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A systematic review and meta-analysis of donor ischaemic preconditioning in liver transplantation.

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Abstract

Background:

Ischaemic Preconditioning (IPC) is a strategy to reduce Ischaemia Reperfusion (IR) injury. Its benefit in human liver transplantation is unclear. The aim of this study was to analyse the current evidence for donor IPC in liver transplantation.

Methods:

Systematic review and meta-analysis of studies involving IPC of liver transplant donors. Ovid Medline, Embase and Cochrane CENTRAL were searched up until January 2015. Data retrieved included the primary outcomes of 1 year mortality, incidence of Primary Graft Non-Function (PGNF) and re-transplantation. Secondary outcomes included Aspartate Aminotransferase (AST) levels on day 3 post-op. Pooled Odds Ratios (OR) were calculated for dichotomous data and Mean Weighted Ratios for continuous data.

Results:

Ten studies included 593 patients (286 IPC; 307 Control). IPC was associated with a reduction in mortality at 1 year (6% vs 11%) although this was not statistically significant (OR 0.54, 95% C.I. 0.28 to 1.04, p=0.06). The IPC group had a significantly lower day 3 AST level (WMD -66.41iU, p=0.04).

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Conclusions:

This meta-analysis demonstrates that IPC reduces liver injury following transplantation and produces a large reduction in 1 year mortality which was not statistically significant. Confirmation of clinical benefit from IPC requires an adequately powered prospective RCT.

Introduction:

Liver transplantation is the only effective treatment for both acute and chronic liver failure. 780 deceased donor liver transplants were performed in the UK in 2014-2015[1]. Due to a recent widening of the eligibility criteria, demand for this scarce resource far outstrips supply of suitable organs. The use of grafts from extended criteria donors in the UK has expanded to meet demand with the use of grafts from donors following cardiac death (DCD) increasing from 6.9% in 2005[2] to 19.1% of grafts inserted in 2013[1]. Ischaemia Reperfusion (IR) injury is the injury that happens to an organ when its blood supply is interrupted and reconstituted and is a major cause of morbidity, mortality and graft loss following liver transplantation - accounting for up to 10 per cent of early graft loss from brain dead donors (DBD)[3]. DCD grafts are associated with a two fold increase in risk of graft loss and recipient mortality in UK centres[2]. A key factor to the reduced outcomes seen with the use of DCD grafts is their susceptibility to IR injury and the associated complications. There are no current accepted treatments for IR injury and as such the development of strategies to prevent or reduce IR injury is a key research goal.

Ischaemic preconditioning (IPC) was first described in 1986[4]. This process of inducing short periods of non-lethal ischaemia to a target organ has been shown to provide protection to the same or other organs during a subsequent sustained ischaemic insult. The reduction of liver damage with IPC has been demonstrated in different small animal models of hepatic ischaemia[5][6] but its role in clinical transplantation remains to be proven. Several small trials have investigated IPC in the donor prior to organ recovery.

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The aim of this study was to evaluate the current evidence in the medical literature regarding the use of IPC in human liver transplantation.

Methods:

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[7]. The study protocol was registered with the University of York Centre for Reviews and Dissemination international prospective register of systematic reviews (2015:CRD42015016055).

The medical literature was searched for RCT's examining the effect of IPC in the clinical setting of deceased donor liver transplantation.

All trials including patients undergoing deceased donor liver transplantation were included in the study. Patients undergoing living donor liver transplantation were excluded.

Data was retrieved from the published studies. The primary outcomes chosen for the analysis were early graft failure and retransplantation within 3 months and mortality within 1 year. The secondary outcomes were episodes of acute rejection, length of time spent in the intensive therapy unit (ITU) and in hospital, number of days ventilated, incidence of post-operative transient renal support, infective complications and Aspartate transferase (AST) on the 3rd post operative day[8]. Papers were included irrespective of language. Both RCTs and matched cohort studies were included. Studies based on overlapping cohorts of patients were excluded.

