Systematic review

Meta-analysis of ischaemic preconditioning for liver resections

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Background: **Vascular clamping reduces blood loss during liver resection but leads to ischaemia–reperfusion injury. Ischaemic preconditioning (IP) may reduce this. This study aimed to evaluate IP in liver resection under clamping.**

Methods: **This was a systematic review and meta-analysis of randomized clinical trials (RCTs) evaluating IP in adults undergoing liver resection under either continuous clamping (CC) or intermittent clamping (IC). Primary outcomes were mortality, liver failure and morbidity. Secondary outcomes included duration of operation, blood loss, length of hospital stay, length of intensive therapy unit stay, transfusion requirements, prothrombin time, and bilirubin and aminotransferase levels. Weighted mean differences were calculated for continuous data, and pooled odds ratios (ORs) for dichotomous data. Results were produced with a random-effects model with 95 per cent confidence intervals (c.i.).**

Results: **A total of 2960 records were identified and 11 RCTs included 669 patients (IP 331, control 338). No significant difference in mortality (6 RCTs; IP 186, control 190; OR 1·36, 95 per cent c.i. 0·13 to 13·68; $P = 0·80$) or morbidity (6 RCTs; IP 186, control 190; OR 0·58, 0·31 to 1·07; $P = 0·08$) was found for IP plus CC *versus* CC. Nor was there a significant difference in mortality (4 RCTs; IP 122, control 121; OR 1·33, 0·24 to 7·32; $P = 0·74$) or morbidity (4 RCTs; IP 122, control 121; OR 0·87, 0·52 to 1·47; $P = 0·61$) for IP plus (CC or IC) *versus* IC. No significant differences were found for secondary outcome measures.**

Conclusion: **This meta-analysis failed to find a significant benefit of IP in liver resection.**

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Introduction

To prevent bleeding during liver resection, various vascular inflow occlusion techniques have been devised. The major disadvantage of these is the resulting ischaemia and consequent postoperative liver dysfunction[1] leading to increased morbidity[2]. On restoring the blood supply, the liver is subjected to a further insult, aggravating the injury already inflicted. This is termed ischaemia–reperfusion injury, which is a complex multifactorial process involving interactions between metabolic, immunological and microvascular processes[3]. It is difficult to prevent and cirrhotic livers are particularly susceptible[1] with postoperative liver failure as a potential complication[4].

Ischaemic preconditioning (IP) is a strategy aimed at reducing ischaemia–reperfusion injury resulting from subsequent inflow occlusion. It consists of a short period of ischaemia followed by reperfusion. This can be used before continuous clamping (CC)[5] or intermittent clamping (IC)[6,7] (*Fig. 1*). IP is typically performed as one cycle comprising 10 min of clamping of the portal triad, termed Pringle's manoeuvre, followed by 10–15 min of reperfusion. Although the exact protective mechanisms are unknown, IP is thought to result in adenosine and nitric oxide release, which protects the liver against subsequent prolonged episodes of continuous ischaemia[8]. IP before CC appears to combine the beneficial effects of ischaemia–reperfusion injury reduction with the avoidance of additional blood loss[3], but whether it actually leads to any additional benefit is disputed[6].

IP was first described in the heart by Murry and colleagues[9]. However, it was not until 2000 that Clavien and co-workers[5] published the first non-randomized study demonstrating a protective effect of IP in human liver. In this study, IP was performed before 30 min of CC using Pringle's manoeuvre, and this reduced serum aminotransferase levels and endothelial cell injury after surgery[5]. This same group followed up this study with a randomized clinical trial (RCT)[10] that confirmed the protection previously demonstrated (with inflow occlusion up to 60 min this time), and highlighted younger patients and those with liver steatosis as particular subgroups who derived the

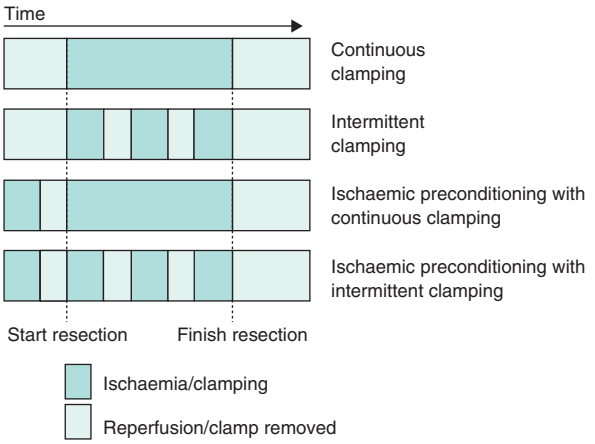

Fig. 1 Ischaemic preconditioning time schedule

most benefit from IP. In a subsequent randomized trial, IP before CC also conferred a high degree of protection in patients with cirrhotic livers, as determined by measurement of serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST)[1].

The aim of this study was to evaluate the current evidence supporting the use of IP in elective liver resection performed under clamping. The objective was to compare adult patients undergoing elective liver resection surgery with or without IP.

Methods

A systematic review and meta-analysis was performed according to recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[11]. The study protocol was registered with the University of York Centre for Reviews and Dissemination international prospective register of systematic reviews before the study search (PROSPERO Record CRD42012002134; http://www.crd.york.ac.uk/PROSPERO).

The medical literature was searched for RCTs examining the effect of IP compared with no IP on the outcome of elective liver resections in adult human patients. Participants both with and without chronic liver disease were included. Primary outcomes were mortality, liver failure and postoperative morbidity. Secondary outcomes included duration of operation, blood loss, length of hospital and intensive therapy unit (ITU) stay, transfusion requirements, markers of liver function such as prothrombin time and bilirubin, and biochemical markers of liver injury such as serum ALT and AST levels. No restrictions were placed on language or publication status.

