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EFFECT OF CORTICOSTEROID ADMINISTRATION ON NEUROLOGICALLY DECEASED ORGAN DONORS AND TRANSPLANT RECIPIENTS : A SYSTEMATIC REVIEW AND META-ANALYSIS

My manuscript is submitted as an original works:

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ABSTRACT

Objectives : This review investigate the impact of corticosteroids on donation rates and transplant outcomes in light of findings from randomized controlled trials (RCTs) and to highlight the sources of uncertainty in this unresolved donor management issue.

Data Sources : We searched electronic databases, trial registries, and conference proceedings for RCTs evaluating corticosteroid therapy in neurologically deceased donors.

Study Selection & Data Extraction : Independent reviewers assessed eligibility, evaluated risk of bias, and abstracted data, including donor hemodynamic data, number of organs recovered, and transplant outcomes. Where possible, we pooled results. For each outcome we assessed the overall quality of evidence using GRADE methodology.

Data Synthesis: Eleven RCTs with different corticosteroid regimens were included. Most trials assessed a once-daily infusion of methylprednisolone. Aside from one study showing improved liver graft function, no individual study or pooled analysis showed benefit of corticosteroids for any outcome: vasopressor use (3 trials; relative risk [RR] 0.96; 95% confidence interval [CI] 0.89 to 1.05), multiple organs recovered (2 trials; RR 0.82; 95% CI 0.61 to 1.11), acute graft rejection (3 trials; RR 0.91; 95% CI 0.60 to 1.39) or graft dysfunction (8 trials; RR 1.01; 95% CI 0.83 to 1.24). Two trials investigated adverse effects and found similar rates between groups. Quality of evidence was moderate or low for all outcomes.

Conclusion : Current clinical trials do not identify benefits or harms of corticosteroid therapy for deceased organ donors. In the face of these results, administering or withholding steroids both appear reasonable courses of action.

Strengths

- Comprehensive search,
- Independent duplicate assessments of study eligibility,
- Risk of bias,
- Data abstraction,
- The pooling of results across studies where possible.

Limitation

- Inability to address differences in effect with different dosing regimens, or between organ types (because of small number of studies to support such subgroup analyses),
- Small risk of bias,
- Indirectness of evidence,
- Inconsistency and imprecision.

INTRODUCTION

For patients with end-stage organ dysfunction, transplantation is a life-saving intervention. Universally, organs available for transplantation are insufficient to meet population needs. (1) Optimal medical management of deceased organ donors may help to address this shortage. (2, 3)

In the process that culminates in neurological death, cerebral herniation can induce a catecholamine storm that, when severe, leads to cardiovascular collapse. Hemodynamic instability of any degree threatens the viability of potentially recoverable

organs (4) and disturbances in the hypothalamo-pituitary-adrenal axis can be an important contributor. (5) Though the prevalence of adrenal insufficiency among neurologically deceased organ donors is uncertain, (6-9) corticosteroid therapy may alleviate hemodynamic collapse during cerebral herniation.

Cerebral herniation also activates a systemic inflammatory response; thus, anti-inflammatory properties of corticosteroid offer another potential mechanism of benefit. (10, 11) Intuitively, inflammation will jeopardize the suitability of organs for transplantation, but prospective cohort studies have generated conflicting results. (12-14)

In theory, treatment of potential organ donors with corticosteroids could improve their hemodynamic status, improve organ suitability and attenuate post-transplant organ dysfunction. The *Society of Critical Care Medicine*, the *American College of Chest Physicians*, and the *Association of Organ Procurement Organizations*, recommend high-dose corticosteroid for organ donation following neurological death. (15) One recent systematic review addressing this topic concluded that existing research neither confirms nor refutes the efficacy of corticosteroid therapy for neurologically deceased donors. (16) To advance this field, we applied GRADE methodology to further define the quality of current evidence, the specific limitations of previously reported trials, and future research needed to clarify the effects of systemic corticosteroid therapy in neurologically deceased donors. (17)

METHODS

Eligibility Criteria

We included published and unpublished randomized controlled trials (RCTs) enrolling neurologically deceased potential organ donors and comparing corticosteroids to placebo, to no administration of corticosteroids, or to other active treatments. We focused on the following outcomes: 1) vasopressor requirement among donors; 2) organ recovery from donors; 3) recipient graft rejection; 4) recipient graft dysfunction (using individual study definitions); and 5) adverse effects of corticosteroids in donors and recipients.

Search Strategy

With the assistance of a medical librarian we searched MEDLINE, EMBASE and Cochrane Central from their inception to January 2015 (Appendix 1). We searched conference proceedings from the *International Society of Organ Donation and Procurement, American Transplant Congress*, the *Canadian Society of Transplantation*, the *Society of Critical Care Medicine*, and the *Canadian Critical Care Forum* over five years, as well as clinical trial registries, and we screened the reference lists of all relevant articles.

Eligibility Review and Data Abstraction

Two reviewers independently screened citations and evaluated the full text of potentially eligible studies in duplicate, then abstracted data onto customized, pre-tested forms. Disagreements between reviewers were resolved through discussion or third party adjudication.

Assessment of Risk of Bias (single studies) and Quality of Evidence (entire body of evidence)

For each study two reviewers evaluated the risk of bias using the Cochrane Collaboration tool for RCTs. (18) This tool evaluates treatment allocation, sequence generation and concealment, blinding, completeness of follow-up, selective outcome reporting and other potential sources of bias.

