A network meta-analysis comparing perioperative outcomes of interventions aiming to decrease ischemia reperfusion injury during elective liver resection

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ABSTRACT

Objective: To compare the perioperative outcomes of interventions aiming to decrease ischemia-reperfusion (IR) injury during elective liver resection.

Method: A comprehensive literature search was performed to identify randomized controlled trials. A Bayesian network meta-analysis was performed using the Markov chain Monte Carlo method in WinBUGS following the guidelines of The National Institute for Health and Clinical Excellence Decision Support Unit. Odds ratios for binary outcomes and mean differences for continuous outcomes were calculated using fixed-effect model or random-effects model according to model-fit.

Results: Forty four trials with 2457 patients undergone liver resection were included, and were divided into eight classes of interventions aimed at decreasing IR injury and a control group which was surgery alone. There was no significant difference between the different interventions in mortality, quantity of blood transfusion, and Intensive Therapy Unit stay between any pairwise comparison. Patients treated with ischemic preconditioning, cardiovascular modulators, and miscellaneous interventions had significantly fewer serious adverse events compared to patients receiving surgery alone. Ischemic preconditioning patients had significantly fewer transfusion proportions and shorter operative time than patients treated with steroids. Ischemic preconditioning had significantly lower operative blood loss compared to all other interventions, and shorter length of hospital stay than surgery alone. Sensitivity analysis showed that the drugs sevoflurane (a volatile anesthetic), verapamil (a calcium channel blocker), and gabexate mesilate (a thrombin inhibitor) produced fewer serious adverse events compared to surgery alone.

Conclusion: Ischemic preconditioning resulted in multiple beneficial clinical end points and further RCTs are needed to confirm its clinical benefits.

INTRODUCTION

Control of the hepatic blood flow has allowed major hepatectomies to be carried out with decreased blood loss but it has done so at the expense of liver damage from ischemic-reperfusion (IR) injury. IR injury is initiated by reactive oxygen species which cause direct apoptotic and necrotic cell death of hepatocytes and sinusoidal endothelial cells (SEC)[1, 2]. A cascade of molecular mediators is activated leading to microvascular and acute inflammatory changes. Platelet plugging, reduced nitric oxide (NO), and vasoconstrictors lead to sinusoidal perfusion failure[1, 2]. Proinflammatory cytokines produced by Kupffer cells result in T-cell and neutrophil activation and transmigration, resulting in more necrosis and/or apoptosis of SEC and hepatocytes[1, 2].

IR injury results in elevated liver enzymes and increased postoperative morbidity[2-6]. Patients with cirrhotic or steatotic liver are more sensitive to IR injury than patients with normal liver[3, 6]. Many interventions have been used to decrease IR injury [3, 7-22] and previous standard pairwise meta-analyses comparing these interventions[23-25] were limited by the fact that indirect comparisons between interventions could not be performed. The aim of this network meta-analysis is to combine direct and indirect evidence across trials in order to compare perioperative outcomes of different interventions aimed at decreasing IR injury during elective hepatectomy.

METHODS

Search strategy

A comprehensive literature search was performed of the following databases: MEDLINE, EMBASE, Science Citation Index Expanded, Cochrane Central Register of Controlled Trials (CENTRAL). Detailed search strategy is provided in Supplementary Table 1. No restrictions were made based on language, publication year, or publication status. Only randomized controlled trials (RCTs) were considered for inclusion.

Outcomes of interest

Primary outcomes

- Mortality
- Serious adverse events, defined as any event that is life-threatening, requires inpatient hospitalization, results in a single organ failure (e.g. liver failure) or multi-organ failure, or requires surgical, endoscopic or radiological intervention to treat it. Serious adverse events correspond to Grade III or above of the Clavien-Dindo classification[26, 27].

Secondary outcomes

- Proportion of patients requiring blood transfusion
- Mean quantity of units of blood transfusion
- Mean operative blood loss in milliliters
- Mean length of hospital stay in days
- Mean length of intensive therapy unit (ITU) stay in days
- Mean operative time in minutes

Data collection

The following data were independently extracted by two review authors from each study: first author, year of publication, country, inclusion and exclusion criteria, participant characteristics, number of participants with liver cirrhosis or liver steatosis, major or minor liver resections performed, study design, and outcomes of interest described above. The risk of bias of the included trials was assessed based on the following bias risk domains: allocation sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and vested interest bias. For each of these risk domains of bias the studies were categorized as low risk, uncertain risk, and high risk of bias.

Statistical analysis

For binary outcomes the odds ratio (OR) was calculated, and for continuous outcomes the mean difference (MD) was calculated. For each outcome of interest, Stata/IC 11 (StataCorp LP) was used to draw a network plot of all the interventions assessed for that specific outcome. Any interventions that were not connected to the other interventions through the network plot were excluded from the analysis of that outcome. A Bayesian network meta-analysis was conducted using the Markov chain Monte Carlo method in WinBUGS 1.4. The treatment contrast (OR for binary outcomes, MD for continuous outcomes) for any two interventions was modelled as a function of comparisons between each individual intervention and an arbitrarily selected reference group[28]. The reference group was selected to be the surgery alone group.

The residual deviance and Deviance Information Criteria (DIC) were used for assessing between study heterogeneity as per the guidance from the National Institute for Health and Clinical Excellence (NICE) Decision Support Unit (DSU) documents[29]. Three different models were run for each outcome: fixed-effect model, random-effects model, and random-effects inconsistency model. The choice of the model was based on the model fit, and a lower DIC indicated a better model fit[29]. Evidence of inconsistency between direct and indirect comparisons was assessed by examining the geometry of the network diagrams and by comparing the deviance and DIC statistics of the consistency and inconsistency models[30]. The probability of ranking of an intervention for each outcome of interest was calculated.

