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Systematic review on the treatment of deceased organ donors

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ABSTRACT

Background: Currently, there is no consensus on which treatments should be a part of standard deceased-donor management to improve graft quality and transplantation outcomes. The objective of this systematic review was to evaluate the effects of treatments of the deceased, solid-organ donor on graft function and survival after transplantation.

Methods: Pubmed, Embase, Cochrane, and Clinicaltrials.gov were systematically searched for randomized controlled trials that compared deceased-donor treatment versus placebo or no treatment.

Results: A total of 33 studies were selected for this systematic review. Eleven studies were included for meta-analyses on three different treatment strategies. The meta-analysis on methylprednisolone treatment in liver donors (two studies, 183 participants) showed no effect of the treatment on rates of acute rejection. The meta-analysis on antidiuretic hormone treatment in kidney donors (two studies, 222 participants) indicates no benefit in the prevention of delayed graft function. The remaining meta-analyses (seven studies, 334 participants) compared the effects of 10 min of ischaemic preconditioning on outcomes after liver transplantation and showed that ischaemic preconditioning improved short-term liver function, but not long-term transplant outcomes.

Conclusions: There is currently insufficient evidence to conclude that any particular drug treatment or any intervention in the deceased donor improves long-term graft or patient survival after transplantation.

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1. Introduction

Due to the persistent shortage of organs available for solid organ transplantation [1], the transplant community has been searching for possibilities to further expand the donor pool. One way to achieve this is by accepting organs retrieved from older and higher risk donors, without compromising good transplantation outcomes. Improving quality of suboptimal organs from donors after brain death (DBD), older expanded-criteria donors (ECD), or donors after circulatory

death (DCD) mandates better assessment and optimisation prior to transplantation. These donors have all suffered cerebral injury, which leads to a profound systemic inflammatory response [2, 3]. Furthermore, DBD and DCD donors face additional disturbances that threaten the quality of the future organ grafts.

In DBD donors, an increased intracranial pressure impairs brain perfusion and causes herniation of the brain stem. This results in the release of catecholamines and a cascade of derangements that lead to endothelial dysfunction and inflammation in the potential grafts-to-be [4, 5]. In addition, the function of the hypothalamus and pituitary gland becomes impaired, which leads to decreased cortisol, triiodothyronine (T3), insulin, and antidiuretic hormone (ADH) plasma levels in the donor [6, 7]. After herniation of the brain stem, a haemodynamically unstable state will follow that requires fluid resuscitation and often inotropic support. In DCD donors, there is no catecholamine release. Instead, withdrawal of medical support results in a significant blood pressure drop until circulatory arrest. This period of circulatory arrest is followed by a in most countries medico-legal five-minute no-touch period prior to confirmation of death, which adds extra warm ischaemic injury and threatens the quality of the potential grafts. In addition to these donor-related injuries, the grafts-to-be subsequently endure a period of preservation and cold ischaemia that are further detrimental to the organ quality.

To improve transplant outcomes in solid organ transplantation, an optimised and more organ-protective Intensive Care regimen should

Abbreviations: ADH, Antidiuretic Hormone; AF, Alkaline phosphatase; AST, Aspartate Transaminase; ALT, Alanine Aminotransferase; CI, Confidence Interval; DBD, Donation after Brain Death; DCD, Donation after Circulatory Death; DGF, Delayed Graft Function; ECD, Expanded Criteria Donors; γ GT, Gamma-glutamyl Transpeptidase; HD, Haemodialysis; HF, Haemofiltration; HES, Hydroxyethyl Starch; INR, International Normalised Ratio for Prothrombin Time (PT); IPC, Ischaemic Preconditioning; IRI, Ischaemia-Reperfusion Injury; LDH, Lactate Dehydrogenase; LVAD, Left Ventricular Assist Device; MD, Mean Difference; MTH, Mild Therapeutic Hypothermia; PEEP, Positive End-Expiratory Pressure; RCT, Randomized Controlled Trial; ROS, Reactive Oxygen Specie; T3, Triiodothyronine; TV, Tidal Volume.

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be adopted. In the last decade, such a strategy has increasingly become important since donor age and comorbidities have increased significantly in most countries. In deceased donor care, this has led to the consideration of numerous treatment options aspiring improvement of graft function and survival after transplantation. Unfortunately, clinical implementation has not happened, whilst a lot of controversy still exists about which treatment could actually benefit donor organs potentially improving transplant outcomes.

The purpose of this systematic review is to provide an update on all systematically tested clinical interventions in the deceased donor and their impact on graft function and/or survival following solid organ transplantation. This review will concern any clinical treatment regimen that was carried out in either DBD or DCD donors using either specific drugs, fluids, or procedures to reduce donor organ injury prior to organ preservation and transplantation.

2. Materials and methods

2.1. Selection criteria

RCTs or quasi-RCTs (trials in which the allocation method is not truly random) were selected that compared differences in graft function and survival between pre organ retrieval-treated, deceased, adult (16 years or older) solid-organ donors (including DCD, DBD, and ECD donors) to untreated or placebo-controlled donors. Primary outcomes for this systematic review were graft function and patient and graft survival. Secondary outcome parameters were surrogate markers of organ injury.

Exclusion criteria for this systematic review were 1. articles not in English; 2. duplicate studies; 3. living donors; 4. average donor age < 16 years old; 5. studies with pregnant participants; 6. animal studies; 7. tissue transplantation; 8. donor treatment after graft procurement; 9. ex-situ treatment of the graft; 10. treatment of the recipient; and 11. no information on organ function or survival.

2.2. Search methods for identification of studies

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [8]. Potential RCTs were identified using electronic and manual search strategies. The final electronic literature searches were performed in Pubmed (5 Nov 2016), Embase (5 Nov 2016), and the Cochrane library (7 Nov 2016). The ClinicalTrials.gov register was also searched (7 Nov 2016) to identify unpublished or ongoing trials. The search was limited to RCTs with a highly sensitive search-strategy filter. The bibliographies of identified studies and reviews were manually searched for additional trials. A qualified librarian reviewed the final search strategy. The search strategy for each consulted database is available in the supplementary data (Fig. S1, Table S1 and S2).

2.3. Data extraction and validity assessment

All identified records were screened on title and abstract after removal of duplicates with an algorithm provided by Refworks (ProQuest-LCC, USA). Full articles of selected records were retrieved and assessed for eligibility; disagreements were resolved by consensus. Abstracts not providing information on the study type or outcome parameters were retrieved for full-text evaluation. Study information was extracted independently by two reviewers. The risk of bias assessment was performed according to the Cochrane risk of bias tool [9]. The assessment of study quality included random sequence generation, allocation concealment, performance bias, detection bias, attrition bias, reporting bias, and "other" bias. Quality assessments were performed independently and disagreements were resolved through discussion.