For each outcome, using GRADE methodology, we evaluated the quality of the entire body of evidence as high, moderate, low or very low, (17) The GRADE system considers each of the following: overall risk of bias, (19) imprecision in estimates of effect, (20) inconsistency in findings across studies, (21) indirectness (the extent to which individual study populations, interventions, and outcome measurements deviate from those of interest to this review) (22) and publication bias. (23)

Statistical Analyses

We calculated chance-corrected agreement for eligibility decisions using the kappa statistic. (18) Dichotomous outcomes are reported as relative risks (RR) with their respective 95% confidence interval (CI) for a two-sided comparison. For pooled analyses, using Revman software version 5.2 (Copenhagen), we chose a fixed effect rather than a random effect model because estimates of between-study variability are necessary for random effects estimates and are uncertain when, as in this context, there are few studies. (18) If graft outcomes were measured at more than one interval we used the shortest one, assuming that steroid effects, if any, would manifest early. Heterogeneity was measured using the Cochrane I^2 statistic. There were too few studies to address publication bias. (18)

RESULTS

Study selection

From 3500 citations, 11 were eligible (Figure 1). (24-34) Between-reviewer agreement at the level of full text review was perfect (kappa = 1). Ten studies were published in English (24, 25, 27-34) and one in French. (26)

Fig 1. Flow Diagram

Study characteristics

Five out of 11 studies explicitly mentioned Ethics Review Board approval, and fewer detailed the approach to research consent. (25, 27-29, 34) Four publications with a focus on recipient outcomes reported separately for different organs from the same donors. Specifically, one trial was reported in two distinct publications addressing outcome related to the kidney (28) and to the liver respectively. (32) A second trial of a single donor cohort reported separately on outcomes related to lung (37) and heart. (30)

Four publications did not state the number of donors enrolled, because recipient outcomes were the focus. (16, 30-33) When reported, the number of donors ranged from 40 to 269, and baseline characteristics were similar between study groups. (25, 27-29, 34) The mean donor age varied from 30 to 40 years. The most common cause for neurological death was vascular injury (e.g. stroke, subarachnoid hemorrhage), followed by traumatic brain injury. (25, 27, 34)

Participant in these studies also included transplant recipients in the eight trials reporting on transplant outcomes, of whom there were 885 kidney recipients and 183 liver recipients. (24, 25, 28-33) Their baseline characteristics were reported in only three

publications. (25, 28, 29) Groups were similar and liver recipients had favourable prognosis at baseline with a mean Model For End-Stage Liver Disease (MELD) score between 14 and 16. (28, 29) Two studies measured graft outcome only among patients transplanted in the participating organ donation centre and excluded all recipients transplanted in other facilities. (28, 30)

Table 1 presents the study corticosteroid regimens. A single intravenous dose of methylprednisolone was the most common regimen, ranging in dose from 1 gram to 5 grams. Three trials tested corticosteroid therapy in isolation; (25, 28, 29) two others evaluated corticosteroids in a factorial design with liothyronine, (27, 34), one as part of combined hormonal therapy with liothyronine (26) and five placebo-controlled trials administered corticosteroids in combination with cyclophosphamide. (24, 30-33) The timing of corticosteroid therapy also varied across studies. Corticosteroids were administered 30 to 60 minutes after death declaration in one study, (26) immediately after consent for organ donation in three studies, (27, 28, 34) and three to eight hours before surgery in seven studies. (24, 25, 29-33) In most studies, methylprednisolone was dosed every 24 hours. (24, 25, 27, 29-34)

Table 1: Prospective Randomized Trials of Steroids Administration in Neurologically Dead Donors- Summary of the Studies

Author, Year	Donors/ Recipients (n)	Organs Recovered	Experimental Intervention	Control intervention
Parallel Design				
Chatterjee, 1977 (27)	50 84	Kidney	MTP 5 g IV single dose after brain death confirmation	Usual care
Dienst, 1977 (34)	NR 106	Kidney	MTP 3 g IV + Cy 3 g IV single doses 5-8 hrs. before organ recovery	Usual care
	NR 45		MTP 5 g IV + Cy 3 g IV single doses 5-8 hrs. before organ recovery	Usual care
	NR 29		MTP 5 g IV + Cy 5 g IV single doses 5-8 hrs. before organ recovery	Placebo
Jeffery, 1978 (35)	NR 52	Kidney	MTP 5 g IV +Cy 7 g IV single doses ≥ 4 hrs. before organ recovery	Usual care
Soulillou, 1979 (36)	NR 62	Kidney	MTP 5 g IV + Cy 5 g IV single doses ≥ 5 hrs. before organ recovery	Placebo
Corry, 1980 (33)	NR 52	Kidney	MTP 60 mg/kg IV +Cy 80 mg/kg IV single doses ≥ 5 hrs. before organ recovery	Usual care
Mariot, 1980 (29)	40 NR	Multi-organs	Hydrocortisone 100 mg IV+ T_3 2 mcg IV after brain death confirmation q.30-60 min. until stable CVP and SBP	Placebo
Kotsch, 2008 (31)	100 100	Liver	MTP 250 mg IV + 100 mg/h IV after brain death confirmation	Usual care
Kainz, 2010 (28)	269 455	Kidney	MTP 1 g single dose ≥ 3 hrs. before organ recovery	Placebo
Amatschek,2012 (32)	90 83	Liver	MTP 1 g single dose ≥ 3 hrs. before organ recovery	Placebo
Factorial Design				
Venkateswaran, 2008 (37)	60 NR	Lung	MTP 1 g IV single dose+/- T_3 0.8 ug/kg +0.113 ug/kg/hr IV after brain death confirmation	Placebo
Venkateswaran , 2009 (30)	80 NR	Heart	MTP 1 g IV single dose +/- T_3 0.8 ug/kg +0.113 ug/kg/hr IV after brain death confirmation	Placebo

Legend : CVP= Central Venous Pressure, Cy = Cyclophosphamide, MTP = Methylprednisolone, NR = Not Reported, SBP = Systolic Blood Pressure, T_3 = Liothyronin

Risk of bias of individual studies

Using the Cochrane tool, (18) four RCTs published after 1995 had low risk of bias. (25-29, 34) Earlier trials reported insufficient information to evaluate risk of bias (Figure 2). (24, 30-33)

Fig 2. Risk of Bias across the Included Studies

Results of individual studies and pooled results

Vasopressor requirement

The three studies (n = 452 donors) that reported on vasopressor administration most commonly used norepinephrine. (25, 28, 29) Individually and when pooled, corticosteroid did not influence the rate of vasopressor use in these studies (pooled RR 0.96; 95% CI 0.89 to 1.05; moderate quality) (Figure 3). The GRADE quality of evidence was rated down to moderate quality primarily because this outcome was relatively susceptible to lack of blinding (Table 2).

