No patients	Intermittent clamping
Belghiti *et al.*[19]	1999	86	15 min/5 min
Capussotti *et al.*[31]	2003	35	15 min/5 min (Cirrhotic liver)

to ischaemic injury, intermittent clamping seems to be better than continuous clamping at least in patients with chronic liver disease.

As the optimal ischaemic time during intermittent clamping remains controversial, Esaki *et al.* conducted a RCT comparing the short-term outcome of hepatectomy using intermittent clamping with an ischaemic interval of 15 vs. 30 min, the duration of reperfusion being 5 min. There was no significant difference in the morbidity, blood loss, transfusion requirements, liver function tests, or hospital stay between the groups. The operating time was lower in the 30-min group.

Ischaemic preconditioning

In the mid 80s, Murry *et al.*observed that brief periods of coronary occlusion followed by a short reperfusion before prolonged ischaemia led to a reduced size of myocardial infarct. This manipulation, hence termed ischaemic preconditioning, increased the heart's tolerance to reperfusion injury after prolonged periods of ischaemia. While the liver is prone to ischaemic injury when the Pringle manoeuver is applied, the incentive to investigate similar preconditioning was obvious. A common protocol in the liver consists of 10 min of ischaemia followed by 10 min of reperfusion.[33]

Clavien *et al.*[34] performed the first study in the human liver. A twofold reduction of post-operative serum transaminases was registered. A reduction of apoptotic cells corroborated this finding. Patients with mild to moderate steatosis with less tolerance to ischaemic injury seemed to have even an increased effect. These findings were reproduced in a prospective randomized setting.[22] Additionally, the authors noted that the effect was lost in patients older than 60 years of age whereas maximal in young patients. In patients with liver steatosis, and upon inflow occlusion for >40 min, ischaemic preconditioning demonstrated a particularly strong protective effect. A RCT by Chouker *et al.*[23] comparing ischaemic preconditioning vs. continuous clamping, showed improved cardiovascular stability by lowering the need for catecholamines after liver reperfusion. In contrast, a third RCT by Azoulay *et al.*[35] included 30 individuals in each group but did not confirm a beneficial effect of ischaemic preconditioning. The authors found no differences in post-operative serum transaminase levels and post-operative morbidity (Table 3). Additionally, a recent Cochrane analysis observed no statistically significant difference in the mortality, liver failure, blood loss, or haemodynamic changes.[29] However, intensive care unit stay and hospital stay were significantly lower in the ischaemic preconditioning group.

Ischaemic preconditioning was also compared with intermittent clamping (Table 4). A RCT by Petrowsky *et al.*[36] showed that these two protective approaches appear to be equally effective against liver injury. Furthermore, is that in this study, ischaemic preconditioning was associated with lower blood loss, lower transfusion amount and shorter transection time. Another study confirmed the equality of the two techniques; however, markers of apoptosis were increased in the preconditioning group if ischaemia exceeded 40 min.[37]

The benefit of ischaemic preconditioning in liver transplantation is ambiguous.[38] Several studies found reduced post-operative serum transaminase levels and a reduction of cell death markers and inflammatory infiltrates.[39–42] However, most studies do not show a benefit for patient or graft survival.[43] In contrast, one study showed a paradoxical increase in reperfusion injury.[44] The recent meta-analysis by Gurusamy *et al.*[45] found no statistically significant difference in mortality, delayed graft function, or primary graft non-function. Currently, no evidence exists to support or refute ischaemic preconditioning in liver transplantation.

Pharmacological preconditioning

Pharmacological preconditioning is a promising field, as a variety of substances proved to be effect in animal experiments. However, very few concepts have made the transition to the human.

In a recent RCT, 64 patients undergoing liver surgery with inflow occlusion were randomized to 30 min of intra-operative preconditioning with sevoflurane or anaesthesia with propofol.[25] Thirty minutes before inflow occlusion, propofol was replaced by sevoflurane in the preconditioning group. Preconditioning with sevoflurane significantly reduced post-operative aspartate aminotransferase (AST) and alanine transaminase (ALT) levels. Furthermore, the overall incidence of postoperative complications and the number of major events was reduced. This beneficial effect was stronger in patients with hepatic steatosis. A potential mechanism may involve the upregulation of iNOS (inducible nitric oxide synthase), as this enzyme was significantly increased in the group with sevoflurane.