RESULTS

Eligible studies

A total of 522 references were identified through electronic searches of CENTRAL (n=60), MEDLINE (n=154), EMBASE (n=119), and Science Citation Index Expanded (n=189). Five more references were identified for further assessment through scanning reference lists. The study flow diagram is shown in Figure 1. After reviewing 75 full-text articles, 31 references were excluded. Forty four RCTs met the inclusion criteria[3, 7-21, 31-58] reporting on 2457 participants. The characteristics of the included trials are shown in Table 1. The risk of bias of the trials is shown in Supplementary Figure 1.

Overall network meta-analysis

An overall network meta-analysis was performed to compare eight classes of active interventions aimed at decreasing IR injury along with a control group which was surgery alone. The classes of intervention were grouped based on their mechanism of action: hypothermia, ischemic preconditioning, antioxidants, immunomodulators, cardiovascular modulators, steroids, treatments that increase hepatic glycogen, and miscellaneous therapies (Table 2). Statistically significant results are shown in Table 3. The classes of interventions with the highest probability of ranking from best to worst for the outcomes of interest are summarized in Table 4.

Mortality

The fixed-effect model was preferred for this outcome based on the DIC statistics, and there was no evidence of inconsistency in the networks. The pairwise odds ratios of the different treatment comparisons identified no significant difference in mortality between the different groups. The network plot for mortality is shown in Figure 2.

Serious adverse events

The fixed-effect model was used and there was no evidence of inconsistency. Significantly fewer serious adverse events were found in the ischemic preconditioning and cardiovascular modulators groups compared to surgery alone. There were significantly fewer serious adverse events in the miscellaneous group compared to surgery alone, ischemic preconditioning, immunomodulators, and steroids. There was no significant difference in the other comparisons.

Proportion of patients transfused

The fixed-effect model was preferred and there was no evidence of inconsistency. Pairwise comparison of the interventions showed that significantly fewer people were transfused with ischemic preconditioning compared to steroids. There was no significant difference in the other comparisons.

Quantity of blood transfusion per patient

The random-effects model was used and there was no evidence of inconsistency. No evidence of any significant difference in quantity of blood transfusion per patient between the different interventions was found.

Operative blood loss

The fixed-effect model was used and there was no evidence of inconsistency. The pairwise mean differences of the different group comparisons showed that ischemic preconditioning had significantly lower operative blood loss compared to all other groups and ranked best treatment with 99.7% probability. The surgery alone group had significantly lower operative blood loss compared to all other groups except ischemic preconditioning. The steroids and increased hepatic glycogen groups were found to have significantly lower operative blood loss compared to the hypothermia, immunomodulators, and miscellaneous groups.

Length of hospital stay

The random-effects model was preferred and there was no evidence of inconsistency. The pairwise comparison of the interventions showed ischemic preconditioning to have significantly shorter length of hospital stay compared to surgery alone by 2.3 days. There was no significant difference in the other comparisons.

ITU stay

The random-effects model was preferred and there was no evidence of inconsistency. Pairwise comparison of the groups showed no evidence of any significant difference in the ITU stay.

Operative time

The fixed-effect model was used and there was no evidence of inconsistency. The pairwise mean differences of the different treatments showed ischemic preconditioning and increased hepatic glycogen to have significantly shorter operative time compared to steroids by 17 and 26 minutes respectively. There was no significant difference in the operating time between the other comparisons.

Sensitivity network meta-analysis – individual interventions

A sensitivity network meta-analysis was performed to compare all the individual interventions included in each class of interventions aimed at decreasing IR injury. No significant difference was found in mortality, quantity of blood transfusion per patient, and ITU stay, between the different interventions. Ischemic preconditioning, sevoflurane, verapamil, and gabexate mesilate had significantly fewer serious adverse events compared to surgery alone. Fewer people were transfused with ischemic preconditioning compared to steroids.

Ischemic preconditioning was found to have significantly lower operative blood loss compared to surgery alone. Ischemic preconditioning and surgery alone had lower operative blood loss compared to hypothermia, prostaglandin E1, steroids, verapamil, S-adenosyl-L-methionine, insulin, branched chain aminoacids, gabexate mesilate, and melatonin. Ischemic preconditioning was found to have significantly shorter length of hospital stay compared to surgery alone. Furthermore, ischemic preconditioning and pre-storing hepatocellular glycogen were found to have significantly shorter operative time compared to steroids.

Sensitivity network meta-analysis – larger groups

A network meta-analysis was performed to compare the following 4 larger groups: surgery alone, hypothermia, ischemic preconditioning, and all pharmacological interventions. There was no significant difference in mortality, proportion of patients transfused, quantity of blood transfusion per patient, ITU stay, and operative time, between the 4 groups. Ischemic preconditioning and pharmacological interventions were found to have significantly fewer serious adverse events compared to surgery alone.

Ischemic preconditioning had a high probability (87%) of being the best treatment for operating time. Ischemic preconditioning had significantly lower operative blood loss compared to surgery alone, hypothermia, and pharmacological interventions, and was confirmed best treatment for operative blood loss with 100% probability. Surgery alone had significantly lower operative blood loss compared to hypothermia and pharmacological interventions. Moreover, ischemic preconditioning and pharmacological interventions resulted in significantly shorter hospital stay compared to surgery alone.