MEDLINE, Embase and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched up to and including the second week of January 2015 using the following search algorithm: ((((hepatic OR liver) adj3 (transplant$ or graft$)).ti,ab.) or (exp Liver Transplantation/)) and (((isch?emic adj(preconditioning or pre conditioning or pre-conditioning)).ti,ab.) or (exp Ischaemic Preconditioning/)).

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Two authors independently reviewed the titles. Appropriate studies were identified and those appropriate following review of abstracts were sourced in full. Two authors independently extracted data from the studies selected for full paper review. Disagreements were resolved by consensus or where necessary by the senior author.

Statistical analysis:

Data on the selected primary and secondary outcomes were entered into a meta-analysis. Dichotomous outcomes were analysed based on event rates using pooled odds ratio (OR) while continuous outcomes were analysed using a weighted means difference (WMD). The analysis was performed on Revman 5® software (The Nordic Cochrane Centre, Copenhagen, Denmark) using a random effects DerSimonian-Laird model and results were reported with 95% confidence intervals. A p value of less than 0.05 or an Odds ration not crossing 1 was considered to be significant. Heterogeneity was assessed using τ^2, χ^2, and I^2 measures and was deemed significant if $p<0.10$ or I^2 was greater than 30%. In keeping with Revman's default setting trials with zero events in each arm of a variable were excluded from the analysis of that variable. If a variable had zero events in one arm, 0.5 events was added to that arm to allow an odds ratio and confidence intervals to be calculated.

Results:

Following the initial search (Fig 1), 458 studies were identified of which 305 remained following removal of duplicates. The 305 titles and abstracts were reviewed and 19 studies were selected for full review. Reasons for study exclusion were animal model (125), review, editorial or reply (73), irrelevant topic (64), no full text or abstract available (20) and duplicated patient data set (4).

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Of the 19 studies reviewed in detail 9 were excluded – reasons for exclusion were conference abstracts (7), duplicated patient dataset (1) and living donor study (1).

Data from ten studies were further analysed[9] [10] [11] [12] [13] [14] [15] [16] [17] [18] which included 593 patients (286 IPC; 307 Control). The characteristics and results of each study are included in Tables 1 and 2. Only DBD grafts were included in these studies. No grafts underwent normothermic machine perfusion or reperfusion. There was no significant difference in mean length of cold ischaemic time between the treatment and control arms of the included studies.

Primary endpoints:

Seven studies[9] [10] [11] [12] [13] [14] [15] (475 patients: 232 IPC, 243 control) included data on 1 year mortality (Fig 2). There was significant variability in the timepoint at which patient mortality was calculated from 3 months up to 1 year. There was no significant heterogeneity between the studies (I^2=0%, p=0.85). IPC was associated with a 45% reduction in post-operative mortality (6% vs 11%) but this was not statistically significant (OR 0.54, 95% C.I. 0.28 to 1.04, p=0.06).

Five studies[9] [10] [11] [12] [15] (322 patients: 152 IPC, 170 control) provided data on the incidence of primary graft non-function (PGNF) (Fig 3). There was no significant heterogeneity between the studies (I^2=0%, p=0.91). The IPC group had a lower incidence of PGNF (0.7% vs 4%) but this was not statistically significant (OR 0.35, 95% C.I. 0.009 to 1.31, p=0.12).

Six studies[10] [11] [12] [14] [15] [16] (274 patients: 182 IPC, 192 control) commented on the need for retransplantation (Fig 4). There was no significant heterogeneity between the studies (I^2=0%, p=0.99). IPC was associated with a reduction in the incidence of retransplantation (3% vs 4%) but this was not significant (OR 0.83, 95% c.i. 0.28 to 2.41, p=0.73).

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Secondary endpoints:

Three studies[11][12][18] (149 patients: 68 IPC, 81 control) included data on day 3 AST levels (Fig 5). There was no significant heterogeneity between the studies (I^2=0%, p=0.46). AST levels on the 3rd post operative day were significantly lower in patients who had been transplanted with grafts from IPC treated donors compared to controls (WMD -66.41 (-129.92 to -2.89) iU, p=0.04).