Only RCTs were included. Studies that used quasi-randomization (allocation to group on the basis of day of admission) were not included. Studies based on overlapping cohorts from the same institution were excluded to avoid duplication of included patients. However, the largest cohorts and most recent or relevant studies from overlapping cohorts were selected and data taken from other publications on the same cohort to ensure that useful data were not excluded. Studies examining IP in the context of liver transplantation were excluded.

MEDLINE, Embase and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched from their inception up to and including May 2013 using the following search algorithm: (((occlusion? OR clamp$ OR exclusion) adj6 (vessel? OR vascular OR arter& OR vein? OR venous OR hepatic OR portal)) OR Pringle OR (isch?em$ adj2 (preconditio$ OR pre-conditio$))) AND (hepatic OR liver) AND (segmentectom$ OR resection?).

A data extraction template was used to summarize the data items sought (*Appendix S1*, supporting information). Two authors independently reviewed the titles and, where appropriate, abstracts of all reports identified by the initial search. Two authors independently extracted data from all identified reports. Disagreements were resolved by consensus. Optical plot reading of a bar graph using Plot digitizer® software (SourceForge.net, New York, USA) was used to establish the standard deviation of a single variable (AST) from a graph in one study[10]. No further assumptions or simplifications were made when extracting data. Where important information was missing, study authors were contacted by e-mail (*Table S1*, supporting information). This was followed up by a letter or further e-mail if no response was received and the missing information was vital for meaningful analysis. Risk of bias was assessed as described previously at both study and outcome level[12].

Statistical analysis

Outcomes of interest, with appropriate comparisons, were entered into a meta-analysis. Dichotomous outcomes were evaluated based on event rates using a pooled odds ratio (OR). For continuous variables, a weighted mean difference (WMD), accounting for different sample sizes across studies, was calculated. RevMan 5® software (The Nordic Cochrane Centre, Copenhagen, Denmark) was used and a random-effects DerSimonian–Laird model chosen to provide the most conservative effects estimate. Results were reported with 95 per cent confidence intervals (c.i.). Heterogeneity was assessed using τ^2, $\chi^2$and I^2 measures. Heterogeneity was considered significant if $P < 0{\cdot}10$ or I^2 exceeded 30 per cent.

The risk of bias across studies was formulated for its effect on the cumulative evidence in terms of selection bias, performance bias, detection bias, attrition bias and reporting bias. Publication bias was assessed using funnel plots.

Subgroup analyses were defined *a priori* and carried out for IP and control before liver resection under CC and also under IC (*Fig. 1*). Further analysis was carried out with exclusion of patients with liver cirrhosis and liver resections performed under selective hepatic vascular occlusion. Pooled analyses including all studies and testing for subgroup differences were also performed.

Results

The search identified 2960 records (*Fig. 2*). After electronically removing duplicates and screening the remaining 1925 abstracts, 22 publications were retrieved and examined in detail. The reasons for exclusion of 1903 records at the abstract stage included: irrelevant topic (1527), animal study (191), unsuitable study design (not RCT; 83), wrong intervention (64), duplication (33), inability to find full-text report (3) and meeting abstract of an included study (2). Reasons for exclusion of 11 articles after reading the full text included: insufficient data reported (3)[13–15], overlapping cohorts (5)[16–20], not a RCT (1)[21], quasi-randomization (1)[5] and statistical inconsistencies (1)[22,23]. The remaining 11 trials[1,3,6,8,10,24–29] were included in this review (669 patients; IP 331, control 338). One full-text report[28] was supplied by authors when they were contacted for further information about a trial that had been published only as an abstract at the time of initial literature search. This study divided certain results into patients who underwent resection of more the three liver segments and those who had two or three segments resected. The characteristics of the included studies are summarized in *Tables 1–3*[1,3,6,8,10,24–29]. The risk of bias is summarized for each study in *Fig. S1* (supporting information) and across studies in *Fig. S2* (supporting information). The results of individual studies are summarized in *Tables 1–3*.

Primary outcomes

Six studies[1,3,8,10,24,25] (376 patients; IP 186, control 190) reported on mortality following IP + CC compared with

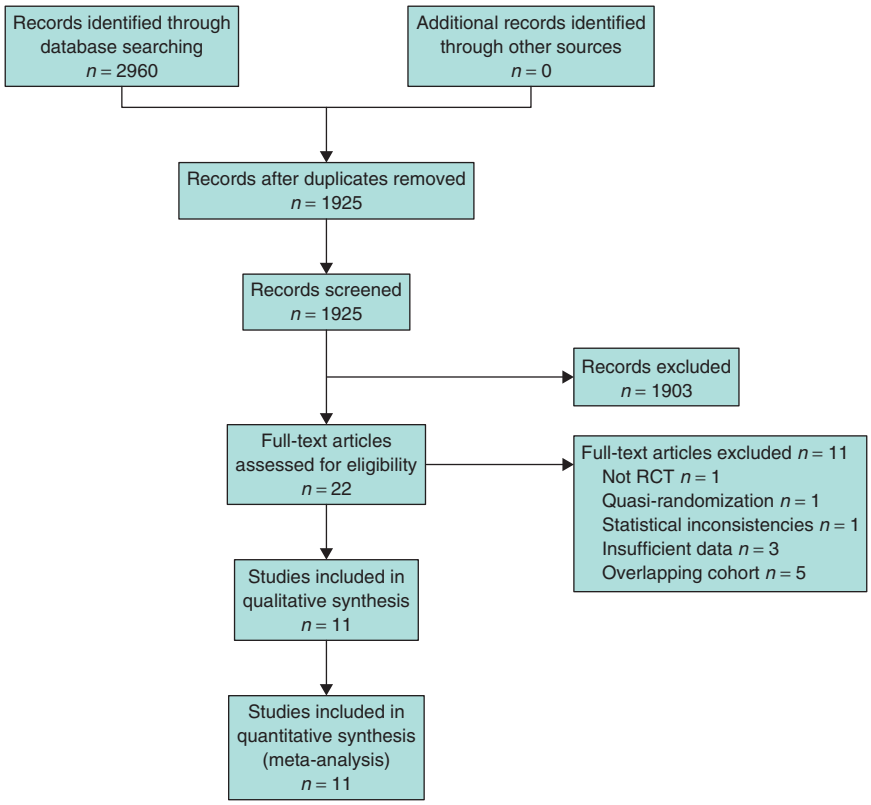

Fig. 2 PRISMA diagram showing selection of articles for review. Other sources included manual searches of reference lists and conference proceedings. RCT, randomized clinical trial