Metaregression – cirrhotic livers

A metaregression was performed based on the percentage of cirrhotic livers included in each trial. No significant difference was identified between the classes of interventions with regards to mortality, proportion of patients transfused, quantity of blood transfused per patient, operating time, hospital stay, and ITU stay. The ischemic preconditioning, antioxidants, and miscellaneous groups had significantly fewer serious adverse events compared to the surgery

alone group. The surgery alone, ischemic preconditioning, steroids, and increased hepatic glycogen groups resulted in significantly lower operative blood loss compared to the immunomodulators and miscellaneous groups of interventions. In addition, ischemic preconditioning had significantly lower operative blood loss compared to surgery alone.

Metaregression – major liver resections

A metaregression was performed based on the percentage of major liver resections performed in each trial. Major liver resection was defined as a right or left hemihepatectomy, or extended hemihepatectomy, or resection of three or more liver segments according to Couinaud[59]. No significant difference was identified between the classes of interventions with regards to mortality, operating time, and ITU stay. Regarding serious adverse events, ischemic preconditioning, cardiovascular modulators, and miscellaneous classes of interventions resulted in significantly fewer serious adverse events compared to surgery alone. Ischemic preconditioning had significantly lower operative blood loss compared to the surgery alone, immunomodulators, cardiovascular modulators, steroids, and increased hepatic glycogen groups. Finally, ischemic preconditioning resulted in significantly shorter length of hospital stay and fewer patients needing blood transfusion compared to surgery alone.

DISCUSSION

This network meta-analysis identified three groups of interventions – ischemic preconditioning, cardiovascular modulators, miscellaneous group – which resulted in fewer serious adverse events compared to the surgery alone group. Although there was a high probability that the miscellaneous group of interventions was best for reducing serious adverse events (74% chance), sensitivity analysis performed showed none of the individual interventions within the miscellaneous group to have high probability of being the best treatment for this outcome. Overall, no individual intervention had a probability higher than 40% of being best treatment for serious adverse events. Although sevoflurane, verapamil, and gabexate mesilate were found to have fewer serious adverse events during sensitivity analysis, none of these treatments significantly reduced ITU or hospital stay, which would be anticipated if an intervention made a significant reduction in serious adverse events. On the other hand, ischemic preconditioning, which resulted in fewer serious adverse events, showed multiple additional clinical benefits including shorter hospital stay, shorter operative time, and decreased blood loss.

The decreased operative time is perhaps counter-intuitive as ischemic preconditioning is an additional operative manoeuver. However, ischemic preconditioning may decrease operative time by decreasing the time taken for parenchymal transection because of reduced blood loss during surgery, facilitating subsequent operative manoeuvers such as parenchymal dissection, and by shortening the time necessary for hemostasis[35, 60]. Blood loss is one of the most important factors affecting the peri-operative outcomes of patients undergoing liver resection[61-63]. This study showed that ischemic preconditioning had significantly lower operative blood loss compared to the surgery alone group and compared to all other interventions, and it had a high probability of being the best treatment for this outcome.

Another important finding was that the surgery alone group had significantly lower operative blood loss compared to all other interventions, except the ischemic preconditioning group. Therefore, not only was ischemic preconditioning the only intervention to significantly reduce blood loss, but also all other interventions resulted in significantly higher operative blood loss compared to the surgery alone group. A possible explanation in the increase in operative blood loss by the other interventions is that by increasing the microvascular flow and perfusion of the

liver in order to decrease IR injury, they result in increased overall blood flow and blood loss during hepatectomy. This apparent disadvantage in increasing blood loss of all other interventions except ischemic preconditioning should be weighed against any apparent benefit of these interventions, e.g. in reducing serious adverse events.

Trials in the literature demonstrated the beneficial effects of ischemic preconditioning on liver resection surgery in patients with background healthy livers, as well as those with background cirrhotic or steatotic livers, by showing a decrease in postoperative liver enzymes which are markers for liver parenchymal injury[3, 12, 13, 43, 64]. Although liver parenchymal injury is associated with derangements in the liver function tests (LFTs), this network meta-analysis did not assess LFTs due to significant variation between the included trials in the way LFTs were assessed. In particular, LFTs were reported at different time intervals, different methods of measurement were used between trials, and different measurement scales were reported. Perioperative outcomes, including adverse events, are thought to be clinically more relevant and were compared in this study.

In all the trials included in this review where ischemic preconditioning was used to decrease IR injury, ischemic preconditioning was performed with liver vascular inflow occlusion (Pringle manoeuver). Nevertheless, there was variability between trials in the timing of ischemic preconditioning and the type of vascular occlusion performed during liver resection. In some trials, ischemic preconditioning was performed with 10 minutes of vascular inflow occlusion and 10 minutes of reperfusion[3, 12, 13, 49, 53], whereas in other trials ischemic preconditioning was performed with 5 minutes of vascular inflow occlusion and 5 minutes of reperfusion[36, 43, 44]. Furthermore, in some trials ischemic preconditioning was followed by vascular inflow occlusion[12, 13, 35, 46, 49], whereas in other trials it was followed by selective hepatic vascular exclusion[8, 9, 53]. The downside of this is that it does not allow for the optimal ischemic preconditioning protocol to be determined accurately, or even whether some protocols were ineffective.