Fig 3. The Effect of Corticosteroids on Vasopressor Requirement

Organ recovery

Four trials evaluated organ recovery rates, but these data were analysed and reported differently across the four trials. None of the individual trials reported results suggesting increased organ recovery with steroids. Two trials (n = 309 donors) reported on the number of donors that provided multiple organs, (25, 26) and the pooled estimate suggested no effect of corticosteroids but with a very wide confidence interval including

substantial benefit (RR 0.82; 95% CI 0.61 to 1.11; moderate quality) (Figure 4). Similarly, in a factorial RCT, investigators did not demonstrate a significant increase in the number of hearts recovered or suitable for transplantation. (27) In a *post hoc* analysis, Venkateswaran observed a decrease in the extravascular lung water index with the administration of corticosteroids; this could potentially increase the number of lungs suitable for transplantation if taken into consideration during donor care. (34) For this group of outcomes, we rated down the quality of evidence to moderate because of imprecision (wide confidence intervals) (Table 2).

Table 2: GRADE Profile

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Steroid**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
Vasopressor Requirement											
3	RCT	serious[a]	not serious	not serious	not serious	none	156/227 (68.7%)	160/225 (71.1%)	**RR 0.96** (0.89 to 1.05)	28 fewer per 1000 (from 36 more to 78 fewer)	⊕⊕⊕ MODERATE
Organ Recovery											
2	RCT	not serious	not serious	not serious	serious[b]	none	46/156 (29.5%)	55/153 (35.9%)	**RR 0.82** (0.61 to 1.11)	65 fewer per 1000 (from 40 more to 140 fewer)	⊕⊕⊕ MODERATE
Acute Graft Rejection											
3	RCT	not serious	serious[c]	not serious	serious[b]	none	29/114 (25.4%)	34/122 (27.9%)	**RR 0.91** (0.60 to 1.39)	25 fewer per 1000 (from 109 more to 111 fewer)	⊕⊕ LOW
Graft Dysfunction											
8	RCT	serious[d]	not serious	serious[e,f,g]	not serious	none	113/500 (22.6%)	148/569 (26.0%)	**RR 1.01** (0.83 to 1.24)	3 more per 1000 (from 44 fewer to 62 more)	⊕⊕ LOW

RCT= Randomized Clinical Trial, RR= Relative Risk

a =Lack of blinding, *b* = Wide confidence interval suggesting appreciable harm or benefit, *c* = Large variation in effect, I2 large, *d* = Selection bias.

e = Different definition of the same outcome, *f* = Surrogate outcomes used to describe graft function, *g* = Co intervention.

Figure 4: The Effect of Corticosteroids on Successful Donation of More Than One Organ

Transplant outcomes (acute graft rejection and graft function)

Three trials (n = 236 recipients) studied acute graft rejection. (28, 29, 32) Trials on acute liver rejection reported conflicting results. (28, 29) Amatschek et al. reported similar risks of acute rejection as measured from routine biopsy specimens at three months. (29) However, Kotsch et al. obtained a lower rate of acute rejection, in the corticosteroid group, on routine biopsies within the first six months. (28) Jeffery et al. did not find a reduction in the number of acute kidney rejection with corticosteroids within the first year. (32) Episodes of rejection were diagnosed on the basis of an increase in serum creatinine of more than 0.2 mg/100ml, clinical findings and absence of alternative diagnosis explaining worsening renal function. Pooled estimates do not suggest that corticosteroids reduce the risk of acute graft rejection (RR 0.91; 95% CI 0.60 to 1.39; low confidence) (Figure 5). For this group of outcomes, we rated down the overall quality of evidence to low because of inconsistency (large variation in effect between studies) and imprecision (Table 2).

Figure 5: The Effect of Corticosteroids on Acute Graft Rejection at Three Months

Of the eight RCTs (n = 1069 recipients) that evaluated graft outcomes, (24, 25, 28-33) two trials provided conflicting results on liver graft function. Kotsch et al. reported a reduction in transaminase levels within the ten days after transplantation among patients receiving corticosteroid therapy. (28) In contrast, Amatschek et al. obtained similar transaminase levels within seven days. (29) Six studies compared a composite risk of one or more of the following data: creatinine level, creatinine clearance, dialysis,

listed for kidney transplantation or death at different time interval. (24, 25, 30-33) Pooled estimates, suggest no effect of corticosteroids on graft function (RR 1.01; 95% CI 0.83 to 1.24; low confidence) (Figure 6). Individual studies had high risk of bias, (lack of blinding and loss to follow up) and also provided only indirect evidence because they combined steroids with cyclophosphamide in the experimental groups. Therefore, we rated the quality of evidence for this outcome as low (Table 2).

Figure 6: Forest Plot of the Effect of Corticosteroids on Graft Dysfunction

Adverse effects

Only two studies evaluated steroid-related adverse events. Investigators reported no effect on infection rates among donors. (28) Bile duct complications and hepatitis C virus reinfection following liver transplantation were similar between groups. (28, 29)

DISCUSSION

We systematically reviewed 11 RCTs evaluating the efficacy of corticosteroid therapy in potential organ donors with respect to clinically important outcomes among both donors and recipients. Individual studies applied a variety of dosing strategies and study outcomes, and very few suggested any difference between corticosteroid and control groups. When two or more studies measured the same outcome, pooled results did not support a treatment effect for hemodynamic stability, the number of organs recovered, or transplant function. The overall quality of evidence was moderate or low for these outcomes, limiting our confidence in the results.

Strengths of our study include a comprehensive search, independent duplicate assessments of study eligibility, risk of bias, and data abstraction, and the pooling of results across studies where possible. Most importantly, we applied the GRADE system to rate the quality of evidence for each outcome that was addressed by more than one study. In doing so, our goal was to support guidelines for clinical care and to highlight areas for improving scientific rigor in this field. A primary limitation of this review was the inability to address differences in effect with different dosing regimens, or between organ types, based on the small number of studies to support such subgroup analyses.