2.4. Data synthesis

Outcome parameters of interest for all transplanted solid organs were: patient and graft survival; development of primary dysfunction, sometimes subdivided in either primary non-function or initial poor function; acute rejection; Intensive Care Unit (ICU) or hospital stay; and post-operative complications (such as post-operative infections or biliary complications, Table 1). Organ-specific parameters of interest were: creatinine clearance, serum creatinine, and delayed graft function (DGF, measured as the need for renal replacement therapy including haemodialysis (HD) or haemofiltration (HF) in the first week post transplantation) (kidney); aspartate transaminase (AST), alanine aminotransferase (ALT), albumin, alkaline phosphatase (AF), bilirubin, gamma-glutamyl transpeptidase (γ GT), and lactate dehydrogenase (LDH) levels, and International Normalised Ratio (INR) (liver); left ventricular function, and left ventricular assist device (LVAD) and HF requirement (heart); and PaO₂/FiO₂ ratio, compliance (plateau pressure at the end of respiration), and organ utilization rates as an indirect way of assessing graft function (lung). Qualitative assessment was performed for single studies that could not be grouped for meta-analyses. For studies that could be grouped, a forest plot was constructed to assess the heterogeneity, using Cochran's Q test and the I²-test (considered significant when $p < .1$ or I² > 30%). A random-effects analysis model was applied, followed by the Mantel-Haenszel test to calculate cumulative relative risk ratios for dichotomous variables. As no more than four studies were included per meta-analysis, funnel plot analyses could not be constructed to distinguish potential asymmetry. All statistical analyses were performed with Review Manager v5.3 (The Cochrane Collaboration 2014).

3. Results

3.1. Literature search and summary of included studies

From 7309 hits in total, 62 studies were assessed. As 29 studies failed to meet our inclusion criteria, a total of 33 articles were included in this systematic review (Fig. 1, Table 1, Table S3). Even though the search strategy was aimed towards all solid organs, only studies on kidney, liver, heart, and lung transplantations were found. In addition, we identified 13 trials that were still ongoing or did not yet publish results (Table 2). As none of the included studies involved interventions in DCD donors, this systematic review describes only trials in DBD donors.

The following treatment strategies for DBD donors were identified: anti-oxidant treatment [10–13], enteral feeding [14], organ retrieval techniques [15, 16], haemodynamic support [17–24], mild therapeutic hypothermia (MTH) [25], immunosuppressants [26–31], ischaemic preconditioning (IPC) [32–39], a lung protection strategy [40, 41], and T3 administration [42]. Table 1 shows a summary of these included studies, while Table S4 shows the risk of bias for these trials. In 16 studies, the methods for patient selection and allocation concealment were adequately performed and described. Eight studies used a placebo-controlled group, whereas the remaining studies had either non-treatment groups ($n = 20$) or compared the intervention to a conventional treatment ($n = 5$).

3.2. Studies that could not be included for meta-analyses

Twenty-two studies [10–18, 21–28, 31, 32, 40–42] were not included for meta-analyses because the type of intervention or outcome parameter could not be compared to other trials included in this review. None of the studies reported a significant effect of the treatment or intervention on ICU or hospital stay.

Four studies tested effects of anti-oxidant treatments in DBD donors on graft function [10–13]. Treatments with *N*-acetylcysteine [12] and L-alanyl-L-glutamine [10] showed no effects following kidney

and liver transplantation, respectively. Studies on Ascorbic acid treatment [11] and donor ventilation with sevoflurane [13] showed improved short-term liver function but did not report effects on patient or graft survival.

Two trials investigated two different hepatic retrieval techniques. Chui et al. [15] showed no differences between single (aortic) or double (aortic and portal) perfusion on liver and kidney transplantation outcomes, whilst D'Amico et al. [16] showed superiority of the double perfusion technique, evidenced by improved short-term liver function, lower rates of re-transplantation, and improved six-month graft and patient survival.

Six out of eight studies on hemodynamic support of the deceased donor could not be grouped for meta-analyses [17, 18, 21–24]. Dopamine treatment improved long-term graft survival after heart [18], but not kidney transplantation [17], despite a reduced incidence of DGF of renal organ grafts [17]. Prostaglandin I₂ treatment improved short-term liver function, but failed to improve patient or graft survival [21]. Protocolised fluid administration did not alter recipient survival after solid organ transplantation [22]. The use of the colloid hydroxyl-ethyl starch (HES) (of unknown molecular weight) did not affect liver function following transplantation [23]; treatment with low molecular weight-HES did increase rates of DGF following renal transplantation [24].

Four out of six trials on the use of immunosuppressive drugs could not be clustered. Administration of neither methylprednisolone and cyclophosphamide [27, 28], nor cyclophosphamide [31], nor prednisolone [26] improved renal transplantation outcomes.

Of the seven studies found on IPC treatment in liver donors, the only study investigating five minutes of IPC showed no benefits following liver transplantation.

The remaining trials investigated possible clinical benefits of enteral feeding [14], MTH [25], albuterol [41] or T3 [42] administration, and a protective lung ventilation strategy [40]. Neither enteral feeding [14], nor albuterol administration [41], nor protective lung ventilation [40] improved survival rates of recipients after heart, lung, liver, or kidney transplantations. MTH decreased the incidence of DGF after kidney transplantation [25]. Lastly, T3 administration did not improve liver function following transplantation [42].

3.3. Studies included for meta-analyses

Eleven studies were identified for further meta-analyses. None of the studies that were included for meta-analyses reported a significant effect of the treatment or intervention on ICU or hospital stay. The meta-analysis on the effects of donor treatment with ADH included 222 participants [19, 20] and showed no difference in the development of DGF after kidney transplantation between treated and untreated DBD donors (Fig. 2).

The meta-analysis on donor methylprednisolone treatment versus placebo or no treatment included a total of 183 participants [29, 30] and showed similar acute rejection rates of liver grafts retrieved from donors treated either with or without methylprednisolone (Fig. 3).

Ten meta-analyses were included on the effects of 10 min of IPC versus no treatment in the liver, with a total of 335 participants from seven trials [33–39]. Results show that IPC treatment did not influence one-year (Fig. 4A,B) or two-year graft and patient survival (Fig. S1A,B). In the short-term, IPC treatment improved AST levels on day one and international normalised ratio (INR) levels on day three after surgery (Fig. 5A,C), but did not affect INR (Fig. 5B) or bilirubin levels (Fig. S1E) one day post-operatively. Also, the incidence of primary non-function or initial poor function was not different between treated and untreated grafts (Fig. S1C,D). The risk of bias for included studies is described in Table S4. In general, the studies included in the meta-analyses were judged to have a relatively high risk of bias.

4. Discussion

This systematic review provides an update on the existing evidence of treatments that were applied to deceased organ donors and aimed to improve graft quality and survival after kidney, liver, heart, and lung transplantations. Our meta-analyses found no consistent evidence to support that any specific donor-management strategy or treatment in DBD donors benefited outcomes after transplantation (see Fig. 6 for an overview of all included studies per organ). This finding is in line with previous and older reviews published on this topic [43–47].

4.1. Anti-oxidants

Brain death and IRI are associated with increased levels of reactive oxygen species (ROS), which play a central role in the deleterious effects following transplantation [48]. Therefore, the use of anti-oxidants to scavenge ROS or support cellular detoxification appears to be an intuitively sound strategy to limit IRI. However, none of the four compounds tested improved survival rates following kidney (*N*-acetylcysteine) [12] or liver (*L*-alanyl-glutamine, ascorbic acid, sevoflurane) [10, 11, 13] transplantation, even though ascorbic acid [11] and donor ventilation with sevoflurane [13] improved short-term liver function. In addition, Minou et al. showed that sevoflurane did have protective effects in marginal livers with various degrees of hepatic steatosis [13]. Recently, a RCT on simultaneous kidney and pancreas transplantations showed that treatment with 600 mg alpha-lipoic acid in both donors and recipients resulted in decreased inflammatory markers in the transplanted grafts [49]. These promising results may encourage more trials with anti-oxidant treatment strategies, either in the donor, during graft preservation or at time of reperfusion.