Other possible sources of bias in this network meta-analysis are the proportion of cirrhotic and steatotic livers included in each trial, and the proportion of patients undergoing major liver resections. Therefore, metaregressions were performed based on the proportion of cirrhotic livers included and the proportion of major liver resections performed in each trial. Unfortunately, due to the low number of trials (7 trials out of 44) reporting on the number of

steatotic livers included, a metaregression based on the proportion of steatotic livers was not possible. The results of the metaregression analyses based on cirrhotic livers and major resections were similar to the overall network meta-analysis, showing no significant differences between interventions with regards to mortality, proportion of patients transfused, operating time, and ITU stay. Metaregression analysis confirmed the benefits of ischemic preconditioning with regards to fewer serious adverse events and lower operative blood loss. Additionally, the metaregression based on the proportion of major liver resections suggested that ischemic preconditioning results in fewer patients needing blood transfusion and shorter length of hospital stay.

The results of this network meta-analysis agree with the results of previous standard pairwise meta-analyses, and would suggest multiple beneficial clinical end points to ischemic preconditioning treatment, including reduced blood transfusion requirements and shorter operative time, and no significant difference in other perioperative outcomes, such as mortality, hospital stay, or ITU stay[25, 60, 65]. The previous standard pairwise meta-analyses[25, 65] did not demonstrate a significant decrease in serious adverse events or operative blood loss with ischemic preconditioning as in this network meta-analysis, possibly due to a lower number of participants or RCTs included. Through indirect comparisons, a network meta-analysis allows more RCTs to be included in the analysis and more comparisons to be made between interventions that have not been previously evaluated directly against each other. Ischemic preconditioning, which can be achieved without any requirement for equipment, costs, or additional expertise, demonstrated a high likelihood of being beneficial to the patients undergoing liver resection. Further RCTs are needed to confirm clinical benefit in order to allow ischemic preconditioning to become standard practice during liver resection.

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FIGURES AND TABLES

Figure 1: Study flow diagram.

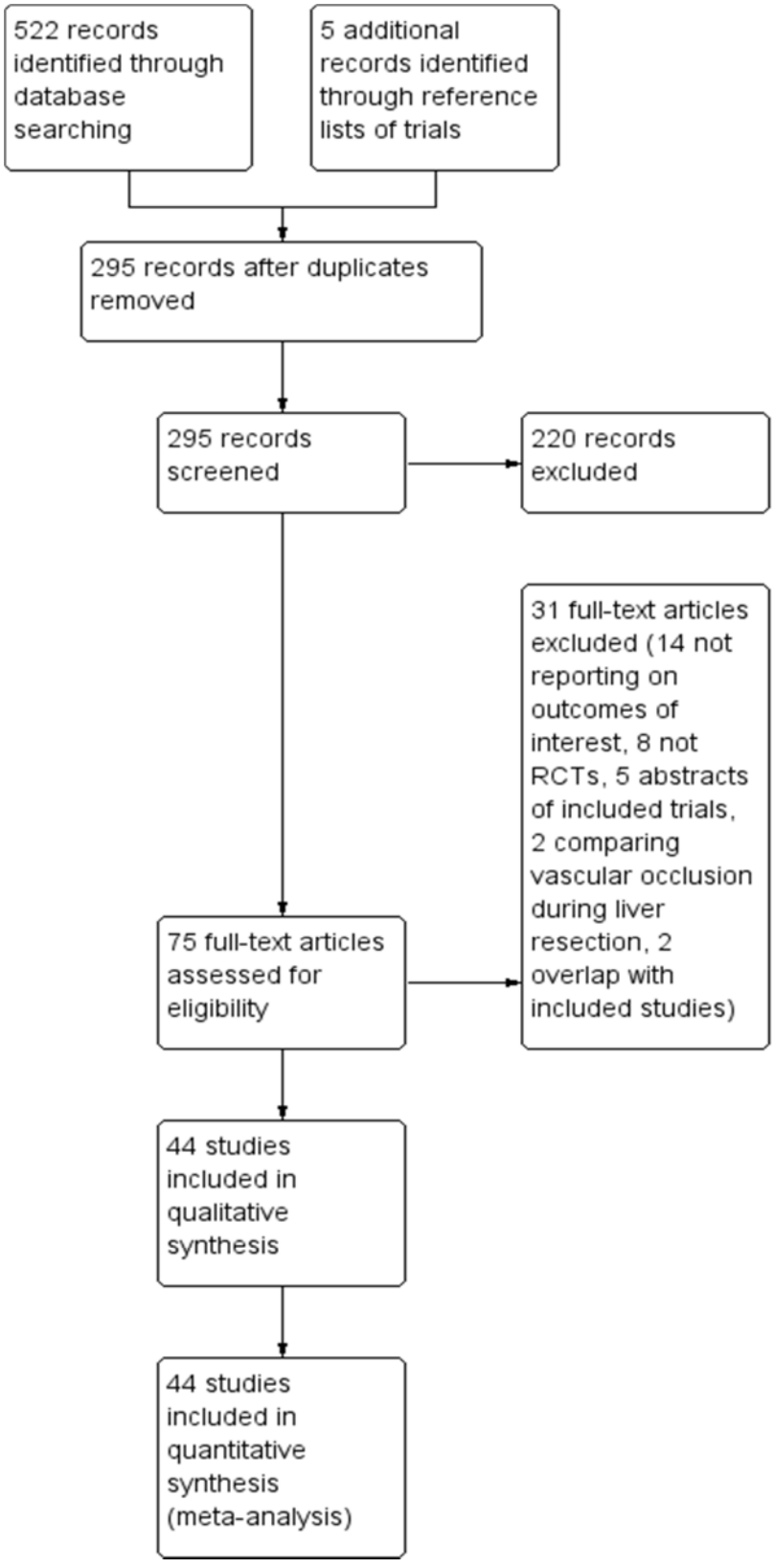


Figure 2: Network plot for mortality. Similar network plots were produced for each outcome of interest. Footnotes: circles represent the intervention as a node in the network; lines represent direct comparisons using RCTs; thickness of lines represents the number of RCTs included in each comparison, also represented by the numbers.