Four studies[9] [10] [13][16] (240 patients: 121 IPC, 119 control) included data on length of ITU stay (Fig 6). There was no significant heterogeneity between the studies (I^2=0%, p=0.74). IPC was associated with an increase in length of ITU stay but this was not statistically significant MWD 1.21 (-1.02 to 3.45) days (p=0.29).

Six studies[9] [10] [11] [12] [13] [16] (362 patients: 174 IPC, 188 control) included data on length of hospital stay (Fig 7). There was significant heterogeneity between the studies (I^2=56%, p=0.06) IPC was associated with an increase in length of total hospital stay but this was not statistically significant MWD 0.56 (-4.77 to 5.9) days (p=0.84).

Seven studies[9] [12] [13] [15] [16] [17] [18] (435 patients; 210 IPC, 225 control) included data on number of patients experiencing an episode of acute rejection (Fig 8). There was significant heterogeneity between the studies (I^2=37%, p=0.14). IPC was associated with a reduction in number of patients experiencing an episode of acute rejection (20% vs 25%) but this was not statistically significant (OR 0.71 95% c.i. 0.39 to 1.31, p=0.28).

Discussion:

IPC is an inexpensive intervention that has been shown to ameliorate hepatic IR injury in small animal models[19] [20] [21]. Several small human trials have investigated IPC of donor livers prior to recovery of organs. The majority of these trials have been pilot feasibility trials and

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none have been adequately powered to determine a significant benefit in terms of the most important clinically relevant outcomes of patient morbidity and mortality following liver transplantation. An audit of liver transplant activity in the UK demonstrated that 90 day patient and graft survival is 90.8% and 89.3% respectively[22] and as such designing a trial around these end-points would be difficult due to the required trial size and associated cost. A meta-analysis investigating the benefit of this intervention in liver transplantation is therefore of importance as a meta-analysis of underpowered trials may reveal significant results.

A Cochrane review involving a literature search performed in early 2007 included 3 RCTs and failed to show any clinical benefit from IPC[23]. Several further RCTs have been performed since this time justifying a further review of the literature.

IPC was associated with 45% reduction in recipient mortality post liver transplantation (6% vs 11%). This large reduction in mortality from a single intervention did not prove to be statistically significant. Similarly IPC was associated with an 82% reduction in the incidence of grafts loss secondary to PGNF (0.7% vs 4%) although this again this was not significant (p=0.12). This data demonstrating lower recipient mortality and graft loss post liver transplant in patients who had received a graft from donors undergoing IPC was not statistically significant but would suggest that a larger prospective randomised trial is required which is powered to demonstrate a reduction in these clinically significant end points. A power calculation was performed with an alpha error of 0.05 and a beta error of 0.2 for both PGNF and 1 year mortality. This calculated that total sample size of 660 patients with 330 in each arm would be required to adequately power a trial to demonstrate a significant reduction in PGNF and a sample size of 974 with 487 patients in each arm would be necessary to demonstrate a significant reduction in 1 year mortality. Such a multi-centre trial would be feasible in the UK.

Recent work has shown that AST levels on the 3rd day following liver transplant, rather than peak transaminase levels, correlate with recipient mortality rate and the incidence of graft loss, need for organ support and incidences of post operative complications and infections[8]. Day 3

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AST was therefore included as a secondary end point for this meta-analysis. Three studies measured AST levels on day 3. Patients that received a graft that underwent IPC had significantly lower AST levels on the 3rd post operative day.

A significant reduction in an important surrogate marker for post transplant outcomes would again suggest a beneficial effect to donor IPC and would also support the need for a further clinical trial.

Patients who received grafts from donors who underwent IPC spent on average 1 day longer in ITU and in 0.6 days longer in hospital. Neither of these were significant but both of these variables are associated with adverse outcomes following liver transplant including a greater need for organ support or the development of complications post transplantation. A large randomised clinical trial is further supported to ensure that donor IPC is not associated with any adverse outcomes.

All of the included trials were small and underpowered to detect a significant reduction in important clinical end points which could lead to inconclusive results from this meta-analysis. Eight studies were randomised controlled trials with little evidence of bias and a low drop out rate post randomisation.