4.2. Enteral feeding

For critically ill patients, enteral feeding is the preferred route for nutritional support [50]. However, nutritional support is usually withheld in DBD donors due to suggested negative side effects of both enteral and parenteral feeding. Negative effect of enteral feeding are thought to be impaired nutritional uptake as a result of the inflammatory response taking place in the bowel of DBD donors [51]. Alternatively, parenteral feeding is related to metabolic, infectious, and mechanical complications [52]. The only RCT on this topic compared fasting of the DBD donor to enteral feeding with a diet containing fatty acids, antioxidants, and glutamine. This study shows that transplant outcomes and inflammatory parameters were not different between groups following on average 12.6 h of enteral feeding [14]. Effects of nutritional duration were not investigated. As about 30% of the donors were able to metabolise enteral nutrition without negative side effects [14], enteral feeding appears to be safe method for nutritional support in DBD donors.

4.3. Organ retrieval techniques

During organ procurement, there are two techniques to flush-out and perfuse the liver graft. The classic, dual perfusion technique flushes the graft via both the aorta and portal vein [53]. Alternatively, most centres now use single aortic perfusion as an simplified, alternative method that is of particular interest during multiple organ harvesting or split liver transplantation [16], followed by additional back-table flush of the liver. The two RCTs that compared these techniques show conflicting results [15, 16]. Chui et al. [15] found no differences between the techniques following liver and kidneys transplantation, while D'Amico et al. [16] found an improved function of marginal livers after dual perfusion. Unfortunately, it is challenging to draw conclusions from these studies: Chui et al. did not provide a full report on their study design, whilst D'Amico et al. focused primarily on marginal donors, which makes extrapolation of these results to the general donor population

Table 1
Summary of randomized controlled trials of interventions in deceased organ donors.

Intervention type	Source	Year	Number of patients randomized	Treatment group (administration mode and time)	Control group	Outcome (subgroup)	Specific end-points (time after transplantation)	Effect organ function (treatment vs. control group)	Effect patient/graft survival
Anti-oxidants	Orban et al. [12]	2015	217	600 mg N-acetylcysteine (bolus, 1 h before and 2 h after angiography)	No treatment	Kidney function	sCr and eGFR (D1,7,14,30); DGF (HD requirement/ oliguria/ sCr >500 µmol/L, D0-7); acute rejection (D0-30); patient and graft survival (≤Y1); and recipient hospital stay	No	No (graft)
	Barros et al. [10]	2015	33	50 g L-alanyl-glutamine (bolus, 40 min before cold ischaemia)	Placebo	Liver function	AST, ALT, bilirubin, INR (D0,1,3,7,30); patient and graft survival (duration unknown)	No	No (patient and graft)
	Kazemi et al. [11]	2015	40	100 mg/kg ascorbic acid (bolus, 6 h before procurement) and subsequent 100 mg/kg/p6h (infusion, until procurement)	No treatment	Liver function	AST, ALT, bilirubin (D1,3,10)	Positive - AST and ALT on D3 vs. D1 (data not specified)	Not measured
	Minou et al. [13]	2012	60	2.0% sevoflurane (end expiratory, during procurement)	No treatment	Liver function (degree of steatosis)	Survival	Peak ALT, AST (D0-2); PNF, IPF (bilirubin ≥10 mg/dL, INR ≥ 1.6, AST/ALT ≥2000 IU/L, D0-7); and recipient ICU/hospital stay	Positive - Peak AST: 792 vs. 1861 IU/L - IPF: 17 vs. 50%
Enteral feeding	Hergenroeder et al. [14]	2013	36	Enteral nutrition containing omega-3-PU FA, anti-oxidants, glutamine (1 g protein/kg per 24 h, until procurement)	No treatment	Survival	Patient and all solid organ-graft survival (M0-6)	Not measured	No (patient and graft)
Organ retrieval techniques	Chui et al. [15]	1998	40	Single aortic perfusion	Double perfusion (aortic and portal)	Kidney and liver function	AST, ALT, INR (D1-2); PNF; patient and graft survival (≤M3)	No	No (patient and graft)
	D'Amico et al. [16]	2007	58	Double perfusion (aortic and portal)	Single aortic perfusion	Liver function	AST, ALT, bilirubin, INR (D1-3,5,7,M1,3,6,9,12); PDF (PNF + IPF, ≤D7); patient and graft survival (≤M6); and re-transplantation	Positive - AST: 763 vs. 2125 IU/L, D2 - ALT: 614 vs. 1580 IU/L, D2 -PDF: 6 vs. 41% - Re-transplant: 0 vs. 5	Positive - patient: 100 vs. 68% - graft: 100 vs. 58%
Haemo-dynamic support	Benck et al. [18]	2011	264	4 µg/kg/min dopamine (infusion, after consent until procurement)	No treatment	Heart function	LVF, LVAD and HF requirement; acute rejection (M0-M1); patient and graft survival (≤M3, Y1,2,3)	No	Positive (patient and graft) - 91 vs. 72%, Y1 - 87 vs. 68%, Y3 Insufficient data reported
	Pennefather et al. [19]	1995	24	300 µg/kg/min arginine vasopressin (infusion, when haemodynamically stable after BD confirmation)	Placebo	Heart, kidney, liver, lung function	Good initial function: - kidney: DGF - liver/lung: unclear - heart: inotropics requirement	No	
	Schnuelle et al. [17]	2009	264	4 µg/kg/min dopamine (infusion, after consent until procurement)	No treatment	Kidney function (infusion and CI time)	sCr, DGF (dialysis requirement) (D0-7); acute rejection (≤M1); patient and graft survival (≤Y3)	Positive - DGF: 25% vs. 35% - DGF subgroup long vs. short infusion time: 21% vs. 36%	No (patient and graft)
	Guesde et al. [20]	1998	97	1 µg desmopressin (bolus, every 2 h when diuresis <300 mL/h after consent until 2 h before procurement)	No treatment	Kidney function	sCr, DGF (HD requirement) (D0-15); survival (≤Y5)	No	No
	Cittanova et al. [24]	1996	27	LMW Hydroxyethyl-starch up to 33 mL/kg with additional fluid gelatin when	Placebo	Kidney function	DGF (HD/HF, D1-8), sCr (D1,2,5,10)	Negative	Not measured

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Table 1 (continued)