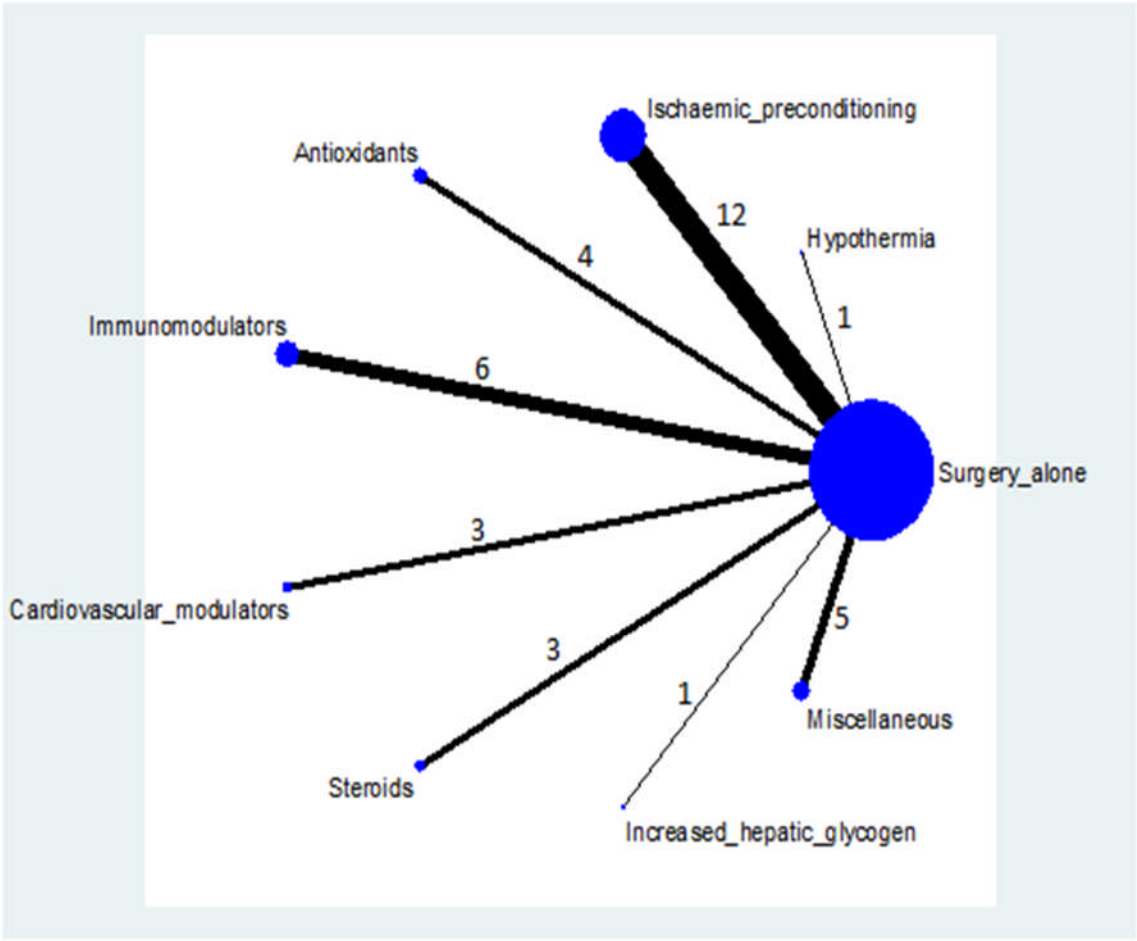


Table 1: Summary of studies included, showing name of first author, year of publication, interventions compared, total number of patients in each study, and the number with percentages of cirrhotic livers and major resections (NR=not reported).

Study	Treatments compared	Total N	Cirrhotic n (%)	Major resections	Study	Treatments compared	Total N	Cirrhotic n (%)	Major resections
Aldrighetti 2006	steroids vs no steroids	73	26 (36)	53 (73)	Li 2004b	ulinastatin vs no ulinastatin	31	27 (87)	NR
Arkadopoulos 2009	ischemic preconditioning vs no ischemic preconditioning	84	0 (0)	84 (100)	Liang 2002	ischemic preconditioning vs no ischemic preconditioning	29	25 (86)	NR
Azoulay 2006	ischemic preconditioning vs no ischemic preconditioning	60	1 (2)	60 (100)	Luo 2009	pre-storing glycogen vs no pre-storing glycogen	38	19 (50)	NR
Bartels 2004	vitamin E vs placebo	47	0 (0)	33 (70)	Marx 2000	dopexamine vs dopamine	19	NR	19 (100)
Beck-Schimmer 2008	sevoflurane vs no sevoflurane	64	0 (0)	28 (44)	Muratore 2003	steroids vs no steroids	53	16 (30)	28 (53)
Beck-Shimmer 2012	sevoflurane vs no sevoflurane	65	0 (0)	26 (40)	Nickkholgh 2011	melatonin vs placebo	36	0 (0)	36 (100)
Cerwenka 1999	antioxidant multivitamin vs no antioxidant multivitamin	50	13 (26)	NR	Nuzzo 2004	ischemic preconditioning vs no ischemic preconditioning	42	0 (0)	14 (33)
Chouker 2004	ischemic preconditioning vs no ischemic preconditioning	33	0 (0)	9 (27)	Orii 2000	amrinone vs placebo vs prostaglandin E1	45	45 (100)	0 (0)
Clavien 2003	ischemic preconditioning vs no ischemic preconditioning	100	0 (0)	75 (75)	Petrowsky 2006	ischemic preconditioning vs no ischemic preconditioning	73	0 (0)	44 (60)
Hahn 2011	ischemic preconditioning vs no ischemic preconditioning	160	60 (38)	117 (73)	Petrowsky 2010	pentoxifylline vs placebo	101	0 (0)	95 (94)
Hassanain 2013	insulin vs no insulin	56	NR	17 (30)	Scatton 2011	ischemic preconditioning vs no ischemic preconditioning	84	0 (0)	78 (93)
Hayashi 2011	steroids vs no steroids	200	NR	26 (13)	Settaf 2001	trimetazidine vs placebo	76	NR	NR
Heizmann 2008	ischemic preconditioning vs no ischemic preconditioning	61	0 (0)	19 (31)	Shirabe 1996	OKY046 vs no OKY 046	17	NR	9 (53)
Hou 2009	ischemic preconditioning vs no ischemic preconditioning	48	24 (50)	16 (33)	Smyrniotis 2006	ischemic preconditioning vs no ischemic preconditioning	54	0 (0)	27 (50)