There was significant variability between trials. There is no consensus regarding the optimal preconditioning stimulus in humans. Of the 10 trials included, 9 trials performed a single IPC stimulus of 10 minutes whilst only one trial performed a single IPC stimulus of 5 minutes [14]. Furthermore there is a lack of validated end-points in clinical trials of liver transplantation and as such the end points measured in individual trials varied significantly making comparison of the trials difficult. Very few trials reported on the incidence of specific post-operative complications including infections. The incidence of these complications reflects underlying graft function however we were unable to comment on the effects of IPC on these important end-points.

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Two trials which were included were cohort studies[16][17], comparing a cohort of patients undergoing IPC to a historical matched cohort. Although cohort studies provide less robust evidence than a randomised clinical trial, neither of these trials were included in the analysis involving AST levels which were significantly reduced by IPC.

Only one trial included marginal grafts in a subgroup analysis[16]. This cohort study demonstrated a reduction in IR injury both in normal and marginal grafts following IPC and a reduction in incidence of acute rejection in marginal grafts that underwent IPC when compared to controls. This study raises the important question of whether IPC is more efficacious in grafts subjected to a more significant IR injury. It was the only study to perform a sub group analysis of extended criteria grafts. A trial investigating the value of IPC or RIPC specifically with extended criteria donors including including DCD donors prior to withdrawal of circulatory and ventilator support would be warranted.

No trial investigated recipient outcome longer than one year post-operatively and as such the long term effect of IPC on post transplant outcomes remains unknown. Furthermore data regarding recipient quality of life post transplantation was not included. This is an important end point in liver transplantation as the aim of transplantation is not only to improve survival but also to improve quality of life.

This analysis has shown that donor IPC prior to graft recovery results in a reduction in acute liver injury as indicated by reduced day 3 AST levels and major but not statistically significant reduction in one year mortality and incidence of PGNF. An adequately powered multi centred RCT is required to confirm the harms of benefits of donor ischaemic preconditioning to recipients undergoing liver transplantation.

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Table 1: Summary of included trials.

Author (year)	Amador *et al* (2005)[9]		Cescon *et al* (2006)[10]		Cescon *et al* (2009)[11]		Franchello *et al* (2009)[12]		Azoulay *et al* (2005)[13]	
Duration of IPC	10 minutes		10 minutes		10 minutes		10 minutes		10 minutes	
Group	IPC	Ctl	IPC	Ctl	IPC	Ctl	IPC	Ctl	IPC	Ctl
No in group	30	30	23	24	19	20	30	45	46	45
1 year mortality	0	2	0	2	3	2	1	3	2	2
Incidence of PGNF	0	3	0	1	0	1	0	1	0	0
Incidence of re-transplantation	-	-	2	2	1	1	1	2	0	0
Day 3 AST levels (iU/L)	644	819	-	-	-	-	270.12 (193.74)	281.46 (292.94)	-	-
Length of ITU stay (days)	6.8 (8)	6.7 (7)	-	-	-	-	-	-	15 (14)	12 (6)
Length of hospital stay (days)	24 (14)	24 (14)	-	-	-	-	13.4 (6.6)	18.12 (12.92)	38 (25)	31 (12)
Incidence of episodes of acute rejection	4	4	-	-	-	-	9	7	9	12

Table 2: Summary of included trials ctd.

Author (year)	Koneru *et al* (2005)[14]		Koneru *et al* (2007)[15]		Degli-Eposti *et al* (2011)[16]		Jassem *et al* (2006)[17]		Fuggle *et al* (2009)[18]	
Duration of IPC	5 minutes		10 minutes		10 minutes		10 minutes		10 minutes	
Group	IPC	Ctl	IPC	Ctl	IPC	Ctl	IPC	Ctl	IPC	Ctl
No in group	34	28	50	51	26	24	9	14	19	16
1 year mortality	-	-	6	11	0	0	0	0	-	-
Incidence of PGNF	0	0	1	1	-	-	0	0	-	-
Incidence of re-transplantation	0	1	1	1	1	1	-	-	-	-
Day 3 AST levels (iU/L)	183 (126-2311)	183 (108-316)	-	-	-	-	-	-	120 (91)	216 (137)
Length of ITU stay (days)	-	-	-	-	12/15	11/12	1	2.8	-	-
Length of hospital stay (days)	-	-	10	10	28/52	29/33	-	-	-	-
Incidence of episodes of acute rejection	-	-	6	11	4	11	2	7	7	5

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Fig 1: PRISMA flow chart.