Table 1 Summary of included studies of ischaemic preconditioning plus continuous clamping *versus* continuous clamping

	Arkadopoulos *et al.*[24] (2009)	Azoulay *et al.*[25] (2006)	Choukèr *et al.*[29] (2005)	Clavien *et al.*[10] (2003)	Heizmann *et al.*[3] (2008)	Li *et al.*[1] (2004)	Nuzzo *et al.*[8] (2004)
Clamping	Continuous	Continuous	Continuous	Continuous	Continuous	Continuous	Continuous
IP	Pringle manoeuvre	Pringle manoeuvre	Pringle manoeuvre	Pringle manoeuvre	Pringle manoeuvre	Pringle manoeuvre	Pringle manoeuvre
Liver resection conditions both groups	Selective hepatic vascular occlusion	Selective hepatic vascular occlusion	Continuous Pringle manoeuvre	Continuous Pringle manoeuvre	Continuous Pringle manoeuvre	Continuous Pringle manoeuvre	Continuous Pringle manoeuvre
IP clamp time (min)	10	10	10	10	10	5	10
Reperfusion time (min)	15	10	10	10	10	5	10
Intermittent ischaemia/reperfusion time (min)	–	–	–	–	–	–	–
All resections ≥ 3 segments	Yes	Yes	No	Yes	No	No	No
Cirrhotic livers	No	Yes (1)	No	No	No	Yes	No
Mortality							
IP	0 of 41	2 of 30	–	0 of 50	1 of 30	0 of 14	0 of 21
Control	0 of 43	0 of 30	–	0 of 50	2 of 31	0 of 15	0 of 21
Liver failure							
IP	–	9 of 30	–	–	1 of 30	0 of 14	–
Control	–	10 of 30	–	–	4 of 31	3 of 15	–
Postop. morbidity							
IP	12 of 41	16 of 30	–	2 of 50	6 of 30	3 of 14	2 of 21
Control	14 of 43	18 of 30	–	2 of 50	14 of 31	10 of 15	1 of 21
Hospital stay (days)*							
IP	–	14(5)	–	–	–	13(3)	–
Control	–	17(11)	–	–	–	19(9)	–
ITU stay (days)*							
IP	–	2(2)	–	–	2(4)	–	–
Control	–	3(4)	–	–	3(6)	–	–
Duration of operation (min)*							
IP	185(34)	289(85)	251(46)†	225(73)	260(63)	191(75)	321(92)
Control	190(27)	309(99)	257(83)†	240(92)	271(58)	208(45)	339(112)
Patients transfused							
IP	16 of 41	8 of 30	0 of 14†	3 of 50	5 of 30	–	3 of 21
Control	17 of 43	14 of 30	0 of 19†	3 of 50	15 of 31	–	4 of 21
Packed cells (units)*							
IP	–	1·1(2·3)	–	–	0·5(1·3)	–	–
Control	–	1·4(2·1)	–	–	0·9(1·2)	–	–
Blood loss (ml)*							
IP	–	1005(850)	1480(573)†	250(290)	1280(910)	469(293)	–
Control	–	1066(748)	1380(710)†	225(325)	1940(760)	602(311)	–
Prothrombin time (%)*							
IP	–	45(13)	–	76(18)	–	–	–
Control	–	41(10)	–	81(14)	–	–	–
Bilirubin (μmol/l)*							
IP	–	63(60)	–	46(43)	24(22)	27(10)	–
Control	–	81(71)	–	56(51)	25(30)	49(35)	–
Albumin (g/l)*							
IP	–	–	–	–	–	36(4)	
Control	–	–	–	–	–	33(5)	–
AST (units/l)*							
IP	288(140)	851(1733)	226(17)‡	364(96)	–	434(144)	–
Control	498(255)	427(166)	420(520)‡	520(186)	–	1856(311)	–
ALT (units/l)*							
IP	–	717(995)	261(205)‡	406	247(210)	431(179)	–
Control	–	403(200)	519(455)‡	519	450(650)	803(280)	–

*Values are mean(s.d.). †Taken from earlier publication[19]; ‡taken from another publication on same cohort[20]. IP, ischaemic preconditioning; ITU, intensive therapy unit; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 2 Summary of included studies of ischaemic preconditioning plus continuous clamping *versus* intermittent clamping