Ishikawa 2010	branched chain amino acids vs no branched chain amino acids	24	10 (42)	5 (21)	Su 2013	S-adenosyl-L-methionine vs no S-adenosyl-L-methionine	79	79 (100)	33 (42)
Kawano 2005	prostaglandin E1 vs no prostaglandin E1	22	NR	NR	Sugawara 1998	prostaglandin E1 vs placebo	24	24 (100)	0 (0)
Kim 1996	hypothermia vs no hypothermia	20	NR	18 (90)	Tang 2007	hepatocellular glycogen vs no hepatocellular glycogen	57	50 (88)	38 (67)
Kim 2002	gabexate mesilate vs no gabexate mesilate	66	31 (47)	27 (41)	Tsujii 2012	sivelestat vs placebo	50	NR	NR
Kim 2006	gabexate mesilate vs no gabexate mesilate	60	40 (67)	51 (75)	Vriens 2002	allopurinol vs no allopurinol	16	0 (0)	NR
Kostopanagiotou 2006	mannitol vs placebo	30	NR	28 (93)	Winbladh 2012	ischemic preconditioning vs no ischemic preconditioning	32	NR	16 (50)
Laviolle 2012	propofol vs desflurane	30	0 (0)	22 (73)	Xia 2009	verapamil vs no verapamil	86	86 (100)	51 (59)
Li 2004a	ischemic preconditioning vs no ischemic preconditioning	29	29 (100)	4 (14)	Yamashita 2001	steroids vs no steroids	33	0 (0)	11 (33)

Table 2: Types of network meta-analyses performed. Footnotes: An overall network meta-analysis was performed to compare eight classes of active interventions aimed at decreasing IR injury along with a control group which was surgery alone. The classes of intervention were grouped based on their mechanism of action. A sensitivity network meta-analysis was performed to compare all the individual interventions included in each class of intervention aimed at decreasing IR injury. Another sensitivity network meta-analysis was performed to compare the following 4 larger groups: surgery alone, hypothermia, ischemic preconditioning, and all pharmacological interventions.

Overall network meta-analysis	**Sensitivity analysis All interventions**	**Sensitivity analysis Larger groups**
Surgery alone	Surgery alone	Surgery alone
Hypothermia	Hypothermia	Hypothermia
Ischemic preconditioning	Ischemic preconditioning	Ischemic preconditioning
Antioxidants	Allopurinol	Pharmacological interventions
	Antioxidant multivitamin	
	Mannitol	
	Melatonin	
	Propofol	
	Vitamin E	
Cardiovascular modulators	Amrinone	
	Dopamine	
	Dopexamine	
	OKY 046	
	Trimetazidine	
	Verapamil	
Immunomodulators	Gabexate mesilate	
	Pentoxifylline	
	Prostaglandin E1	
	Sivelestat	
Increased hepatic glycogen	Insulin	
	Pre-storing hepatocellular glycogen	
Steroids	Steroids	
Miscellaneous	Branched chain amino acids	
	Desflurane	
	S-adenosyl-L-methionine	
	Sevoflurane	
	Ulinastatin	

Table 3: Statistically significant pairwise odds ratios (yellow treatment over blue treatment) and mean differences (yellow treatment minus blue treatment) of the comparisons of the classes of interventions for all outcomes of interest. Footnotes: OR=odds ratio; MD=mean difference; (95% credible intervals); NA=not applicable; NO=no statistically significant outcomes for this pairwise comparison; 1=serious adverse events; 2=proportion of patients transfused, 3=operative blood loss, 4=length of hospital stay, 5=operative time. There was no statistically significant difference between the interventions for the outcomes: mortality, quantity of blood transfusion per patient, and ITU stay.