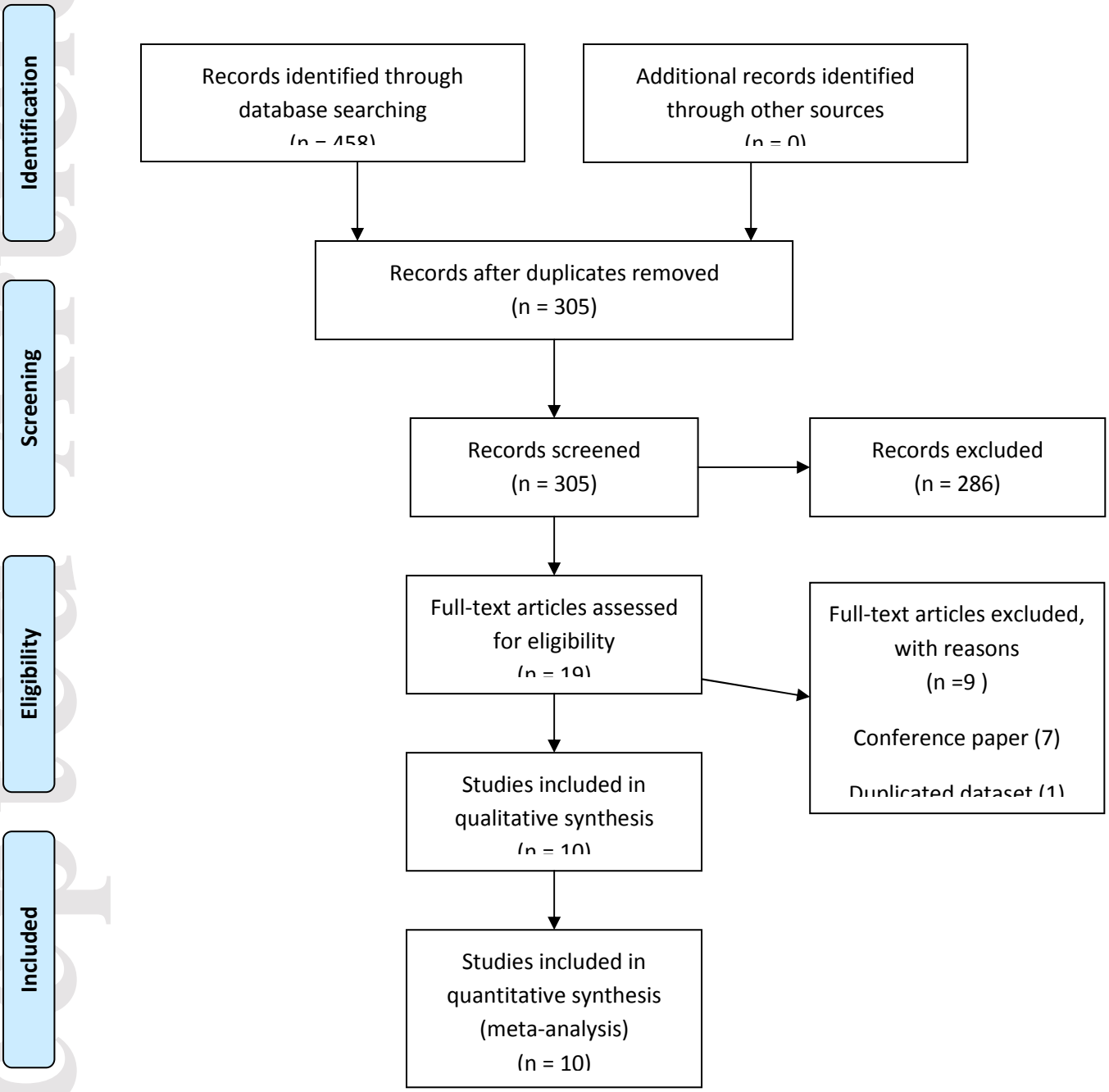

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Fig 2: Forest plot comparing mortality between the groups.