Applying GRADE methodology, the overall quality of evidence was downgraded as a result of the risk of bias, indirectness of evidence, inconsistency and imprecision. While the risk of bias among five studies reported in the past 20 years was relatively low, the risk of bias was uncertain for six earlier studies, and may be high. (35) Risk of bias was related to lack of blinding and possible selection bias in the unexplained post-randomization exclusion of specific transplant recipients from some studies. (28, 30)

Indirectness of evidence was another important reason for rating down the overall quality of evidence. There were two types of indirectness. Five studies combining all steroid interventions (but not control interventions) with other hormone therapies (1), or with cyclophosphamide (4), provide only indirect evidence of the potential treatment effects of corticosteroids alone. Indirectness also comes into play when evaluating studies of varied dosing regimens; it is conceivable that the apparent lack of effect overall is a result of assessing relatively helpful regimens alongside of those that are relatively harmful.

Finally, we also rated down the quality of evidence for two outcomes on the basis of imprecision. The small number of studies, patients within studies, and events among

patients resulted not only in wide confidence intervals but also precluded subgroup analyses and assessment for publication bias. In summary, because the quality of evidence is low for at least two outcomes, this review cannot support strong recommendations for clinical care.

Inferences from this systematic review are also limited by varied outcomes of graft dysfunction, varied definitions for each specific term, and the inability to apply outcome definitions across organ groups, which is important in this field because one organ donor may donate kidneys, liver, lung, heart, and/or pancreas or small bowel. For example, outcomes of renal graft function across studies included graft failure, (24, 33) graft survival, (30, 31) and delayed graft function. (25) Even the measurement of renal 'graft failure' was problematic for pooling across studies: Chatterjee et al. defined graft failure as a composite outcome of kidney removal after transplantation, return to hemodialysis or death, (24) while Soulillou et al. defined graft failure as any requirement for hemodialysis or a serum creatinine level (threshold not specified) after transplantation. (33) Unified outcome measures for specific organs, and potentially generic outcome measures across organ groups, would help to advance the science of organ donor management.

Our results are similar to those previously reported. (16, 36) However, we went beyond prior reviews in conducting meta-analyses and using the GRADE approach for rating the quality of evidence. Unfortunately, the moderate or low quality of evidence does not allow strong inferences about the use of steroids in these populations. (15, 37) Although observational studies frequently overestimate treatment effects, and these might have been confounded by surgical interventions, organ preservation techniques and transplant recipient characteristics, evidence from the current RCTs is also limited in

quality. In a recent European multicentre observational study (n = 259), administration of corticosteroids to deceased organ donors with a neurological determination of death was associated with a lower dose of norepinephrine (steroid group [SG] = 1.18 +/- 0.92 mg/h vs control group [CG] =1.49 +/- 1.29 mg/h, p = 0.03) and shorter duration of vasopressor support (SG = 874 min vs CG = 1160 min., p < 0.0001). (38) The incidence of delayed graft function among recipients was similar between the two groups (SG = 30.8% vs CG = 26.6%, p=0.14). These findings are consistent with expected effects regarding the impact of corticosteroid therapy in potential organ donors.

This systematic review highlights three challenges of research addressing the medical management of deceased organ donors: the scarcity of donors, practical challenges of studying therapeutic interventions and subsequent outcomes among very separate study populations, (i.e., organ donors and transplant recipients), and the complexity of definitions of graft function. These challenges will only be met through research collaborations, recruiting all eligible patients into clinical trials, and possibly with models of consent that are adapted to the reality of organ donation.

CONCLUSION

Current clinical trials do not identify benefits of corticosteroid therapy for deceased organ donors or their transplant recipients. The quality of this evidence is insufficient, however, to rule out the possibility of important benefits with respect to donation rates or transplant outcomes for any organ. In light of the lack of any signal for harm, there is no imperative to modify current recommendations for clinical care, based on observational studies, to consider corticosteroid therapy in the management of organ donors.

All authors have made material contributions to this manuscript according to the rules of authorship of ICMJE. Specifically, here are the contributions of each author:

F D'Aragon: Conception of the design, acquisition of data,analysis and interpretation of the data, draft and revised the manuscript, approved the final version to be published;

E Belley Cote: Conception of the design, acquisition of data,analysis and interpretation of the data, draft and revised the manuscript and approved final version to be published;

A Argawal: Conception of the design,acquisition and analysis of the data, draft and revised the manuscript, approved final version to be published;

AJ Frenette: Conception of the design, acquisition and analysis of the data, draft and revised manuscript and approved the final version to be published;

F Lamontagne: Conception of the design, acquisition and analysis of the data, draft and revised mansucript and approved the final version to be published;

G Guyatt: Conception of the design, acquisition and analysis of the data, draft and revised the manuscript and approved the final version to be published;

S Dhanani: Conception of the design, acquisition and analysis of the data, draft and revised the manuscript and approved the final version to be published;

M Meade: Conception of the design, data acquisition and analysis, draft and revised the manuscript and approved the final version to be published.