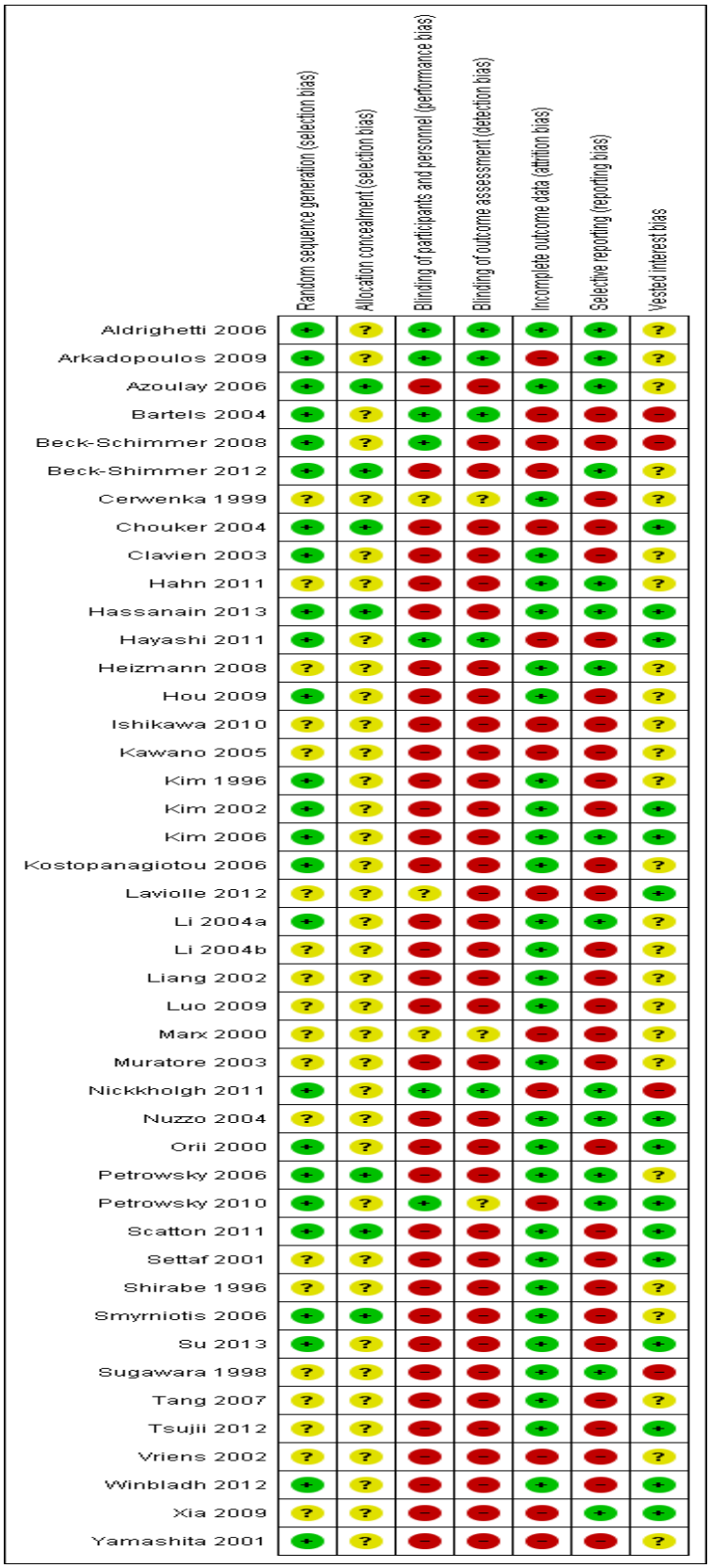
CLASSES OF INTERVENTIONS	Hypothermia	Ischemic preconditioning	Antioxidants	Immunomodulators
Surgery alone	MD 247.1 (143.59 to 350.61)[3]	OR 0.66 (0.44- 0.98)[1] MD -35.97 (-53.76 to -18.18)[3] MD -2.34 (-4.06 to -0.62)[4]	MD 207 (34.13 to 379.87)[3]	MD 231.2 (145.82 to 316.58)[3]
Hypothermia	NA	MD -283.07 (-388.09 to -178.05)[3]	NO	NO
Ischemic preconditioning	NA	NA	MD 242.97 (69.19 to 416.75)[3]	MD 267.17 (179.96 to 354.38)[3]
Antioxidants	NA	NA	NA	NO
	Cardiovascular modulators	**Steroids**	**Increased hepatic glycogen**	**Miscellaneous**
Surgery alone	OR 0.39 (0.18-0.87)[1] MD 142.2 (61.59 to 222.81)[3]	MD 69.32 (21.46 to 117.18)[3]	MD 92.04 (25.2 to 158.88)[3]	OR 0.21 (0.08-0.51)[1] MD 209.7 (118.32 to 301.08)[3]
Hypothermia	NO	MD -177.78 (-291.82 to -63.74)[3]	MD -155.06 (-278.27 to -31.85)[3]	NO
Ischemic preconditioning	MD 178.17 (95.62 to 260.72)[3]	OR 2.31 (1.03-5.18)[2] MD 105.29 (54.23 to 156.35)[3] MD 16.68 (0.79 to 32.57)[5]	MD 128.01 (58.85 to 197.17)[3]	OR 0.31 (0.12-0.85)[1] MD 245.67 (152.58 to 338.76)[3]
Antioxidants	NO	NO	NO	NO

Immuno-modulators	NO	MD -161.88 (-259.76 to -64)[3]	MD -139.16 (-247.59 to -30.73)[3]	OR 0.31 (0.1-0.96)[1]
Cardiovascular modulators	NA	NO	NO	NO
Steroids	NA	NA	MD -25.94 (-48.22 to -3.66)[5]	OR 0.31 (0.1-0.99)[1] MD 140.38 (37.23 to 243.53)[3]
Increased hepatic glycogen	NA	NA	NA	MD 117.66 (4.45 to 230.87)[3]

Table 4: Classes of interventions aiming to decrease hepatic IR injury with the highest probability of ranking from best to worst (1st to 9th) for the outcomes of interest. Footnotes: P=probability of ranking; NA=not applicable because less than 9 interventions were analyzed for this outcome. Interventions not included in the analysis for this outcome: 1=hypothermia; 2=antioxidants, miscellaneous; 3=hypothermia, cardiovascular modulators; 4=hypothermia, increased hepatic glycogen; 5=hypothermia, cardiovascular modulators, steroids, increased hepatic glycogen, miscellaneous, 6=hypothermia.