	Petrowsky *et al.*[26] (2006)	Smyrniotis *et al.*[27] (2006)
Clamping	Intermittent	Intermittent
IP	Pringle manoeuvre	Pringle manoeuvre
Liver resection conditions	Continuous Pringle manoeuvre (IP group) Intermittent Pringle manoeuvre (control group)	Selective hepatic vascular occlusion (IP group) Intermittent selective hepatic vascular occlusion (control group)
IP clamp time (min)	10	10
Reperfusion time (min)	10	10
Intermittent ischaemia/reperfusion time (min)	15/5	15/5
All resections ≥3 segments	Yes	No
Cirrhotic livers	No	No
Mortality		
IP	1 of 36	0 of 27
Control	0 of 37	0 of 27
Liver failure		
IP	0 of 36	–
Control	2 of 37	–
Postop. morbidity		
IP	14 of 36	9 of 27
Control	14 of 37	10 of 27
Hospital stay (days)*		
IP	15(10)	–
Control	13(9)	–
ITU stay (days)*		
IP	4(7)	–
Control	2(3)	–
Duration of operation (min)*		
IP	316(126)	211(31)
Control	300(116)	237(28)
Patients transfused		
IP	9 of 36	–
Control	11 of 37	–
Packed cells (units)*		
IP	1·7(1·8)	–
Control	2·9(3·0)	–
Blood loss (ml)*		
IP	426(450)	520(247)
Control	492(456)	720(220)
Prothrombin time (%)*		
IP	74(19)	49(8)†, 47(6)‡
Control	72(17)	48(5)†, 47(7)‡
Bilirubin (μmol/l)*		
IP	50(41)	56(6)†, 50(8)‡
Control	49(82)	52(6)†, 53(11)‡
AST (units/l)*		
IP	645(390)	735(216)†, 485(176)‡
Control	528(353)	680(115)†, 515(233)‡
ALT (units/l)*		
IP	414(360)	–
Control	522(377)	–

*Values are mean(s.d.). †Ischaemia time 40 min or more; ‡ischaemia time less than 40 min. IP, ischaemic preconditioning; ITU, intensive therapy unit; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

CC. Of these, only three included an appropriate power calculation and none was powered on mortality. The outcome measures used were apoptotic rate in hepatocytes[24], all ischaemia-related complications including death[3], and probability of better outcome, which was determined from the following statement: 'The assumption was made that the difference between the two groups was such that the probability for a better outcome for one patient in the preconditioning group *versus* the patient in the control group was at least 0·7'[10]. There was no significant heterogeneity among the studies ($I^2 = 29$ per cent, $P = 0{\cdot}23$). No significant reduction in mortality following IP was

Table 3 Summary of included studies of ischaemic preconditioning plus intermittent clamping *versus* intermittent clamping

	Scatton *et al.*[6] (2011)	Winbladh *et al.*[28] (2012)	Winbladh *et al.*[28] (2012)
Clamping	Intermittent	Intermittent	Intermittent
IP	Pringle manoeuvre	Pringle manoeuvre	Pringle manoeuvre
Liver resection conditions both groups	Intermittent Pringle manoeuvre	Intermittent Pringle manoeuvre	Intermittent Pringle manoeuvre
IP clamp time (min)	10	10	10
Reperfusion time (min)	10	10	10
Intermittent/reperfusion time (min)	15/5	15/5	15/5
All resections ≥3 segments	No	No	Yes
Cirrhotic livers	No	No	No
Mortality			
IP	2 of 43	0 of 8	0 of 8
Control	2 of 41	0 of 8	0 of 8
Liver failure			
IP	1 of 43	–	–
Control	2 of 41	–	–
Postop. morbidity			
IP	24 of 43	3 of 8	4 of 8
Control	28 of 41	2 of 8	3 of 8
Hospital stay (days)*			
IP	15(12)	–	–
Control	15(10)	–	–
ITU stay (days)*			
IP	2(2)	–	–
Control	3(5)	–	–
Duration of operation (min)*			
IP	282(107)	242(57)	292(60)
Control	299(123)	261(42)	359(112)
Patients transfused			
IP	10 of 41	–	–
Control	11 of 43	–	–
Blood loss (ml)*			
IP	793(1134)	–	–
Control	562(382)	–	–
Bilirubin (μmol/l)*			
IP	–	34(99)	39(111)
Control	–	27(59)	30(41)
Albumin (g/l)*)			
IP	–	28(4)	30(4)
Control	–	28(4)	29(7)
AST (units/l)*			
IP	–	402(701)	748(2059)
Control	–	472(738)	432(707)
ALT (units/l)*			
IP	538(359)	479(959)	616(1451)
Control	525(401)	549(1146)	433(871)

*Values are mean(s.d.). IP, ischaemic preconditioning; ITU, intensive therapy unit; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

detected (OR 1·36, 95 per cent c.i. 0·13 to 13·68; $P = 0·80$) (*Fig. 3*).

Four studies[6,26–28] (243 patients; IP 122, control 121) reported the mortality rate following IP + (CC or IC) compared with IC. In two of these trials the event rate was zero. Again, the three studies[6,26,27] that performed power calculations were not designed to detect a difference in mortality but to assess for a reduction in serum aminotransferase levels. There was no significant heterogeneity among the studies ($I^2 = 0$ per cent, $P = 0·53$). No significant reduction was found in mortality following IP (OR 1·33, 0·24 to 7·32; $P = 0·74$) (*Fig. 3*).

Three studies[1,3,25] (150 patients; IP 74, control 76) reported on liver failure following IP + CC compared with CC. Liver failure was defined either as a total bilirubin concentration exceeding 90 μmol/l or a prothrombin time below 30 per cent of normal within 7 days after surgery[25], bilirubin level over 86 μmol/l and/or prothrombin activity below 40 per cent for at least 3 postoperative days[3], or total bilirubin level more than two times normal and massive