Intervention type	Source	Year	Number of patients randomized	Treatment group (administration mode and time)	Control group	Outcome (subgroup)	Specific end-points (time after transplantation)	Effect organ function (treatment vs. control group)	Effect patient/graft survival
	Klein et al. [21]	1999	112	needed 500 µg prostaglandin I2 (bolus, before procurement)	No treatment	Liver function	AST, ALT, bilirubin, GLDH, AF, γGT (D0–28); PNF; in-hospital survival; vascular thrombosis, and recipient ICU/hospital stay	Positive - AST/ALT, D0,1 - GLDH, D1–4	No (patient and graft)
	Randell et al. [23]	1990	16	500 mL 6% hydroxyethyl-starch and additionally 1000 mL when CVP <5 mmHg and crystalloids (infusion, before procurement)	Crystalloids	Liver function	PNF	No	Not measured
	Al-Khafaji et al. [22]	2015	556	Protocolised resuscitation using a consensus-based pulse pressure variation algorithm (until procurement)	Standard donor management	Recipient survival (ECD donors)	Number of transplanted organs per donor, recipient (hospital free) survival (≤M6)	Not measured	No (patient)
Mild therapeutic hypothermia	Niemann et al. [25]	2015	394	Mild therapeutic hypothermia (34–35 °C, after declaration of BD until procurement)	Normothermia (36.5–37.5 °C)	Kidney function (ECD donors)	DGF (dialysis requirement D0–D7)	Positive - DGF: 28.2% vs. 39.2% - DGF subgroup ECD vs. SCD: 31% vs. 57%	Not measured
Immuno-suppressants	Kainz et al. [26]	2010	306	1000 mg methylprednisolone (bolus, ≥ 3 h before procurement)	Placebo	Kidney function (donor ages >50)	SCr, DGF (D0–7)	No	No (graft)
	Chatterjee et al. [31]	1981	50	60 mg/kg cyclophosphamide (infusion, t ≥ 4 h before procurement when possible)	No treatment	Kidney function	Graft failure (≤Y1)	Not measured	No (graft)
	Souillou et al. [27]	1979	34	5 g methylprednisolone and 5 g cyclophosphamide (infusion, t ≥ 5 h before procurement)	Placebo	Kidney function	SCr, graft survival, (M3,6,12)	No	No (graft)
	Jeffery et al. [28]	1978	Unclear	5 g methylprednisolone and 7 g cyclophosphamide (infusion, t ≥ 4 h before procurement when possible)	No treatment	Kidney function	sCr, rejection, patient and graft survival (M3,6,12)	No	No (patient and graft)
	Amatschek et al. [29]	2012	83	1000 mg methylprednisolone (bolus, between 3 and 6 h before procurement)	Placebo	Liver function	AST and ALT (D0–7); rejection, patient and graft survival (≤Y3); bile duct complications, recipient ICU/hospital stay	No	No (patient and graft)
	Kotsch et al. [30]	2008	100	250 mg methylprednisolone (bolus at consent + 100 mg/h IV until procurement)	No treatment	Liver function	AST, ALT, bilirubin, AF, γGT (D0–10); acute rejection (AR), PNF (≤M6); and biliary lesions	Positive - AST: 327 vs. 1470 / ALT: 461 vs. 758 / AP: 127 vs. 157 / γGT: 135 vs. 236 (D1) - AST: (31 vs. 41 / ALT: 75 vs. 115 / bilirubin: 2.3 vs. 4.9(D10) - Bilirubin: 0.6 vs. 1.0 (M6) - AR: 22% vs. 36%, M6	No (graft)
Ischaemic pre-conditioning	Zapati-Chavira et al. [39]	2015	13	10 min IPC (hilar clamping, followed by 10 min reperfusion before procurement)	No treatment	Liver function	AST, ALT, bilirubin, INR (D1,3,7); PNF, IPF; patient and graft survival (M6, 24); and recipient ICU stay	Slightly negative - Bilirubin: 3.5 vs. 1.6 mg/dL	No
	Cescon et al. [35]	2009	40	10 min IPC (hilar clamping, followed by 15 min reperfusion before procurement)	No treatment	Liver function	AST, ALT, bilirubin, INR (D1–7, 14, 21); PNF, IPF; patient and graft survival (Y0–Y1), and recipient ICU stay	No	No
	Franchello et al. [38]	2009	75	10 min IPC (hilar clamping, followed by 30 min reperfusion before procurement)	No treatment	Liver function	AST, ALT, bilirubin, INR (D1,3,7); acute rejection, PNF; graft survival (M6); infections (M1), and recipient hospital stay	Slightly positive for subgroup marginal grafts: - AST: 936 vs. 1268 (D1), 339 vs. 288 (D3), UI/L	No

	Jassem et al. [37]	2009	44	10 min IPC (hilar clamping, followed by (on average) 30 min reperfusion before procurement)	No treatment	Liver function	AST (D1–5); bilirubin and INR (D7, 14,30); acute rejection	Slightly positive - AST: 410 vs. 965 (D1), 198 vs. 488 (D2), 120 vs. 216 (D3) IU/L	Not measured
	Koneru et al. [33]	2007	101	10 min IPC (hilar clamping, followed by median of 39 min reperfusion before procurement)	No treatment	Liver function (marginal grafts)	AST, ALT, bilirubin, INR (D1–3,7,14,30); injury score (biopsy); acute rejection (D0–30); PNF; patient and graft survival (\leq Y2); blood transfusions; lung edema, and recipient ICU/hospital stay	Negative - AST: 385 vs. 250 IU/L, D2 - ALT: 699 vs. 520 (D1), 583 vs. 353 (D2) IU/L	No (patient and graft)
	Amador et al. [36]	2007	60	10 min IPC (hilar clamping, followed by 10 min reperfusion before procurement)	No treatment	Liver function	AST, ALT, bilirubin, INR (D1–10); PNF (D0–7); acute rejection; patient (Y2,Y4) and graft survival (2Y); vascular and biliary complications, and recipient ICU/hospital stay	Positive - AST: 894 vs. 1216 (D0), 918 vs. 1322 (D1), 500 vs. 756 (D2), 201 vs. 344 (D3), 120 vs. 170 (D4) U/L - ALT 671 vs. 1216 (D0), 235 vs. 304 (D7) U/L - Bilirubin 2.5 vs. 3.6 mg/dL (D1)	No (patient and graft)
	Cescon et al. [34]	2006	53	10 min IPC (hilar clamping followed by 15 min reperfusion before procurement)	No treatment	Liver function	AST, ALT, bilirubin, INR (D1-D7,D14,D21); injury score (biopsy); PNF and IPF; patient and graft survival (\leq Y1); recipient ICU stay	Positive - AST (D1,2) - ALT (D1–3,7) Exact numbers not given	No (patient and graft)
	Koneru et al. [32]	2005	62	5 min IPC (hilar clamping followed by >30 min reperfusion before procurement)	No treatment	Liver function	AST, ALT, bilirubin, INR (D1,3,7); injury score (biopsy); PNF; patient and graft survival (\leq M6); and recipient hospital stay	No	No (patient and graft)
Lung protection strategies	Ware et al. [41]	2014	506	5 mg q4h albuterol sulphate (nebulization every 4 h, from study enrolment until procurement)	Placebo	Lung function (marginal grafts)	PaO ₂ /FiO ₂ , static compliance; lung/kidney/heart/pancreas utilization rates; patient survival (D30, \leq Y1); and recipient hospital stay	Slightly negative - Lung utilization (marginal grafts): 9% vs. 20% - Kidney utilization: 77 vs. 88%	No (patient)
	Mascia et al. [40]	2010	118	Protective ventilation strategy (TV 6–8 mL/kg and PEEP 8–10 cm, during 6 h observational period until organ procurement)	Conventional ventilation strategy (TV 10–12 mL/kg and PEEP 3–5 cm)	Survival	Patient survival (\leq M6)	Not measured	No (patient)
Thyroid hormone	Randell et al. [42]	1992	25	2 μ m/h triiodothyronine (infusion, at start procurement)	No treatment	Liver function	Max. ALAT, bilirubin, albumin (D0–7); and recipient ICU/hospital stay	No	Not measured

ALT: Alanine Aminotransferase; AP: Alkaline Phosphatase; AR: Acute Rejection; AST: Aspartate Aminotransferase; BD: Brain Death; CI: Cold Ischaemia; D: Day; ECD: Extended Criteria Donor; eGFR: Estimated Glomerular Filtration Rate; γ GT: gamma-glutamyl transpeptidase; HD: Haemodialysis; HF: Haemofiltration; INR: ICU: Intensive Care Unit; International Normalised Ratio; IPF: Initial Poor Function; LVAD: Left Ventricular Assist Device; LVF: Left Ventricular Function; M: Month; PDF: Primary Dysfunction; PNF: Primary Non-Function; SCD: Standard Criteria Donor; sCr: Serum Creatinine; Y: Year.