	RANKS								
OUTCOMES	**1st**	**2nd**	**3rd**	**4th**	**5th**	**6th**	**7th**	**8th**	**9th**
Mortality	Increased hepatic glycogen P=0.253	Immuno-modulators P=0.225	Immuno-modulators P=0.212	Ischemic preconditioning P=0.205	Surgery alone P=0.231	Surgery alone P=0.290	Surgery alone P=0.221	Steroids P=0.179	Hypothermia P=0.292
Serious adverse events	Miscellaneous P=0.742	Cardiovascular modulators P=0.374	Cardiovascular modulators P=0.246	Ischemic preconditioning P=0.226	Ischemic preconditioning P=0.293	Ischemic preconditioning P=0.235	Surgery alone P=0.404	Surgery alone P=0.455	NA 1
Proportion of patients transfused	Immuno-modulators P=0.424	Ischemic preconditioning P=0.395	Ischemic preconditioning P=0.272	Surgery alone P=0.404	Surgery alone P=0.280	Steroids P=0.477	Hypothermia P=0.665	NA 2	NA
Quantity of blood transfusion	Steroids P=0.318	Antioxidants P=0.226	Antioxidants P=0.198	Surgery alone P=0.282	Surgery alone P=0.317	Surgery alone P=0.179	Miscellaneous P=0.255	NA 3	NA
Operative blood loss	Ischemic preconditioning P=0.997	Surgery alone P=0.985	Steroids P=0.451	Increased hepatic glycogen P=0.492	Cardiovascular modulators P=0.478	Miscellaneous P=0.256	Miscellaneous P=0.296	Immuno-modulators P=0.316	Hypothermia P=0.388
Length of hospital stay	Miscellaneous P=0.324	Ischemic preconditioning P=0.268	Ischemic preconditioning P=0.297	Ischemic preconditioning P=0.208	Surgery alone P=0.226	Surgery alone P=0.425	Immuno-modulators P=0.294	NA 4	NA
ITU stay	Immuno-modulators P=0.453	Ischemic preconditioning P=0.427	Surgery alone P=0.427	Surgery alone P=0.426	NA 5	NA	NA	NA	NA
Operating time	Increased hepatic glycogen P=0.430	Increased hepatic glycogen P=0.324	Ischemic preconditioning P=0.369	Surgery alone P=0.341	Surgery alone P=0.358	Steroids P=0.343	Miscellaneous P=0.343	Cardiovascular modulators P=0.465	NA 6

Supplementary Figure 1: Risk of bias summary: review authors' judgments about each risk of bias item for each included study. Footnotes: green plus sign = low risk of bias, yellow question mark = unclear risk of bias, red minus sign = high risk of bias.



Supplementary Table 1: Detailed search strategy.

Database	Time span	Search strategy
Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (Wiley)	October 6th 2013	#1 (ischaemia OR ischaemia OR ischemic OR ischaemic OR reperfusion) AND (injury OR injuries OR damage OR damages) #2 MeSH descriptor Reperfusion Injury explode all trees #3 (#1 OR #2) #4 liver OR hepatic OR hepato* #5 MeSH descriptor Liver explode all trees #6 (#4 OR #5) #7 resection OR resections OR segmentectomy OR segmentectomies #8 (#6 AND #7) #9 hepatectomy OR hepatectomies #10 MeSH descriptor Hepatectomy explode all trees #11 (#8 OR #9 OR #10) #12 (#3 AND #11)
MEDLINE (Pubmed)	January 1947 to October 2013	(((ischaemia OR ischaemia OR ischemic OR ischaemic OR reperfusion) AND (injury OR injuries OR damage OR damages)) OR "Reperfusion Injury"[Mesh])) AND (((liver OR hepatic OR hepato* OR "liver"[MeSH]) AND (resection OR resections OR segmentectomy OR segmentectomies)) OR hepatectomy OR hepatectomies OR "hepatectomy"[MeSH]) AND ((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))
EMBASE (OvidSP)	January 1974 to October 2013	1 (ischaemia or ischaemia or ischemic or ischaemic or reperfusion).af. 2 (injury or injuries or damage or damages).af. 3 1 and 2 4 exp Reperfusion Injury/ 5 3 or 4 6 (liver or hepatic or hepato*).af.

		7 (resection or resections or segmentectomy or segmentectomies).af. 8 6 and 7 9 (hepatectomy or hepatectomies).af. 10 exp Liver Resection/ 11 8 or 9 or 10 12 5 and 11 13 exp crossover-procedure/ or exp double-blind procedure/ or exp randomized controlled trial/ or single-blind procedure/ 14 (random* OR factorial* OR crossover* OR cross over* OR cross-over* OR placebo* OR double* adj blind* OR single* adj blind* OR assign* OR allocat* OR volunteer*).af. 15 13 OR 14 16 12 AND 15
Science Citation Index Expanded (http://www.webofknowledge.com/?DestApp=WOS)	January 1945 to October 2013	#1 TS=((ischaemia OR ischaemia OR ischemic OR ischaemic OR reperfusion) AND (injury OR injuries OR damage OR damages)) #2 TS=((liver OR hepatic OR hepato*) AND (resection OR resections OR segmentectomy OR segmentectomies) OR hepatectomy OR hepatectomies) #3 TS=(random* OR rct* OR crossover OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*) #4 #1 AND #2 AND #3