Table 3 Randomized controlled trials comparing ischaemic preconditioning vs. continuous clamping

Author	Year	No patients	Ischaemic preconditioning
Clavien *et al.*[22]	2003	100	10 min/10 min/continuous
Chouker *et al.*[23]	2004	75	10 min/10 min/continuous
Azoulay *et al.*[35]	2006	60	10 min/10 min/vascular exclusion of the liver preserving caval flow

Table 4 Randomized controlled trials comparing ischaemic preconditioning with intermittent clamping

Author	Year	No patients	Clamping
Petrowsky *et al.*[36]	2006	73	IPC: 10 min/10 min/continuous vs. intermittent: 15 min/5 min
Smyrniotis *et al.*[37]	2006	54	IPC: 10 min/10 min/continuous vs. intermittent: 15 min/5 min

IPC, ischaemic preconditioning.

Another RCT in the transplantation setting from Lang and colleagues[46] supports this hypothesis. During liver transplantation, patients were randomized to receive a volatile, high but non-toxic dose of nitric oxide (80 ppm). Inhaled nitric oxide significantly decreased the length of hospital stay, improved serum transaminase levels and coagulation times, and reduced the number of apoptotic hepatocytes.

A small number of clinical trials have addressed other substances, involved in different mechanisms of hepatic reperfusion injury.

The synthetic protease inhibitor gabexate mesilate was evaluated in randomized patients undergoing liver surgery.[47] Intravenous administration prior to surgery decreased markers of hepatic injury, serum transaminases and suppressed plasmatic interleukin-6 levels. A similar effect was shown in a clinical trial, analysing the effect of pre-operative administration of 500 mg of methylprednisolone.[48] During resection, intra-operative preconditioning with 600 mg of alpha-lipoic acid also reduced markers of hepatic damage by inflow occlusion.[49]

Again in the transplant setting, administration of 250 mg of methylprednisolone prior to organ harvesting significantly ameliorated ischemia/reperfusion injury and lowered the incidence of acute rejection.[50] Systemic administration of the pan-caspase inhibitor IDN6556 reduced post-operative serum transaminase levels.[51] In another study, systemic pre-operative administration of thymoglobulin decreased ischaemia/reperfusion injury after orthotopic liver transplantation.[52]

Conclusions and recommendations

The armamentarium of liver surgeons should contain the regular vascular clamping methods to reduce blood loss during complex liver resection or to prevent massive haemorrhage in cases of accidental injury to major vessels during mobilization of the liver or during parenchymal transection. Nowadays, thanks to better knowledge of surgical liver anatomy, to refinements in surgical techniques and to maintenance of a low CVP during parenchymal transection, vascular clamping cannot be systematically recommended (level A). When used, portal triad clamping is associated with a tendency towards reduced blood loss and blood transfusion without impact on morbidity (level A). Among the different methods of vascular occlusion, intermittent clamping appears to be better tolerated especially in patients with chronic liver disease (level A). Ischaemic preconditioning before continuous portal triad clamping reduces reperfusion injury after warm ischaemia, particularly in steatotic patients (level A). Clinically, ischaemic preconditioning and intermittent clamping are equally effective but in cases of complex liver resection, where the clamping time could be long, intermittent clamping must be preferred (level A). Ischaemic preconditioning has unclear effects in transplantation and there is currently no evidence to support or refute the use of ischaemic preconditioning in donor liver retrievals. There are increasing alternative conditioning strategies, including the use of volatile anesthetics, which may provide new and easily applicable therapeutic options to protect the liver.

Conflicts of interest

None declared.