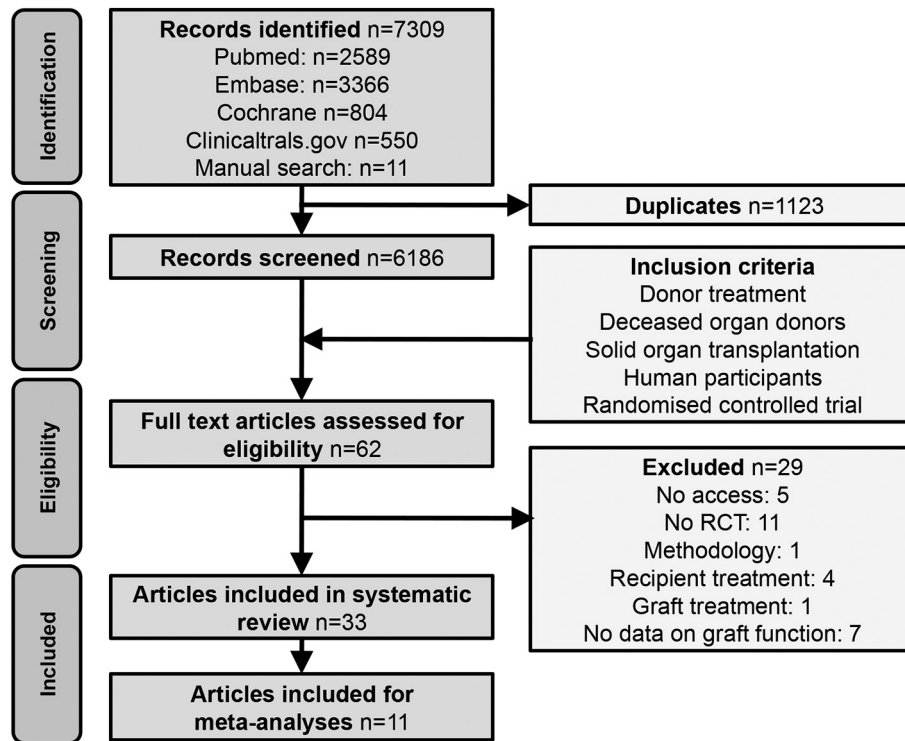


Fig. 1. PRISMA diagram of the literature search. Flow chart summarising the search strategies and subsequent selection of trials for this systematic review and the performed meta-analyses.

difficult. In conclusion, there is currently no strong evidence suggesting superiority of either perfusion technique.

4.4. Haemodynamic support

Diabetes insipidus is a common finding amongst DBD donors and may cause haemodynamic instability in the donor due to hypovolaemia and electrolyte disturbances [20]. However, treatment strategies to improve haemodynamic instability in the donor are frequently based on personal experience as there is no general consensus on what treatment is most effective.

Treatment of hypovolaemia with crystalloids has been suggested to cause organ oedema, diminished organ perfusion, and impaired oxygen diffusion in the lungs. Therefore, the use of colloids was introduced to avoid this build-up of extravascular fluids. In DBD donor care, two RCTs studied the effects of donor treatment with the colloid HES. The study by Randell et al. [23] showed no difference in graft function after the administration of HES (unknown molecular weight) compared to saline prior to liver transplantation. However, treatment of DBD donors with low molecular weight HES resulted in harmful short-term effects in kidney grafts [24]. This result has led to the notion that HES should not be administered to potential kidney donors. However, it should be noted that both studies have a high risk of bias, which may have influenced the results and possibly their interpretation. A different approach to achieve donor euvoalaemia is to monitor the pulse pressure variation and correct hypotension according to a protocol that includes fluid or vasopressor drug administration [22]. However, implementation of this protocol failed to improve the recipient survival rate or number of organs transplanted per donor.

Alternatively, five RCTs tested the effects of pharmaceuticals as a means to provide haemodynamic support. Firstly, administration of ADH did not improve graft function (Fig. 2), but did result in decreased urine output and, therefore, the need for fluid therapy. Secondly, administration of dopamine in DBD donors had a positive effect on short-term renal graft function [17], whilst in heart transplantation it improved

long-term graft and patient survival [18]. Finally, administration of prostaglandin I₂ improved transaminase levels immediately and one day after liver transplantation, but failed to improve graft survival [21].

In conclusion, unstable haemodynamic parameters should be treated appropriately with volume replacement and haemodynamic resuscitation. However, volume replacement with HES should be used with caution, especially when kidney donation is considered. Haemodynamic support using dopamine appears to be beneficial in heart and possibly in kidney transplantation. Thus, further studies on the use of dopamine as part of standard donor care and its effects on other organ grafts is desirable.

4.5. Hypothermia during donor management

Promising results published by Niemann et al. show that MTH of the deceased donor (cooling of the donor from 37 °C to 34–35 °C at the Intensive Care Unit) preserved kidney function during donor management in the Intensive Care Unit, with decreased DGF rates after transplantation. These results are in line with a retrospective cohort study on patients with a myocardial infarction, for whom MTH treatment prior to and during their percutaneous coronary intervention improved survival rates and preserved renal function [54]. However, these protective effects of MTH could not be reproduced in RCTs on patients with cardiac arrests [55, 56] or intracranial aneurysms [57]. Long-term effects of MTH treatment are eagerly awaited before implementation of this technique can be considered as standard donor care [25]. Furthermore, the study by Niemann only included statically cold-stored kidneys, whilst hypothermic machine perfusion has demonstrated to significantly reduce DGF and improve graft survival, especially in older and higher-risk donor kidneys [58]. Therefore, the question arises whether both treatment regimens are necessary and which one is more cost-effective. Recently, a new trial has started that will compare the effects of donor MTH with hypothermic machine perfusion on graft function after transplantation⁶².

Table 2
Identified studies that are still recruiting or have not yet published results.