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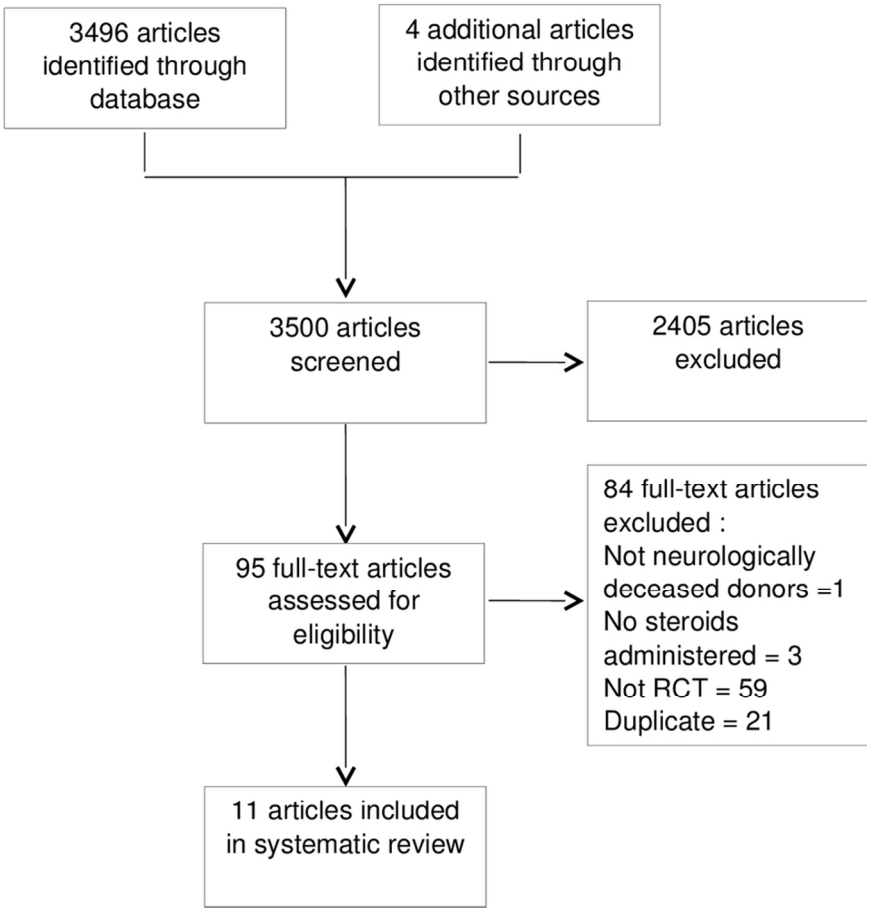

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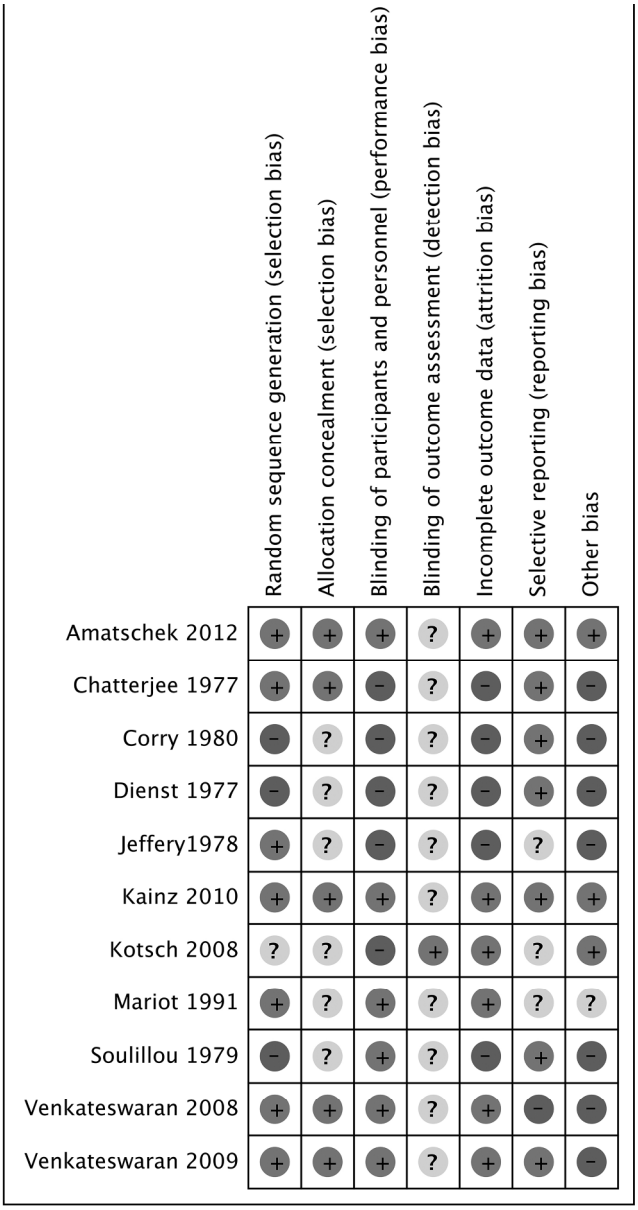

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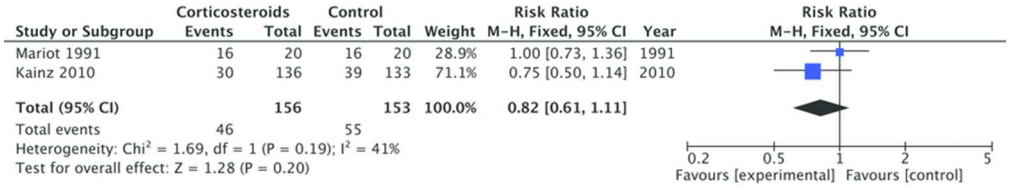

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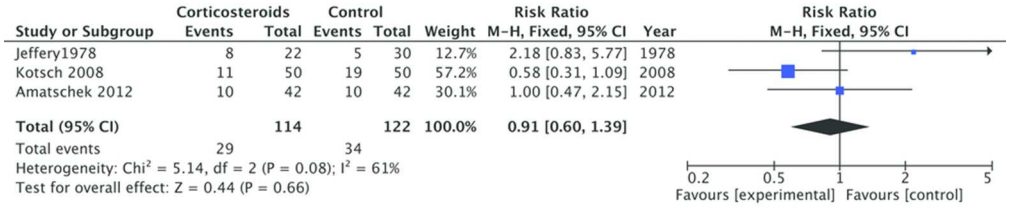