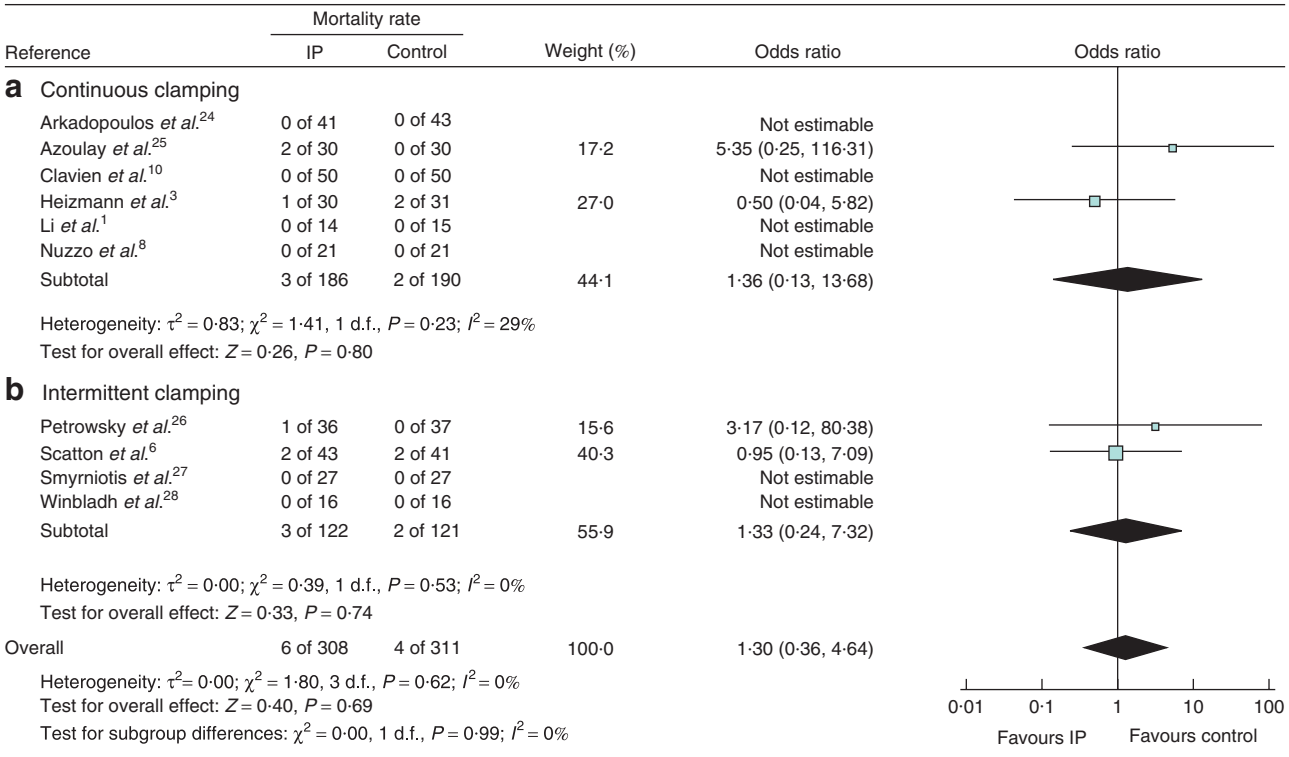

Fig. 3 Forest plot of mortality in studies of **a** ischaemic preconditioning (IP) plus continuous clamping *versus* continuous clamping and **b** IP plus continuous or intermittent clamping *versus* intermittent clamping. A Mantel–Haenszel random-effects model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals

ascites[1]. There was no significant heterogeneity among the studies ($I^2 = 7$ per cent, $P = 0{\cdot}34$). No significant reduction was found in liver failure following IP (OR 0·54, 0·19 to 1·50; $P = 0{\cdot}24$) (*Fig. 4*). In further analyses excluding patients with cirrhosis[1] or those undergoing selective vascular exclusion[25] there was still no significant impact of IP on liver failure.

Two studies[6,26] (157 patients; IP 79, control 78) reported on liver failure following IP + (CC or IC) compared with IC. Liver failure was defined by the Dindo–Clavien classification[30]. There was no significant heterogeneity among the studies ($I^2 = 0$ per cent, $P = 0{\cdot}66$). No significant reduction was found in liver failure following IP (OR 0·33, 0·05 to 2·24; $P = 0{\cdot}26$) (*Fig. 4*).

Six studies[1,3,8,10,24,25] (376 patients; IP 186, control 190) reported on morbidity following IP + CC compared with CC. There was no significant heterogeneity among the studies ($I^2 = 22$ per cent, $P = 0{\cdot}27$). No significant reduction was found in morbidity following IP (OR = 0·58, 0·31 to 1·07; *P* 0·08) (*Fig. 5*). In further analyses excluding patients with cirrhosis[1] or those undergoing selective vascular exclusion[24,25] or both, there was still no significant impact of IP on morbidity.

Four studies[6,26–28] (243 patients; IP 122, control 121) reported on morbidity following IP + (CC or IC) compared with IC. There was no significant heterogeneity among the studies ($I^2 = 0$ per cent, $P = 0{\cdot}63$). No significant reduction was found in morbidity following IP (OR 0·87, 0·52 to 1·47; $P = 0{\cdot}61$) (*Fig. 5*). In further analyses of only patients who had IP before IC[6,28] or excluding those undergoing selective vascular exclusion[27], there was still no significant impact of IP on morbidity.

Secondary outcomes

The results for secondary outcome measures are summarized in (*Fig. S3*, supporting information).

Seven studies[1,3,8,10,24,25,19] (409 patients; IP 200, control 209) reported duration of operation in procedures with IP + CC compared with CC. There was no significant heterogeneity among the studies ($I^2 = 0$ per cent, $P = 0{\cdot}99$). Duration of operation was not significantly shorter with IP: WMD 8·4 (95 per cent c.i. −1·8 to 18·7) min ($P = 0{\cdot}11$). In a further analysis excluding patients with cirrhosis[1] or those undergoing selective vascular exclusion[24,25] or both, there was still no significant impact of IP on operating time.