Trial id	Investigator	Treatment	Participants	Start inclusion	Stop inclusion	Title	Sponsor
NCT02581111	Dhar	Naloxone	250	2015	2016	Randomized Placebo-controlled Trial of Intravenous Naloxone to Improve Oxygenation in Hypoxemic Lung-Eligible Brain-Dead Organ Donors	Washington University School of Medicine, USA
NCT02435732	Fernandez	C1 inhibitor	72	2016	2018	A Phase I, Single Center, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Tolerability of C1 Inhibitor (CINRYZE) as a Donor Pretreatment Strategy in Brain-Dead Donors Who Meet a Kidney Donor Risk Index (KDRI) Above 85%	University of Wisconsin, Madison, USA
NCT02211053	Frenette	Levothyroxine	60	2014	2016	Evaluation of the Efficacy and Safety of Levothyroxine in Brain Death Organ Donors: a Randomized Controlled Trial (ECHOT4)	Hopital du Sacre-Coeur de Montreal, Canada
NCT01860716	García-Gil	Melatonin	60	2013	2013	Impact of Melatonin in the Pretreatment of Organ Donor and the Influence in the Evolution of Liver Transplant: a Prospective, Randomized Double-blind Study	Hospital Clínico Universitario Lozano Blesa, Spain
NCT02907554	Ichai	Cyclosporine A	648	2016	2018	Effects of Cyclosporine A Pretreatment of Deceased Donor on Kidney Graft Function: A Randomized Controlled Trial	University Hospital, Clermont-Ferrand, France
NCT01939171	Jiminez	Thymoglobulin	20	2010	2013	Conditioning of the Cadaver Donor by Thymoglobulin Administered to Reduce the Pro-inflammatory State After Brain Death.	Instituto de Investigación Hospital Universitario La Paz, Spain
NCT01160978	Jokinen	Simvastatin	46	2010	2015	Donor Simvastatin Treatment in Organ Transplantation	Helsinki University Hospital, Finland
NCT02341833	Joris	2% sevoflurane	240	2015	2017	Effects of Preconditioning With Sevoflurane During Organ Procurement From Brain-Dead Donors: Impact on Early Function of Liver Allografts	University Hospital of Liege, Belgium
NCT00975702	Koneru	Remote ischaemic preconditioning	85	2009	2014	Phase III Study of Efficacy of Remote Ischaemic Preconditioning in Improving Outcomes in Organ Transplantation (RIPCOT)	The State University of New Jersey, USA
NCT01515072	Koneru and Washburn	Remote ischaemic preconditioning	320	2011	2014	Remote Ischaemic Preconditioning in Neurological Death Organ Donors (RIPNOD)	The State University of New Jersey, USA
NCT01140035	Niemann	Intensive insulin treatment	200	2009	2011	Intensive Insulin Therapy in Deceased Donors - to Improve Renal Allograft Function and Transplanted Allograft Outcomes	University of California, San Francisco, USA
NCT02525510	Niemann	Hypothermia/normothermia and static cold storage/machine perfusion	500	2015	2019	Deceased Organ Donor Interventions to Protect Kidney Graft Function	University of California, San Francisco, USA
NCT00718575	Selzner	Ischaemic preconditioning	50	2008	2012	A Prospective, Randomized Trial to Investigate the Effects of Glucose/ Ischaemic Preconditioning Donor Pretreatment on Reperfusion Injury in Deceased-Donor Liver Transplantation	University Health Network, Toronto, Canada

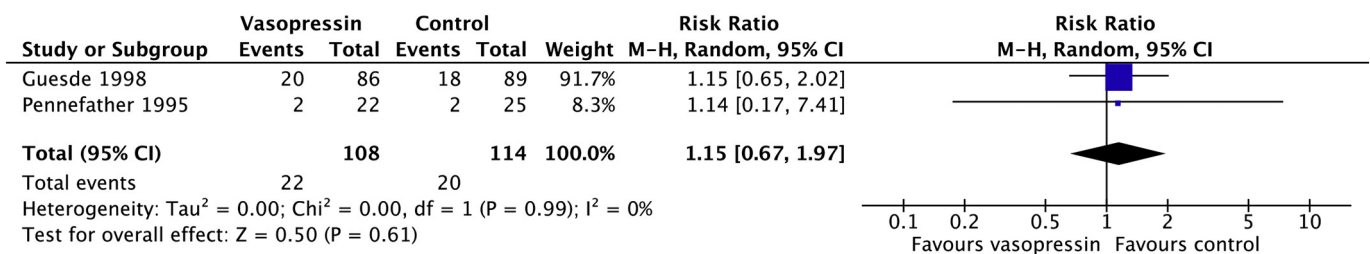


Fig. 2. Meta-analysis for antidiuretic hormone treatment in kidney transplantation. A forest plot comparing the effects of antidiuretic hormone treatment versus placebo or no treatment on delayed graft function, defined as the need for haemodialysis within two weeks post-kidney transplantation.

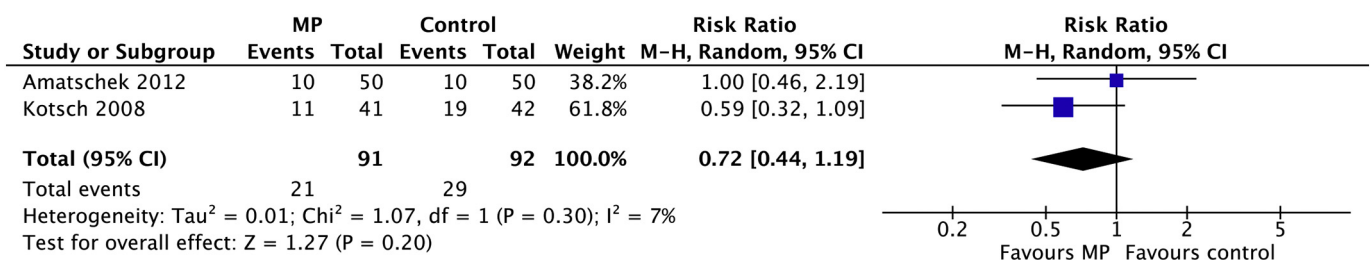


Fig. 3. Meta-analysis for methylprednisolone treatment in liver transplantation. A forest plot comparing the effects of methylprednisolone treatment versus placebo or no treatment on the incidence of acute rejection within one to six months after liver transplantation.

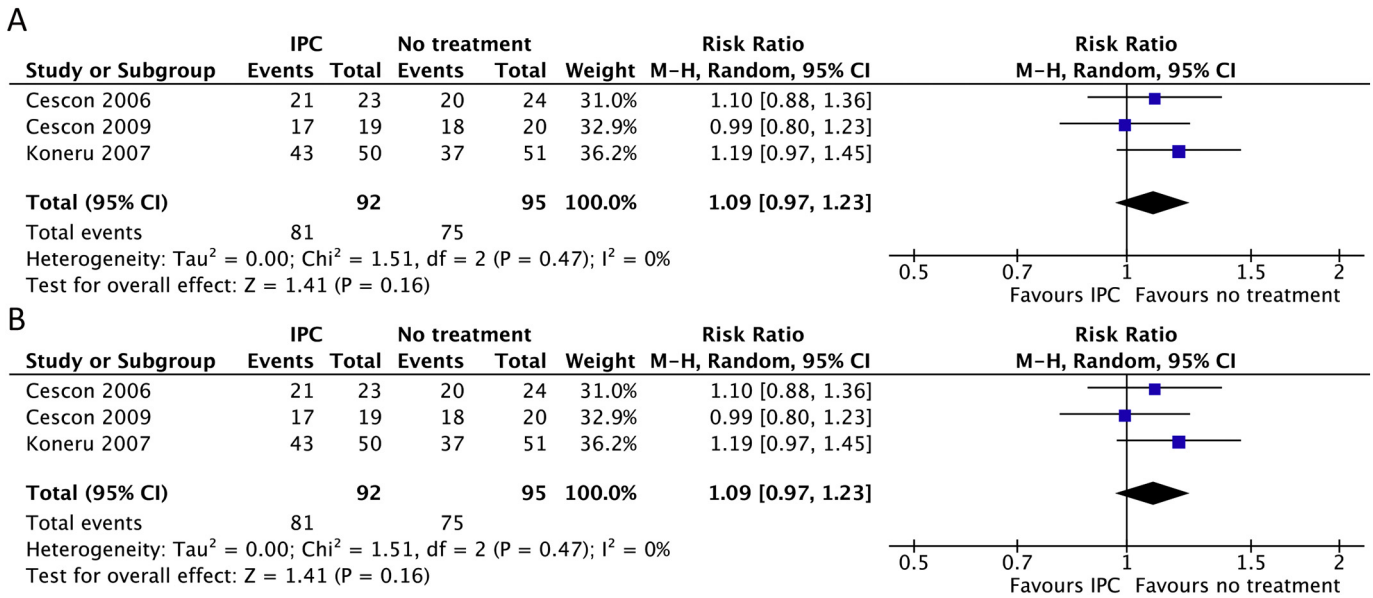


Fig. 4. Meta-analyses for the effect of ischaemic preconditioning (IPC) treatment on survival. Forest plot comparing the effects of 10 min of IPC treatment during liver transplantation: A. one-year graft survival and B. one-year patient survival.