References

1. Belghiti J, Hiramatsu K, Benoist S, Massault P, Sauvanet A, Farges O. (2000) Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. *J Am Coll Surg* 191:38–46.
2. Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S *et al.* (2002) Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. *Ann Surg* 236:397–406.
3. Poon RT, Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK *et al.* (2004) Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1222 consecutive patients from a prospective database. *Ann Surg* 240:698–708.
4. Clavien PA. (1999) *Malignant Liver Tumor: Current and Emerging Therapies*. Malden: Blackwell Science.
5. Cunningham JD, Fong Y, Shriver C, Melendez J, Marx WL, Blumgart LH. (1994) One hundred consecutive hepatic resections. Blood loss, transfusion, and operative technique. *Arch Surg* 129:1050–1056.
6. Sitzmann JV, Greene PS. (1994) Perioperative predictors of morbidity following hepatic resection for neoplasm. A multivariate analysis of a single surgeon experience with 105 patients. *Ann Surg* 219:13–17.
7. Kooby DA, Stockman J, Ben-Porat L, Gonen M, Jarnagin WR, Dematteo RP *et al.* (2003) Influence of transfusions on perioperative and long-term outcome in patients following hepatic resection for colorectal metastases. *Ann Surg* 237:860–869; discussion 9–70.
8. Yamamoto J, Kosuge T, Takayama T, Shimada K, Yamasaki S, Ozaki H *et al.* (1994) Perioperative blood transfusion promotes recurrence of hepatocellular carcinoma after hepatectomy. *Surgery* 115:303–309.
9. Tsao JI, Loftus JP, Nagorney DM, Adson MA, Ilstrup DM. (1994) Trends in morbidity and mortality of hepatic resection for malignancy. A matched comparative analysis. *Ann Surg* 220:199–205.
10. Pringle J. (1908) Notes on the arrest of hepatic hemorrhage due to traumat. *Ann Surg* 48:541.
11. Huguet C, Gavelli A, Chieco PA, Bona S, Harb J, Joseph JM *et al.* (1992) Liver ischemia for hepatic resection: where is the limit? *Surgery* 111:251–259.
12. Huguet C, Gavelli A, Bona S. (1994) Hepatic resection with ischemia of the liver exceeding one hour. *J Am Coll Surg* 178:454–458.
13. Kimura F, Miyazaki M, Suwa T, Sugiura T, Shinoda T, Itoh H *et al.* (2002) Evaluation of total hepatic vascular exclusion and pringle maneuver in liver resection. *Hepatogastroenterology* 49:225–230.
14. Abdalla EK, Noun R, Belghiti J. (2004) Hepatic vascular occlusion: which technique? *Surg Clin North Am* 84:563–585.
15. Melendez JA, Arslan V, Fischer ME, Wuest D, Jarnagin WR, Fong Y *et al.* (1998) Perioperative outcomes of major hepatic resections under low central venous pressure anesthesia: blood loss, blood transfusion, and the risk of postoperative renal dysfunction. *J Am Coll Surg* 187:620–625.