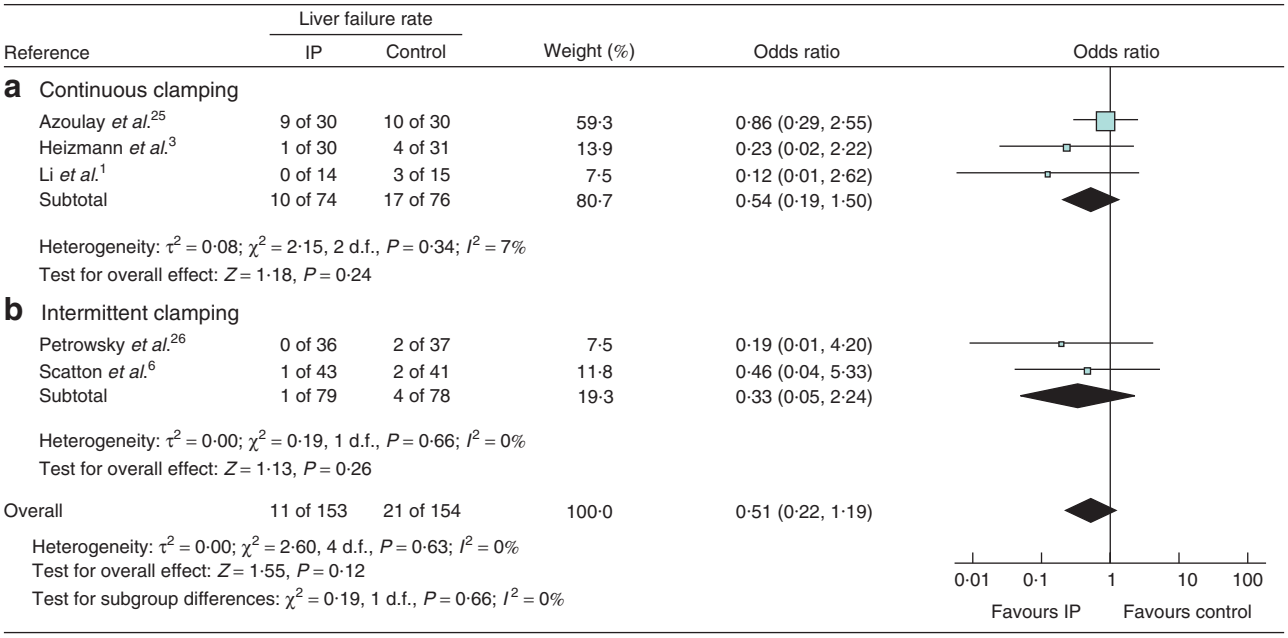

Fig. 4 Forest plot of liver failure in studies of **a** ischaemic preconditioning (IP) plus continuous clamping *versus* continuous clamping and **b** IP plus continuous or intermittent clamping *versus* intermittent clamping. A Mantel–Haenszel random-effects model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals

Four studies[6,26–28] (243 patients; IP 122, control 121) reported duration of operation in procedures with IP + (CC or IC) compared with IC. There was no significant heterogeneity among the studies ($I^2 = 0$ per cent, $P = 0{\cdot}55$). Operating time was significantly shorter with IP: WMD 23·2 (9·5 to 36·9) min ($P < 0{\cdot}001$). Significance was lost when patients undergoing selective vascular exclusion were excluded[27] or when considering only the two studies[6,28] that assessed IP + IC in comparison with IC.

Five studies[1,3,10,25,19] (283 patients; IP 138, control 145) reported on blood loss following IP + CC compared with CC. There was significant heterogeneity among the studies ($I^2 = 62$ per cent, $P = 0{\cdot}03$). The amount of blood lost was non-significantly lower with IP: WMD 115 (−89 to 318) ml ($P = 0{\cdot}27$). In further analysis excluding patients with cirrhosis[1] or those undergoing selective vascular exclusion[25] or both, there was still no impact of IP on blood loss.

Three studies[6,26,27] (211 patients; IP 106, control 105) reported blood loss following IP + (CC or IC) compared with IC. There was significant heterogeneity among the studies ($I^2 = 63$ per cent, $P = 0{\cdot}07$). Blood loss was non-significantly lower with IP: WMD 66 (−137 to 270) ml ($P = 0{\cdot}52$). The significance was not altered when patients undergoing selective vascular exclusion[27] were excluded.

No significant difference was noted in ITU stay between any of the groups. There was also no difference in overall hospital stay in the IC studies. Length of stay was significantly shorter in patients randomized to IP + CC compared with CC: WMD 4·3 (1·1 to 7·4) days ($P = 0{\cdot}009$). However, only two studies[1,25] (89 patients; IP 44, control 45) reported on this outcome measure.

Six studies[3,8,10,24,25,19] (380 patients; IP 186, control 194) reported on the proportion of patients who received blood transfusion following IP + CC compared with CC. There was no significant heterogeneity among the studies ($I^2 = 0$ per cent, $P = 0{\cdot}42$). There was a significant reduction in the proportion of patients having blood transfusion following IP (OR 0·57, 0·34 to 0·96; $P = 0{\cdot}03$). In further analysis excluding those undergoing selective vascular exclusion[24,25] significance was maintained (OR 0·43, 0·19 to 0·96; $P = 0{\cdot}04$). No difference was noted between groups in the IC studies.

Two studies[10,25] (160 patients; IP 80, control 80) reported on prothrombin time following IP + CC compared with CC. There was significant heterogeneity among the studies ($I^2 = 76$ per cent, $P = 0{\cdot}04$). No significant difference was found in prothrombin time: WMD 0·4 (−8·4 to 9·2) per cent ($P = 0{\cdot}93$).