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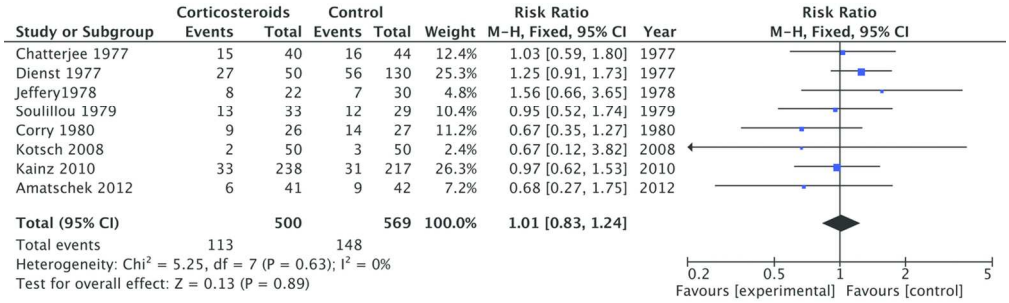

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	S2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

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Effect of Corticosteroid Administration on Neurologically Deceased Organ Donors and Transplant Recipients : A Systematic Review and Meta-Analysis

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EFFECT OF CORTICOSTEROID ADMINISTRATION ON NEUROLOGICALLY DECEASED ORGAN DONORS AND TRANSPLANT RECIPIENTS : A SYSTEMATIC REVIEW AND META-ANALYSIS

My manuscript is submitted as an original works:

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ABSTRACT

Objectives : This review investigates the impact of corticosteroids on donation rates and transplant outcomes in light of findings from randomized controlled trials (RCTs) and to highlight the sources of uncertainty in this unresolved donor management issue.

Data Sources : We searched electronic databases, trial registries, and conference proceedings for RCTs evaluating corticosteroid therapy in neurologically deceased donors.

Study Selection & Data Extraction : Independent reviewers assessed eligibility, evaluated risk of bias, and abstracted data, including donor hemodynamic data, number of organs recovered, and transplant outcomes. Where possible, we pooled results. For each outcome we assessed the overall quality of evidence using GRADE methodology.

Data Synthesis: Eleven RCTs with different corticosteroid regimens were included. Most trials assessed a once-daily infusion of methylprednisolone. Aside from one study showing improved liver graft function, no individual study or pooled analysis showed benefit of corticosteroids for any outcome: vasopressor use (3 trials; relative risk [RR] 0.96; 95% confidence interval [CI] 0.89 to 1.05), multiple organs recovered (2 trials; RR

0.82; 95% CI 0.61 to 1.11), acute graft rejection (3 trials; RR 0.91; 95% CI 0.60 to 1.39) or graft dysfunction (8 trials; RR 1.01; 95% CI 0.83 to 1.24). Two trials investigated adverse effects and found similar rates between groups. Quality of evidence was moderate or low for all outcomes.

Conclusion : Current clinical trials are limited in numbers and size to identify benefits or harms of corticosteroid therapy for deceased organ donors. In the face of these results, administering or withholding steroids both appear reasonable courses of action.

STRENGTHS AND LIMITATIONS

An exhaustive search strategy and strict adherence to systematic review methodology make this review the most rigorous on the topic.

Our comprehensive GRADE approach improves the transparency regarding the quality of the available evidence on the effect of steroids in potential organ donors.

Available data only allows for limited inference on the effects of steroid on graft outcome due to varied definitions of graft outcomes.

The clinical relevance of our results is limited by the inability to assess for differences in steroid effects associated with variations in dose or timing of administration.

INTRODUCTION

For patients with end-stage organ dysfunction, transplantation is a life-saving intervention. Universally, organs available for transplantation are insufficient to meet population needs.[1] Optimal medical management of deceased organ donors may help to address this shortage.[2, 3]

In the process that culminates in neurological death, cerebral herniation can induce a catecholamine storm that, when severe, leads to cardiovascular collapse. Hemodynamic instability of any degree threatens the viability of potentially recoverable organs[4] and disturbances in the hypothalamo-pituitary-adrenal axis can be an important contributor.[5] Though the prevalence of adrenal insufficiency among neurologically deceased organ donors is uncertain,[6-9] corticosteroid therapy may alleviate hemodynamic collapse during cerebral herniation.

Cerebral herniation also activates a systemic inflammatory response; thus, anti-inflammatory properties of corticosteroid offer another potential mechanism of benefit.[10, 11] Intuitively, inflammation will jeopardize the suitability of organs for transplantation, but prospective cohort studies have generated conflicting results.[12-14]

In theory, treatment of potential organ donors with corticosteroids could improve their hemodynamic status, improve organ suitability and attenuate post-transplant organ dysfunction. The *Society of Critical Care Medicine*, the *American College of Chest Physicians*, and the *Association of Organ Procurement Organizations*, recommend high-dose corticosteroid for organ donation following neurological death.[15] One recent systematic review addressing this topic concluded that existing research neither confirms nor refutes the efficacy of corticosteroid therapy for neurologically deceased donors.[16] To advance this field, we applied GRADE methodology to further define the

quality of current evidence, the specific limitations of previously reported trials, and future research needed to clarify the effects of systemic corticosteroid therapy in neurologically deceased donors.[17]

METHODS

This manuscript was drafted in accordance with the PRISMA guidelines on reporting of systematics review and meta-analyses.[18]

Eligibility Criteria

We included published and unpublished randomized controlled trials (RCTs) enrolling of children and adults neurologically deceased potential organ donors and comparing corticosteroids to placebo, to no administration of corticosteroids, or to other active treatments. We focused on the following outcomes: 1) vasopressor requirement among donors; 2) organ recovery from donors; 3) recipient graft rejection; 4) recipient graft dysfunction (using individual study definitions); and 5) adverse effects of corticosteroids in donors and recipients.

Search Strategy

With the assistance of a medical librarian we searched MEDLINE, EMBASE and Cochrane Central from their inception to January 2017. The MEDLINE search strategy is found in Appendix 1. We searched conference proceedings from the *International Society of Organ Donation and Procurement, American Transplant Congress*, the *Canadian Society of Transplantation*, the *Society of Critical Care Medicine*, and the *Canadian Critical Care Forum* over five years, as well as clinical trial registries, and we screened the reference lists of all relevant articles.

Eligibility Review and Data Abstraction

Two reviewers independently screened citations and evaluated the full text of potentially eligible studies in duplicate, then abstracted data onto customized, pre-tested forms. Disagreements between reviewers were resolved through discussion or third party adjudication. We abstracted data pertaining to study characteristics and design, population, intervention, comparison and all clinical outcomes. We clarified missing data through email correspondence with the study author.