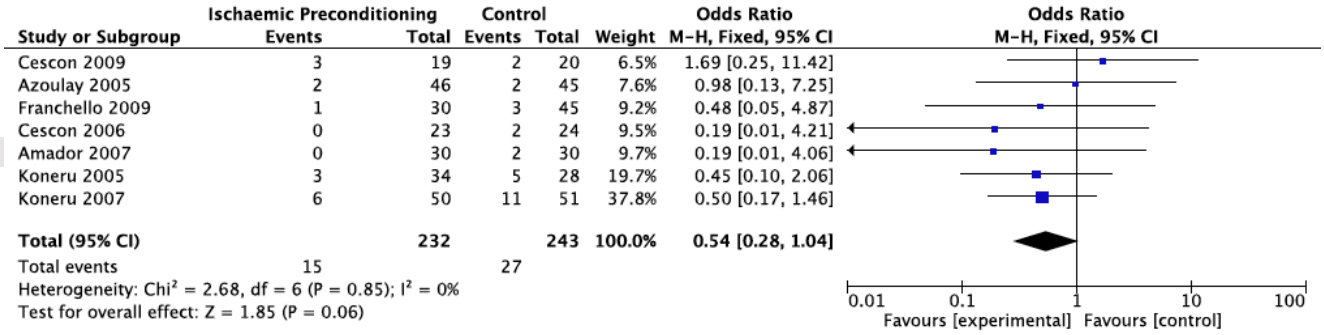

Fig 3: Forest plot comparing incidence of PGNF between the groups.

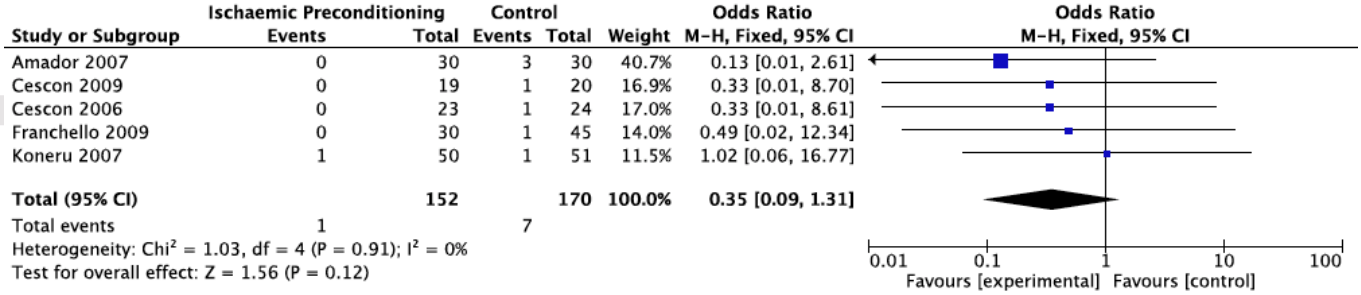

Fig 4: Forest plot comparing incidence of re-transplantation between the groups.