Two studies[26,27] (127 patients; IP 63, control 64) reported on prothrombin time following IP + (CC or IC) compared with IC. There was no significant heterogeneity among the studies ($I^2 = 0$ per cent, $P = 0{\cdot}91$). No significant

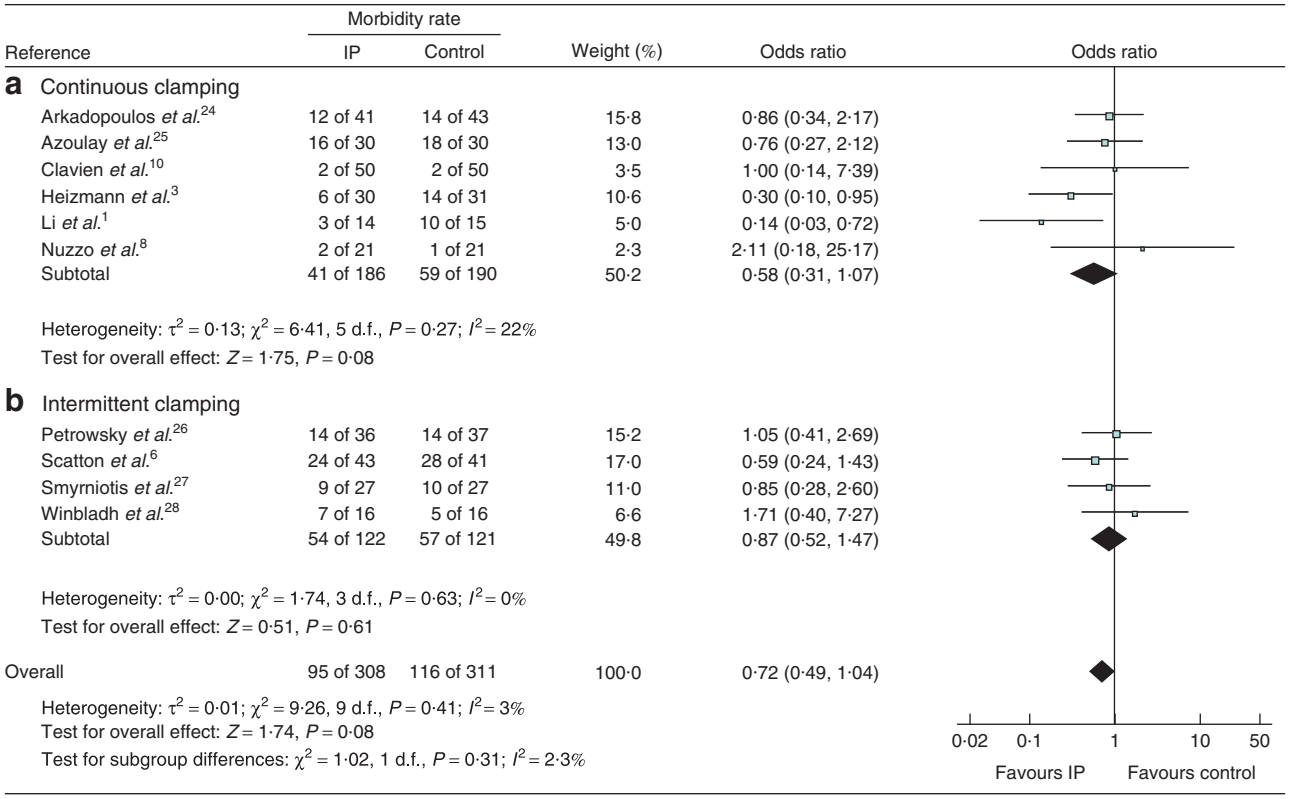

Fig. 5 Forest plot of postoperative morbidity in studies of **a** ischaemic preconditioning (IP) plus continuous clamping *versus* continuous clamping and **b** IP plus continuous or intermittent clamping *versus* intermittent clamping. A Mantel–Haenszel random-effects model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence intervals

difference was found in prothrombin time: WMD 0·7 (−2·5 to 3·9) per cent ($P = 0·66$).

Four studies[1,3,10,25] (250 patients; IP 124, control 126) reported on bilirubin levels following IP + CC compared with CC. There was no significant heterogeneity among the studies ($I^2 = 17$ per cent, $P = 0·31$). No significant difference was found in bilirubin levels: WMD 9·9 (−0·2 to 20·0) μmol/l ($P = 0·05$).

Three studies[26–28] (159 patients; IP 79, control 80) reported on bilirubin levels following IP + (CC or IC) compared with IC. There was no significant heterogeneity among the studies ($I^2 = 0$ per cent, $P = 0·62$). No significant difference was found in bilirubin levels: WMD 2·0 (−1·8 to 5·8) μmol/l ($P = 0·29$).

Five studies[1,10,24,25,20] (323 patients; IP 160, control 163) reported on AST levels following IP + CC compared with CC. There was significant heterogeneity among the studies ($I^2 = 98$ per cent, $P < 0·001$). No significant difference was found in AST levels: WMD 361·6 (−29·0 to 752·3) units/l ($P = 0·07$).

Three studies[26–28] (159 patients; IP 79, control 80) reported on AST levels following IP + (CC or IC) compared with IC. There was no significant heterogeneity among the studies ($I^2 = 0$ per cent, $P = 0·77$). No significant difference was found in AST levels: WMD 43·8 (−41·3 to 128·9) units/l ($P = 0·31$).

Four studies[1,3,20,25] (200 patients; IP 99, control 101) reported on ALT levels following IP + CC compared with CC. There was significant heterogeneity among the studies ($I^2 = 74$ per cent, $P = 0·01$). No significant difference was found in ALT levels: WMD 173·6 (−49·1 to 396·3) units/l ($P = 0·13$).

Three studies[6,26,28] (184 patients; IP 92, control 92) reported on ALT levels following IP + (CC or IC) compared with IC. There was no significant heterogeneity among the studies ($I^2 = 0$ per cent, $P = 0·77$). No significant difference was found in ALT levels: WMD 45·1 (−72·7 to 162·9) units/l ($P = 0·45$).