4.6. Immunosuppression

Brain death results in pro-inflammatory changes, both systemically and in the organ grafts [4]. Additionally, endogenous cortisol levels decrease after the onset of brain death [59, 60]. Therefore, it is conceivable that donor treatment with immunosuppressive drugs could prevent pro-inflammatory changes and improve graft quality, as was suggested in experimental animal studies [61, 62] and a large retrospective cohort study [63]. However, our meta-analysis on the effects of prednisolone

treatment showed no changes in the frequency of acute rejection following liver transplantation (Fig. 3). Furthermore, immunosuppressive drug treatment did neither improve long-term graft function, nor patient, nor graft survival following kidney and liver transplantation [26–31], despite a decrease in DBD-related pro-inflammatory changes in these organs. In addition, the one study that investigated the effects of immunosuppressive therapy in marginal donors (higher donor age), found no differences in kidney function or graft survival [19]. Finally, the short-term benefits of prednisolone treatment in liver graft

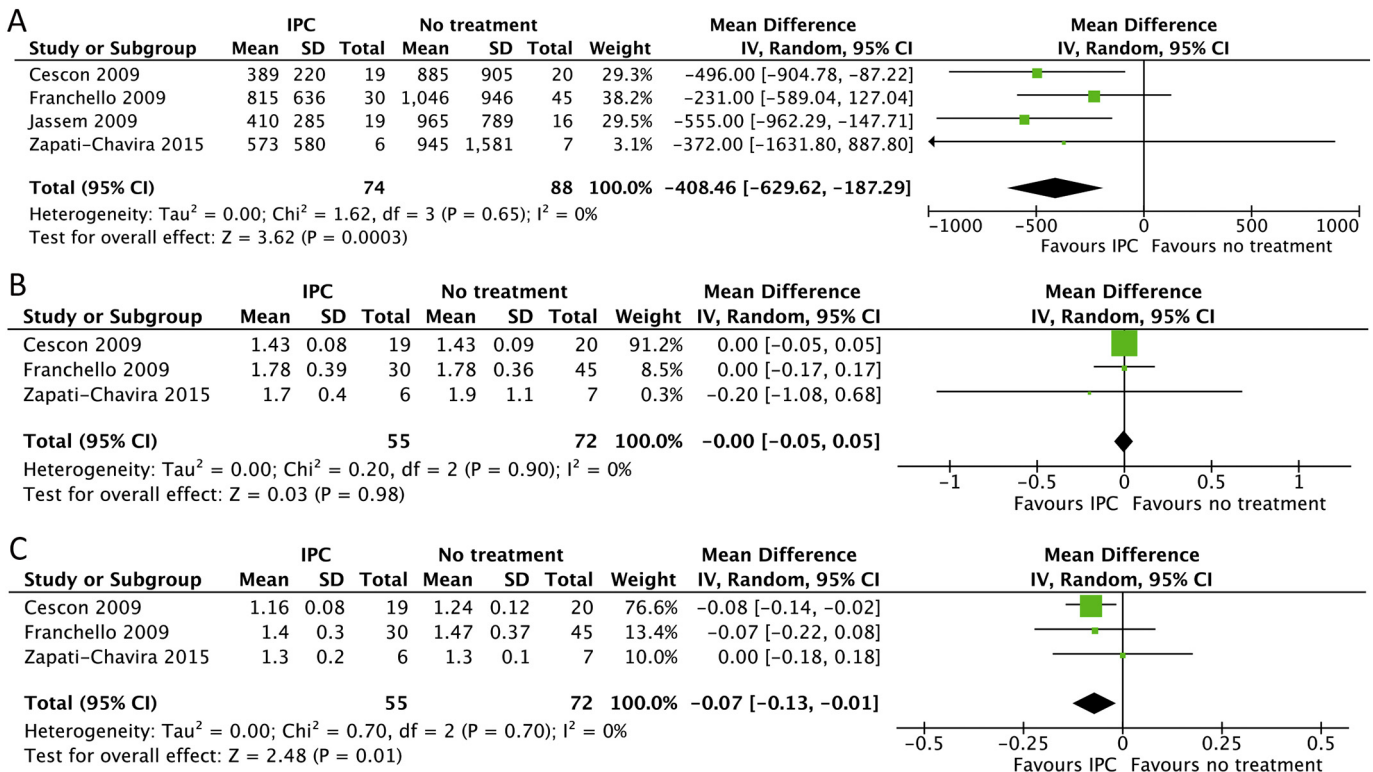


Fig. 5. Meta-analyses for the effect of ischaemic preconditioning (IPC) treatment on liver function. Forest plot comparing the effects of 10 min of IPC treatment in liver transplantation: A. the difference in AST levels one day after transplantation, B. the difference in INR levels one day after transplantation, and C. the difference in INR levels three days after transplantation.

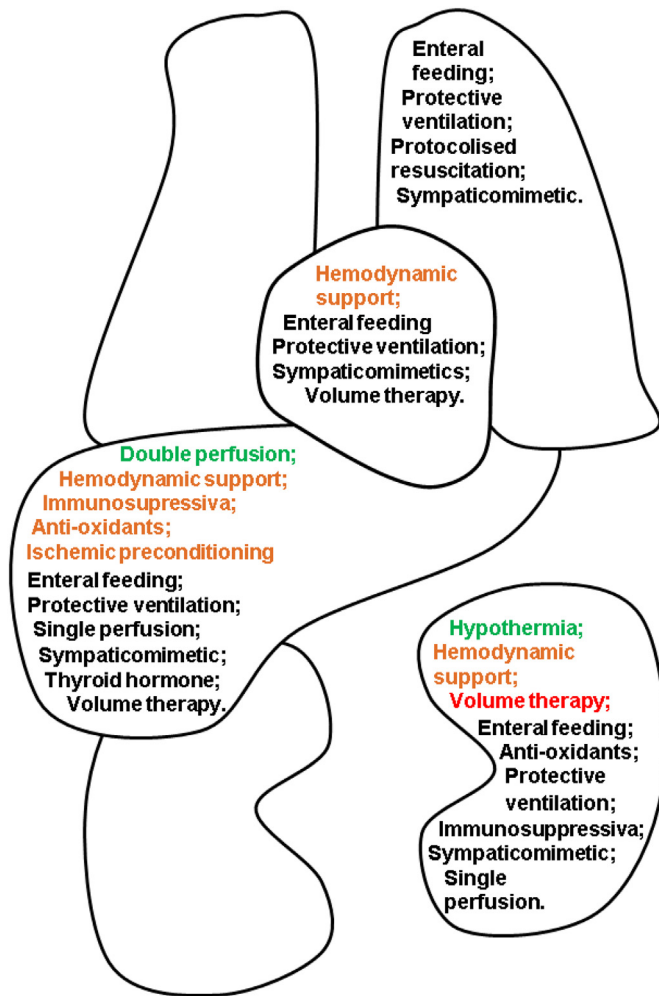


Fig. 6. Overview of all systematically tested, clinical treatments or interventions in the brain-dead donor with outcome parameters pertaining the lungs, liver, heart, and kidneys. Treatments or interventions denoted in black did not affect graft function or graft and patient survival. Treatments or interventions denoted in green were beneficial, those in red were detrimental, and those in orange inconclusive.

as observed by Kotsch et al. [30], could not be reproduced in a similar study by Amatschek et al. [29]. In conclusion, these studies do not support the routine use of methylprednisolone alone, or in combination with cyclophosphamide, in the management of DBD donors.