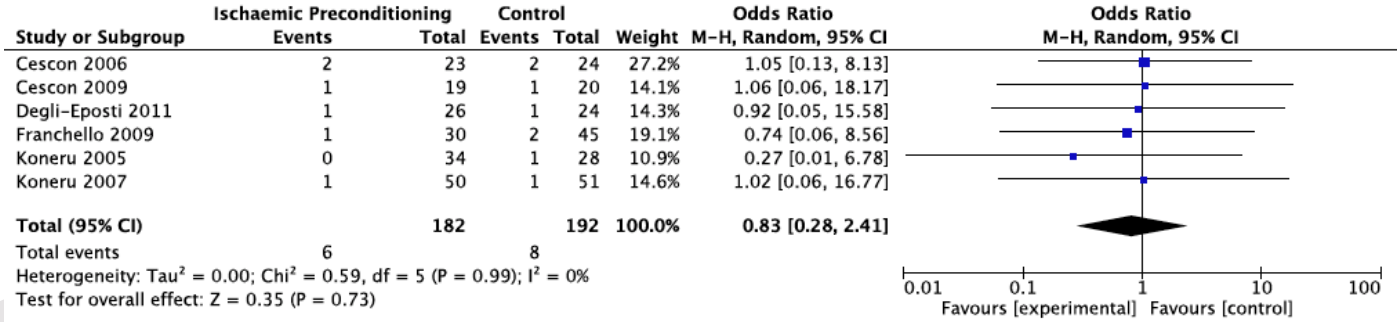

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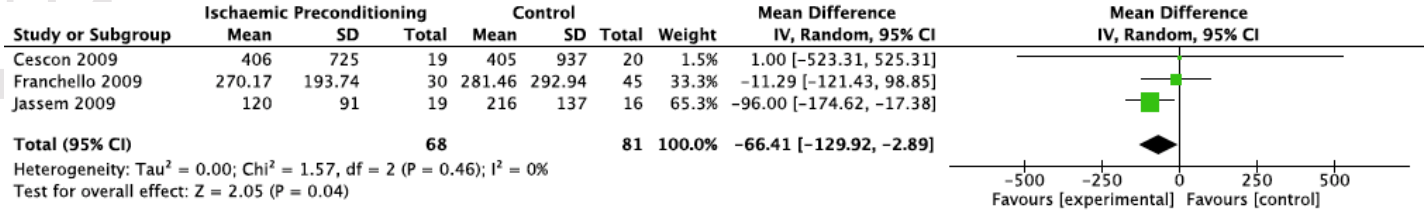
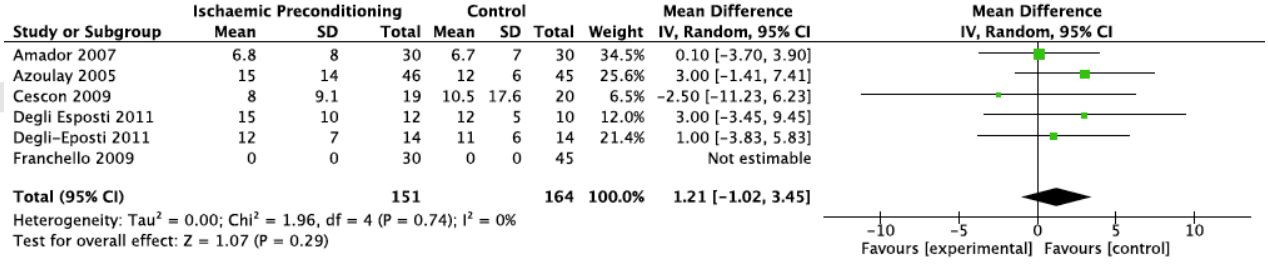
Fig 5: Forest plot comparing AST levels on the 3rd post operative day between the groups.



Study or Subgroup	Ischaemic Preconditioning Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cescon 2009	406	725	19	405	937	20	1.5%	1.00 [-523.31, 525.31]
Franchello 2009	270.17	193.74	30	281.46	292.94	45	33.3%	-11.29 [-121.43, 98.85]
Jassem 2009	120	91	19	216	137	16	65.3%	-96.00 [-174.62, -17.38]
Total (95% CI)			**68**			**81**	**100.0%**	**-66.41 [-129.92, -2.89]**

Heterogeneity: Tau² = 0.00; Chi² = 1.57, df = 2 (P = 0.46); I² = 0%
Test for overall effect: Z = 2.05 (P = 0.04)