Publication bias

Publication bias is summarized within funnel plots (*Fig. S4*, supporting information). Asymmetrical funnel plots were identified but, given the low number of studies included,

it is not possible to draw statistically robust conclusions from these.

Discussion

This meta-analysis has failed to find a significant benefit of adding IP before CC or IC in liver resection over CC or IC alone in reducing mortality, liver failure, postoperative morbidity, ITU stay, volume of blood loss, prothrombin time or aminotransferase levels. However, compared with CC alone, IP + CC appeared to be associated with a reduction in length of hospital stay and the proportion of patients requiring blood transfusion. Only two studies reported on length of hospital stay, so this may be a chance finding because of low numbers or study bias. The proportion of patients transfused was assessed in a total of six trials with 380 patients. The significance of the result was also maintained when patients operated on using selective vascular occlusion were excluded to form a more homogeneous sample. Reducing transfusion requirements when CC is used forms the most forceful argument for supporting IP in liver resection. Despite this, there was no evidence of decreased blood loss following IP before either CC or IC. The lack of significance in blood loss reduction could be explained by difficulty in accurately quantifying blood loss in this setting and greater variability in blood loss within studies (with wider confidence intervals on pooling). Conversely, the choice of transfusion can be subjective and transfusion thresholds may have differed owing to lack of blinding and study bias. It is therefore difficult to recommend IP based on its potential to reduce transfusion requirements.

Compared with IC alone, the only possible suggested significant benefit of IP + (CC or IC) observed in this meta-analysis was shorter operating times. However, this does not make obvious sense because IP is in effect an extra operating manoeuvre that takes time. IP may facilitate subsequent operative manoeuvres such as parenchymal dissection and haemostasis. However, significance was lost when patients undergoing selective vascular exclusion[27] were excluded or when considering only studies with IP before IC[6,28]. Therefore, no firm conclusion can be drawn from this result.

The possible disadvantages of IP include an additional ischaemic injury and the need for potentially time-consuming, surgeon-dependent intraoperative manoeuvres. Although no significant benefit of IP was found in this meta-analysis, no harm was suggested either. This includes, as previously mentioned, no increase in duration of operation. Therefore, no clinical recommendation for or against the use of IP can be made on this basis.

A previous meta-analysis[31] on this topic incorporated four RCTs[1,10,19,27] published up until 2006. It assessed only IP + CC (110 patients) compared with CC (111 patients). The study showed lower ALT levels but no associated improvement in outcome (morbidity, mortality, blood loss and transfusion requirements) in those randomized to IP.

A later Cochrane meta-analysis[32] included four trials[3,10,19,25] published up until 2008. It again assessed only IP + CC (135 patients) compared with CC (136 patients). A reduction in blood transfusions with IP was reported, but no difference in other measures. The present meta-analysis has incorporated a further seven trials[1,6,8,24,26–28], including some more recently published, and also additionally evaluated the use of IP + (CC or IC) compared with IC.

Two further studies not included in the Cochrane meta-analysis[32] but incorporated here evaluated IP followed by CC compared with IC[26,27]. One of these studies[26] showed the techniques to be comparable in reducing liver injury, but suggested that there was less bleeding and that parenchymal transection times were shorter with IP. The other study[27], which used selective vascular exclusion during liver resection, showed comparable outcomes for IP followed by CC *versus* IC with short ischaemia times. However, AST levels were lower and there was less apoptosis in the IC group when the ischaemia time exceeded 40 min. A number of trials have been published since the last meta-analysis[32] and were included here. Two of the more recent RCTs[6,28] assessed IP before IC *versus* IC alone. In neither trial was IP found to be beneficial in reducing liver injury in terms of biochemical or clinical outcomes, but in one study[28] it did seem to improve aerobic hepatic glucose metabolism as determined by microdialysis.

In a study[24] evaluating the use of IP before continuous selective vascular occlusion in major liver resection, IP led to significantly lower peak serum levels of AST and an attenuation of the apoptotic response in the liver remnant, but no change in overall morbidity. This is similar to the findings of another trial[25] involving major hepatectomies performed under selective vascular occlusion, which also found no major clinical benefit of IP. In addition, there was no biochemical benefit, but the trial included no analysis of biopsies of the liver remnant to evaluate the apoptotic response.

A limitation of this meta-analysis is the heterogeneity of the studies included. To overcome this, CC and IC control groups were analysed separately where possible. In addition, the trials[6,28] investigating IP before IC were analysed separately. Populations that would contribute particularly to the heterogeneity (for example studies including only patients with cirrhosis[1] or inflicting much greater ischaemic insults by selective vascular exclusion

during resection[24,25,27]) were also excluded from subanalyses, before drawing conclusions. Despite this, a number of potential confounders still exist including the amount of liver resected, severity of ischemia–reperfusion injury, liver resection clamping conditions (Pringle's manoeuvre or selective vascular occlusion), age and co-morbidities of the study population, and the liver pathology.

Future research in this area could further evaluate the impact of IP in specific subgroups of patients who may benefit the most (such as those with cirrhosis)[1,22]. It could also investigate different IP techniques (for example remote ischaemic preconditioning), or evaluate IP before IC, which to date has been assessed in only two trials[6,28]. Furthermore, none of the studies published so far has been designed to look at long-term outcome following IP, and this should be explored.

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Supporting information

Additional supporting information may be found in the online version of this article:

Appendix S1 Data extraction template (Word document)

Table S1 Additional information sought from authors (Word document)

Fig. S1 Risk of bias summary (Word document)

Fig. S2 Risk of bias graph (Word document)

Fig. S3 Forest plots for secondary outcome measures: duration of operation, blood loss, hospital stay, intensive therapy unit stay, transfusion requirements, prothrombin time, and bilirubin, aspartate aminotransferase and alanine aminotransferase levels (Word document)

Fig. S4 Funnel plots (Word document)