4.7. Ischaemic preconditioning

Ischaemia-reperfusion injury (IRI) is an unavoidable deleterious process during organ transplantation. Initially, the organs suffer from a period of ischaemia during procurement, followed by injury during subsequent reperfusion in the recipient. Murry et al. first introduced the concept of IPC as a method to induce transient ischaemia, preparing the organs for subsequent IRI [64]. We identified eight studies on IPC, all performed prior to liver transplantation. Pooled data from our meta-analyses shows a short-term benefit of ten-minute IPC treatment that seems independent of the duration of warm ischemia, evidenced by improved post-operative AST and INR levels. Even though long-term effects on patient and graft survival were lacking and the different studies showed some conflicting results, data from our meta-analysis highly suggests a potential benefit of IPC prior to liver transplantation, particularly as AST levels in the first week after transplantation have been correlated to early graft survival (<3 months) [65]. The RCT by Franchello et

al. reported improved AST levels in a subgroup of marginal donors (>65 years old and/or with steatosis) [38]. Further studies powered to detect changes in short-term survival rates and adjusted for graft quality should be performed to elucidate whether IPC should be included in standard donor care. Furthermore, there are currently several on-going trials investigating remote IPC, a technique where (repetitive) cycles of ischaemia are applied to a remote organ or tissue such as a limb with, consequently, a possible wider therapeutic timeframe in the donor (Table 2).

4.8. Lung protection strategies

DBD donors are at increased risk of pulmonary damage caused by increased pulmonary hydrostatic pressure, catecholamine release, and pro-inflammatory changes [66]. However, the optimal lung ventilation strategy in deceased donor care has been a topic of controversy [67]. Conventionally, high tidal volumes (TV) (10–12 mL/kg) were applied, ensuring hypocapnia and a decrease in intracranial hypertension, and combined with low positive end-expiratory pressures (PEEP) (3–5 cm H₂O) to provide optimal oxygenation [66]. Recent studies on patients with the acute respiratory distress syndrome support an alternative strategy with a low TV and high PEEP, as this strategy appears to have improved outcomes of acute lung injury by reducing ventilation related-injury and preventing atelectasis [66, 68]. Based on these studies, Mascia et al. studied this protective ventilation strategy with low TV (6–8 mL/kg) and high PEEP (8–10 cm H₂O) in DBD donor care [66]. Even though this ventilation strategy did not improve patient survival, there was a significant increase (27–54%) in the number of lungs transplanted [40]. These data have supported the implementation of this protective lung ventilation strategy as the preferred ventilation strategy for deceased donors, according to the recent guidelines from the Eurotransplant region as well as the American Thoracic Society [69, 70].

An alternative strategy to protect the lungs is the use of beta-2-adrenergic agonists, which increase the rate of fluid clearance from the lungs, potentially lowering the risk of pulmonary oedema and subsequent infiltrates, and improving oxygenation capacity [71]. However, treatment of the donor with aerosolised albuterol did not improve lung function, recipient survival, or lung utilization rates [41]. A subgroup analysis of marginal donor lungs only even indicated lower lung utilization in the albuterol-treated group. Finally, albuterol treatment resulted in a lower kidney utilization rate of 77% vs. 88% in the placebo-treated group. As such, donor treatment with albuterol does not seem to improve lung function and may have a negative impact on marginal donor lungs as well as kidney grafts.

4.9. Triiodothyronine

Brain death causes ischaemia of the brain and subsequent cessation of the hypothalamic-pituitary axis. As a result, plasma levels of the active thyroid hormone T₃ diminish in a matter of hours, whereas variable levels of levothyroxine (T₄), reverse T₃, and thyroid stimulating hormone have been observed [43]. A large retrospective cohort of 66,629 donors suggested that T₃ treatment improved the haemodynamic profile of donors and increased the number of organs transplanted [72]. However, the only RCT that has evaluated post-transplantation graft function failed to show any effects of T₃ therapy on liver function [42]. During the screening process, we did identify nine RCTs that assessed effects of T₃ treatment on haemodynamic stability in the donor. Of these studies, none found any differences in haemodynamic donor parameters or inotropic needs [42, 73–80]. As a result, the current national guidelines of National Health Service Blood and Transplant in the UK no longer advise administration of a rather costly T₃ as part of the DBD donor management.

4.10. Limitations of this review

Firstly, the number of RCTs that investigated treatment strategies in the donor and their impact on graft function and survival after transplantation is limited. Furthermore, as our search strategy focused on donor treatment only, potentially promising treatment strategies of the graft after procurement and during preservation were excluded that may be of a pre-transplant treatment potential. In addition, several studies we did include were performed with a low number of participants, did not report power calculations or were underpowered to detect changes in the outcome parameters as stipulated in this review. Consequentially, potential effects on organ function or survival might have been missed and interpretation of the data from these studies should be done with caution. Furthermore, we acknowledge that some outcome parameters, such as plasma bilirubin to assess liver function or number of organs transplanted in the case of the kidney, are possibly weakly correlated to organ injury. However, as these endpoints were assessed in conjunction with other biomarkers, the prognostic value of these endpoints is strengthened. The few number of studies also limited us from assessing the risk of publication bias or perform subgroup analyses. Therefore, drawing conclusions from these studies is risky, particularly when grouping for meta-analyses was not possible. Additionally, we found limited studies on lung transplantation, and no studies on pancreas or intestinal transplantations. Lastly, we realise that several promising treatment strategies published in relevant animal models are not included in this article. However, we believe that these studies were outside the scope of this review as interpretation of these results are not yet influential in clinical decision making in deceased donor care.

5. Conclusions

The current global shortage of suitable donor organs and often uncertainty which organ to accept or decline, underlines the need for optimisation of deceased donor care. Treatment strategies aim at reducing the detrimental effects of haemodynamic, hormonal, inflammatory, and metabolic disturbances prior to organ retrieval. Better conditioning of the grafts-to-be and reducing, or even preventing, donor-related injury prior to preservation and transplantation have become important goals to transplant higher risk donor organs, without compromising outcomes after transplantation. Unfortunately, current donor management protocols may vary considerably per centre and are based on low-level evidence. In this systematic review, we could not find consistent evidence supporting that any individual treatment that has been tested until now will protect donor organs or improve survival after transplantation. More organised and defined RCTs are required to identify and validate possible benefits of innovative treatments before clinical implementation can be recommended as part of standard donor care. We feel that a concerted action between professionals in Intensive Care and organ transplantation is needed to gain better insight and stimulate clinically relevant interventions in DBD donors.

Authors' contributions

AE and LD both performed the initial search, selection and assessment of the articles, and wrote the manuscript. HL and RP contributed to the revision of this manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors have no conflict of interests to declare.

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Appendix A. Supplementary data

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