Assessment of Risk of Bias (single studies) and Quality of Evidence (entire body of evidence)

For each study two reviewers evaluated the risk of bias using the Cochrane Collaboration tool for RCTs.[19] The risk of bias was judge to be at low risk, high risk or unclear risk with the following domains: treatment allocation, sequence generation and concealment, blinding, completeness of follow-up, selective outcome reporting and other potential sources of bias.

For each outcome, using GRADE methodology, we evaluated the quality of the entire body of evidence as high, moderate, low or very low,[17] The GRADE system considers each of the following: overall risk of bias,[20] imprecision in estimates of effect,[21] inconsistency in findings across studies,[22] indirectness (the extent to which individual study populations, interventions, and outcome measurements deviate from those of interest to this review)[23] and publication bias.[24]

Statistical Analyses

We calculated chance-corrected agreement for eligibility decisions using the kappa statistic.[19] Dichotomous outcomes are reported as relative risks (RR) with their respective 95% confidence interval (CI) for a two-sided comparison. For pooled analyses, using Revman software version 5.2 (Copenhagen), we chose a fixed effect

rather than a random effect model because estimates of between-study variability are necessary for random effects estimates and are uncertain when, as in this context, there are few studies.[19] If graft outcomes were measured at more than one interval we used the shortest one, assuming that steroid effects, if any, would manifest early. Heterogeneity was measured using the chi square test for homogeneity and the Cochrane I^2.[19] I^2 greater than 50% was considered significant heterogeneity. The Egger test to address publication bias was not performed as less than 10 studies were identified.

RESULTS

Study selection

From 4352 citations, 11 were eligible (Figure 1).[25-35] Between-reviewer agreement at the level of full text review was perfect (kappa = 1). Ten studies were published in English[25, 26, 28-35] and one in French.[27]

Study characteristics

Five out of 11 studies explicitly mentioned Ethics Review Board approval, and fewer detailed the approach to research consent.[26, 28-30, 35] Four publications with a focus on recipient outcomes reported separately for different organs from the same donors. Specifically, one trial was reported in two distinct publications addressing outcome related to the kidney[26] and to the liver respectively.[30] A second trial of a single donor cohort reported separately on outcomes related to lung[36] and heart.[28]

Four publications did not state the number of donors enrolled, because recipient outcomes were the focus.[16, 31-34] When reported, the number of donors ranged from 40 to 269, and baseline characteristics were similar between study groups.[26, 28-30, 35] The

mean donor age varied from 30 to 40 years. The most common cause for neurological death was vascular injury (e.g. stroke, subarachnoid hemorrhage), followed by traumatic brain injury.[26, 28, 35]

Participants in these studies also included transplant recipients in the eight trials reporting on transplant outcomes, of whom there were 885 kidney recipients and 183 liver recipients.[25, 26, 29-34] Their baseline characteristics were reported in only three publications.[26, 29, 30] Groups were similar and liver recipients had favourable prognosis at baseline with a mean Model For End-Stage Liver Disease (MELD) score between 14 and 16.[29, 30] Two studies measured graft outcome only among patients transplanted in the participating organ donation centre and excluded all recipients transplanted in other facilities.[29, 31]

Table 1 presents the study corticosteroid regimens. A single intravenous dose of methylprednisolone was the most common regimen, ranging in dose from 1 gram to 5 grams. Three trials tested corticosteroid therapy in isolation;[26, 29, 30] two others evaluated corticosteroids in a factorial design with liothyronine,[28, 35] one as part of combined hormonal therapy with liothyronine[27] and five placebo-controlled trials administered corticosteroids in combination with cyclophosphamide.[25, 31-34] The timing of corticosteroid therapy also varied across studies. Corticosteroids were administered 30 to 60 minutes after death declaration in one study,[27] immediately after consent for organ donation in three studies,[28, 29, 35] and three to eight hours before surgery in seven studies.[25, 26, 30-34] In most studies, methylprednisolone was dosed every 24 hours.[25, 26, 28, 30-35]

Table 1: Prospective Randomized Trials of Steroids Administration in Neurologically Dead Donors- Summary of the Studies

Author, Year	Donors/ Recipients (n)	Organs Recovered	Experimental Intervention	Control intervention
Parallel Design				
Chatterjee, 1977 [25]	50 84	Kidney	MTP 5 g IV single dose after brain death confirmation	Usual care
Dienst, 1977 [32]	NR 106	Kidney	MTP 3 g IV + Cy 3 g IV single doses 5-8 hrs. before organ recovery	Usual care
	NR 45		MTP 5 g IV + Cy 3 g IV single doses 5-8 hrs. before organ recovery	Usual care
	NR 29		MTP 5 g IV + Cy 5 g IV single doses 5-8 hrs. before organ recovery	Placebo
Jeffery, 1978 [33]	NR 52	Kidney	MTP 5 g IV +Cy 7 g IV single doses ≥ 4 hrs. before organ recovery	Usual care
Soulillou, 1979 [34]	NR 62	Kidney	MTP 5 g IV + Cy 5 g IV single doses ≥ 5 hrs. before organ recovery	Placebo
Corry, 1980 [31]	NR 52	Kidney	MTP 60 mg/kg IV +Cy 80 mg/kg IV single doses ≥ 5 hrs. before organ recovery	Usual care
Mariot, 1980 [27]	40 NR	Multi-organs	Hydrocortisone 100 mg IV+ T_3 2 mcg IV after brain death confirmation q.30-60 min. until stable CVP and SBP	Placebo
Kotsch, 2008 [29]	100 100	Liver	MTP 250 mg IV + 100 mg/h IV after brain death confirmation	Usual care
Kainz, 2010 [26]	269 455	Kidney	MTP 1 g single dose ≥ 3 hrs. before organ recovery	Placebo
Amatschek,2012 [30]	8390 83	Liver	MTP 1 g single dose ≥ 3 hrs. before organ recovery	Placebo
Factorial Design				
Venkateswaran, 2008 [35]	60 NR	Lung	MTP 1 g IV single dose+/- T_3 0.8 ug/kg +0.113 ug/kg/hr IV after brain death confirmation	Placebo
Venkateswaran , 2009 [28]	80 NR	Heart	MTP 1 g IV single dose +/- T_3 0.8 ug/kg +0.113 ug/kg/hr IV after brain death confirmation	Placebo