16. Bhattacharya S, Jackson DJ, Beard CI, Davidson BR. (1999) Central venous pressure and its effects on blood loss during liver resection. *Br J Surg* 86:282–283.
17. Makuuchi M, Mori T, Gunven P, Yamazaki S, Hasegawa H. (1987) Safety of hemihepatic vascular occlusion during resection of the liver. *Surg Gynecol Obstet* 164:155–158.
18. Ezaki T, Seo Y, Tomoda H, Furusawa M, Kanematsu T, Sugimachi K. (1992) Partial hepatic resection under intermittent hepatic inflow occlusion in patients with chronic liver disease. *Br J Surg* 79:224–226.
19. Belghiti J, Noun R, Malafosse R, Jagot P, Sauvanet A, Pierangeli F *et al.* (1999) Continuous versus intermittent portal triad clamping for liver resection: a controlled study. *Ann Surg* 229:369–375.
20. Capussotti L, Muratore A, Ferrero A, Massucco P, Ribero D, Polastri R. (2006) Randomized clinical trial of liver resection with and without hepatic pedicle clamping. *Br J Surg* 93:685–689.
21. Franco D, Smadja C, Meakins JL, Wu A, Berthoux L, Grange D. (1989) Improved early results of elective hepatic resection for liver tumors. One hundred consecutive hepatectomies in cirrhotic and noncirrhotic patients. *Arch Surg* 124:1033–1037.
22. Clavien PA, Selzner M, Rudiger HA, Graf R, Kadry Z, Rousson V *et al.* (2003) A prospective randomized study in 100 consecutive patients undergoing major liver resection with versus without ischemic preconditioning. *Ann Surg* 238:843–850.
23. Chouker A, Schachtner T, Schauer R, Dugas M, Lohe F, Martignoni A *et al.* (2004) Effects of Pringle manoeuvre and ischaemic preconditioning on haemodynamic stability in patients undergoing elective hepatectomy: a randomized trial. *Br J Anaesth* 93:204–211.
24. Schmidt R, Tritschler E, Hoetzel A, Loop T, Humar M, Halverscheid L *et al.* (2007) Heme oxygenase-1 induction by the clinically used anesthetic isoflurane protects rat livers from ischemia/reperfusion injury. *Ann Surg* 245:931–942.
25. Beck-Schimmer B, Breitenstein S, Urech S, De Conno E, Wittlinger M, Puhan M *et al.* (2008) A randomized controlled trial on pharmacological preconditioning in liver surgery using a volatile anesthetic. *Ann Surg* 248:909–918.
26. Sackett DL, Straus SH, Richardson WS, Rosenberg W, Haynes RB. (2000) *Evidence-Based Medicine. How to Practice and Teach EBM*, 2nd edn. Edinburgh: Churchill Livingstone.
27. Man K, Fan ST, Ng IO, Lo CM, Liu CL, Wong J. (1997) Prospective evaluation of Pringle maneuver in hepatectomy for liver tumors by a randomized study. *Ann Surg* 226:704–711.
28. Man K, Lo CM, Liu CL, Zhang ZW, Lee TK, Ng IO *et al.* (2003) Effects of the intermittent Pringle manoeuvre on hepatic gene expression and ultrastructure in a randomized clinical study. *Br J Surg* 90:183–189.
29. Gurusamy KS, Kumar Y, Sharma D, Davidson BR. (2007) Methods of vascular occlusion for elective liver resections. *Cochrane Database Syst Rev* 4:CD006409.
30. Rahbari NN, Wente MN, Schemmer P, Diener MK, Hoffmann K, Motschall E *et al.* (2008) Systematic review and meta-analysis of the effect of portal triad clamping on outcome after hepatic resection. *Br J Surg* 95:424–432.
31. Capussotti L, Nuzzo G, Polastri R, Giuliante F, Muratore A, Giovannini I. (2003) Continuous versus intermittent portal triad clamping during hepatectomy in cirrhosis. Results of a prospective, randomized clinical trial. *Hepatogastroenterology* 50:1073–1077.
32. Murry CE, Jennings RB, Reimer KA. (1986) Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 74:1124–1136.
33. Yadav SS, Sindram D, Perry DK, Clavien PA. (1999) Ischemic preconditioning protects the mouse liver by inhibition of apoptosis through a caspase-dependent pathway. *Hepatology* 30:1223–1231.
34. Clavien PA, Yadav S, Sindram D, Bentley RC. (2000) Protective effects of ischemic preconditioning for liver resection performed under inflow occlusion in humans. *Ann Surg* 232:155–162.
35. Azoulay D, Lucidi V, Andreani P, Maggi U, Sebagh M, Ichai P *et al.* (2006) Ischemic preconditioning for major liver resection under vascular exclusion of the liver preserving the caval flow: a randomized prospective study. *J Am Coll Surg* 202:203–211.