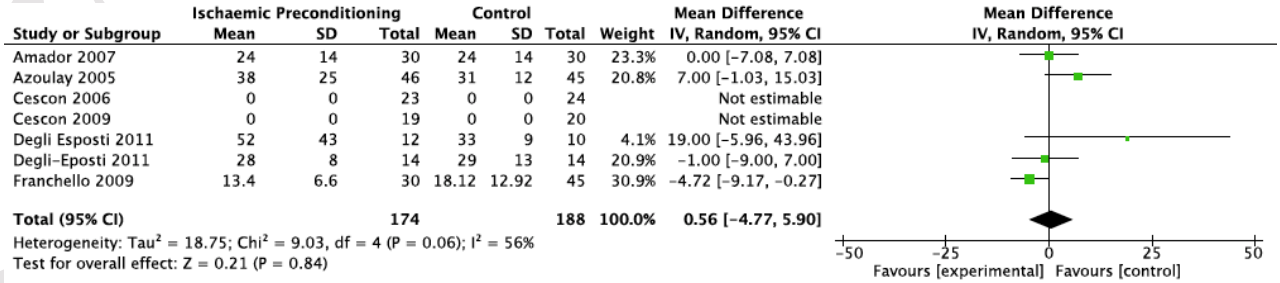
Fig 6: Forest plot comparing length of ITU stay between the groups.



Study or Subgroup	Ischaemic Preconditioning Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Amador 2007	6.8	8	30	6.7	7	30	34.5%	0.10 [-3.70, 3.90]
Azoulay 2005	15	14	46	12	6	45	25.6%	3.00 [-1.41, 7.41]
Cescon 2009	8	9.1	19	10.5	17.6	20	6.5%	-2.50 [-11.23, 6.23]
Degli Esposti 2011	15	10	12	12	5	10	12.0%	3.00 [-3.45, 9.45]
Degli-Eposti 2011	12	7	14	11	6	14	21.4%	1.00 [-3.83, 5.83]
Franchello 2009	0	0	30	0	0	45		Not estimable
Total (95% CI)			**151**			**164**	**100.0%**	**1.21 [-1.02, 3.45]**

Heterogeneity: Tau² = 0.00; Chi² = 1.96, df = 4 (P = 0.74); I² = 0%
Test for overall effect: Z = 1.07 (P = 0.29)

Fig 7: Forest plot comparing length of hospital stay between the groups.



Study or Subgroup	Ischaemic Preconditioning Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Amador 2007	24	14	30	24	14	30	23.3%	0.00 [-7.08, 7.08]
Azoulay 2005	38	25	46	31	12	45	20.8%	7.00 [-1.03, 15.03]
Cescon 2006	0	0	23	0	0	24		Not estimable
Cescon 2009	0	0	19	0	0	20		Not estimable
Degli Esposti 2011	52	43	12	33	9	10	4.1%	19.00 [-5.96, 43.96]
Degli-Eposti 2011	28	8	14	29	13	14	20.9%	-1.00 [-9.00, 7.00]
Franchello 2009	13.4	6.6	30	18.12	12.92	45	30.9%	-4.72 [-9.17, -0.27]
Total (95% CI)			**174**			**188**	**100.0%**	**0.56 [-4.77, 5.90]**

Heterogeneity: Tau² = 18.75; Chi² = 9.03, df = 4 (P = 0.06); I² = 56%
Test for overall effect: Z = 0.21 (P = 0.84)

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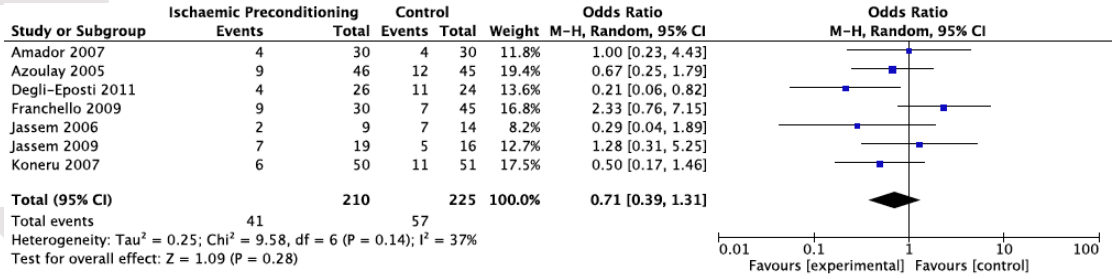
Fig 8: Forest plot comparing incidence of acute rejection episodes between the groups.



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