36. Petrowsky H, McCormack L, Trujillo M, Selzner M, Jochum W, Clavien PA. (2006) A prospective, randomized, controlled trial comparing intermittent portal triad clamping versus ischemic preconditioning with continuous clamping for major liver resection. *Ann Surg* 244:921–928.
37. Smyrniotis V, Theodoraki K, Arkadopoulos N, Fragulidis G, Condi-Pafiti A, Plemenou-Fragou M *et al.* (2006) Ischemic preconditioning versus intermittent vascular occlusion in liver resections performed under selective vascular exclusion: a prospective randomized study. *Am J Surg* 192:669–674.
38. DeOliveira ML, Graf R, Clavien PA. (2008) Ischemic preconditioning: promises from the laboratory to patients–sustained or disillusioned? *Am J Transplant* 8:489–491.
39. Azoulay D, Del Gaudio M, Andreani P, Ichai P, Sebag M, Adam R *et al.* (2005) Effects of 10 minutes of ischemic preconditioning of the cadaveric liver on the graft's preservation and function: the ying and the yang. *Ann Surg* 242:133–139.
40. Cescon M, Grazi GL, Grassi A, Ravaioli M, Vetrone G, Ercolani G *et al.* (2006) Effect of ischemic preconditioning in whole liver transplantation from deceased donors. A pilot study. *Liver Transpl* 12:628–635.
41. Jassem W, Fuggle SV, Cerundolo L, Heaton ND, Rela M. (2006) Ischemic preconditioning of cadaver donor livers protects allografts following transplantation. *Transplantation* 81:169–174.
42. Amador A, Grande L, Marti J, Deulofeu R, Miquel R, Sola A *et al.* (2007) Ischemic pre-conditioning in deceased donor liver transplantation: a prospective randomized clinical trial. *Am J Transplant* 7:2180–2189.
43. Koneru B, Fisher A, He Y, Klein KM, Skurnick J, Wilson DJ *et al.* (2005) Ischemic preconditioning in deceased donor liver transplantation: a prospective randomized clinical trial of safety and efficacy. *Liver Transpl* 11:196–202.
44. Koneru B, Shareef A, Dikdan G, Desai K, Klein KM, Peng B *et al.* (2007) The ischemic preconditioning paradox in deceased donor liver transplantation-evidence from a prospective randomized single blind clinical trial. *Am J Transplant* 7:2788–2796.
45. Gurusamy KS, Kumar Y, Sharma D, Davidson BR. (2008) Ischaemic preconditioning for liver transplantation. *Cochrane Database Syst Rev* 1:CD006315.
46. Lang JD Jr, Teng X, Chumley P, Crawford JH, Isbell TS, Chacko BK *et al.* (2007) Inhaled NO accelerates restoration of liver function in adults following orthotopic liver transplantation. *J Clin Invest* 117:2583–2591.
47. Kim YI, Hwang YJ, Song KE, Yun YK, Lee JW, Chun BY. (2002) Hepatocyte protection by a protease inhibitor against ischemia/reperfusion injury of human liver. *J Am Coll Surg* 195:41–50.
48. Aldrighetti L, Pulitano C, Arru M, Finazzi R, Catena M, Soldini L *et al.* (2006) Impact of preoperative steroids administration on ischemia-reperfusion injury and systemic responses in liver surgery: a prospective randomized study. *Liver Transpl* 12:941–949.

49. Dunschede F, Erbes K, Kircher A, Westermann S, Seifert J, Schad A *et al.* (2006) Reduction of ischemia reperfusion injury after liver resection and hepatic inflow occlusion by alpha-lipoic acid in humans. *World J Gastroenterol* 12:6812–6817.

50. Kotsch K, Ulrich F, Reutzel-Selke A, Pascher A, Faber W, Warnick P *et al.* (2008) Methylprednisolone therapy in deceased donors reduces inflammation in the donor liver and improves outcome after liver transplantation: a prospective randomized controlled trial. *Ann Surg* 248:1042–1050.

51. Baskin-Bey ES, Washburn K, Feng S, Oltersdorf T, Shapiro D, Huyghe M *et al.* (2007) Clinical trial of the pan-caspase inhibitor, IDN-6556, in human liver preservation injury. *Am J Transplant* 7:218–225.

52. Bogetti D, Sankary HN, Jarzembowski TM, Manzelli A, Knight PS, Thielke J *et al.* (2005) Thymoglobulin induction protects liver allografts from ischemia/reperfusion injury. *Clin Transpl* 19:507–511.