Legend : CVP= Central Venous Pressure, Cy = Cyclophosphamide, MTP = Methylprednisolone, NR = Not Reported, SBP = Systolic Blood Pressure, T_3 = Liothyronin

Risk of bias of individual studies

Using the Cochrane tool,[19] four RCTs published after 1995 had low risk of bias.[26-30, 35] Earlier trials reported insufficient information to evaluate risk of bias (Figure 2).[25, 31-34]

Results of individual studies and pooled results

Vasopressor requirement

The three studies (n = 452 donors) that reported on vasopressor administration most commonly used norepinephrine.[26, 29, 30] Individually and when pooled, corticosteroid did not influence the rate of vasopressor use in these studies (pooled RR 0.96; 95% CI 0.89 to 1.05; moderate quality) (Figure 3). The GRADE quality of evidence was rated down to moderate quality primarily because this outcome was relatively susceptible to lack of blinding (Table 2).

Organ recovery

Four trials evaluated organ recovery rates, but these data were analysed and reported differently across the four trials. None of the individual trials reported results suggesting increased organ recovery with steroids. Two trials (n = 309 donors) reported on the number of donors that provided multiple organs,[26, 27] and the pooled estimate suggested no effect of corticosteroids but with a very wide confidence interval including substantial benefit (RR 0.82; 95% CI 0.61 to 1.11; moderate quality) (Figure 4). Similarly, in a factorial RCT, investigators did not demonstrate a significant increase in the number of hearts recovered or suitable for transplantation.[28] In a *post hoc* analysis, Venkateswaran observed a decrease in the extravascular lung water index with the administration of corticosteroids; this could potentially increase the number of lungs suitable for transplantation if taken into consideration during donor care. (35) For this

group of outcomes, we rated down the quality of evidence to moderate because of imprecision (wide confidence intervals) (Table 2).

Table 2: GRADE Profile

Quality assessment							Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	
3	RCT	serious[a]	not serious	not serious	not serious	none	⊕⊕⊕ MODERATE
2	RCT	not serious	not serious	not serious	serious[b]	none	⊕⊕⊕ MODERATE
3	RCT	not serious	serious[c]	not serious	serious[b]	none	⊕⊕ LOW
8	RCT	serious[d]	not serious	serious[e,f,g]	not serious	none	⊕⊕ LOW

RCT= Randomized Clinical Trial, RR= Relative Risk
a =Lack of blinding, *b* = Wide confidence interval suggesting appreciable harm or benefit, *c* = Large variation in effect, I2 large, *d* = Selection bias.
e = Different definition of the same outcome, *f* = Surrogate outcomes used to describe graft function, *g* = Co intervention.

Transplant outcomes (acute graft rejection and graft function)

Three trials (n = 235 recipients) studied acute graft rejection.[29, 30, 33] Trials on acute liver rejection reported conflicting results.[29, 30] Amatschek et al. reported similar risks of acute rejection as measured from routine biopsy specimens at three months.[30] However, Kotsch et al. obtained a lower rate of acute rejection, in the corticosteroid group, on routine biopsies within the first six months.[29] Jeffery et al. did not find a reduction in the number of acute kidney rejection with corticosteroids within the first year.[33] Episodes of rejection were diagnosed on the basis of an increase in serum creatinine of more than 0.2 mg/100ml, clinical findings and absence of alternative diagnosis explaining worsening renal function. Pooled estimates do not suggest that corticosteroids reduce the risk of acute graft rejection (RR 0.91; 95% CI 0.60 to 1.39; low confidence) (Figure 5). For this group of outcomes, we rated down the overall quality of evidence to low because of inconsistency (large variation in effect between studies) and imprecision (Table 2).

Of the eight RCTs (n = 1068 recipients) that evaluated graft outcomes,[25, 26, 29-34] two trials provided conflicting results on liver graft function. Kotsch et al. reported a reduction in transaminase levels within the ten days after transplantation among patients receiving corticosteroid therapy.[29] In contrast, Amatschek et al. obtained similar transaminase levels within seven days.[30] Six studies compared a composite risk of one or more of the following data: creatinine level, creatinine clearance, dialysis, listed for kidney transplantation or death at different time interval.[25, 26, 31-34] Pooled estimates, suggest no effect of corticosteroids on graft function (RR 1.01; 95% CI 0.83 to 1.24; low confidence) (Figure 6). Individual studies had high risk of bias, (lack of blinding and loss to follow up) and also provided only indirect evidence because they combined steroids

with cyclophosphamide in the experimental groups. Therefore, we rated the quality of evidence for this outcome as low (Table 2).

Adverse effects

Only two studies evaluated steroid-related adverse events. Investigators reported no effect on infection rates among donors.[29] Bile duct complications and hepatitis C virus reinfection following liver transplantation were similar between groups.[29, 30]

DISCUSSION

We systematically reviewed 11 RCTs evaluating the efficacy of corticosteroid therapy in potential organ donors with respect to clinically important outcomes among both donors and recipients. Individual studies applied a variety of dosing strategies and study outcomes, and very few suggested any difference between corticosteroid and control groups. When two or more studies measured the same outcome, pooled results did not support a treatment effect for hemodynamic stability, the number of organs recovered, or transplant function. The overall quality of evidence was moderate or low for these outcomes, limiting our confidence in the results.

Strengths of our study include a comprehensive search, independent duplicate assessments of study eligibility, risk of bias, and data abstraction, and the pooling of results across studies where possible. Most importantly, we applied the GRADE system to rate the quality of evidence for each outcome that was addressed by more than one study. It provides a transparent assessment of our confidence in the estimates of the effect of steroids on key clinical outcomes in potential organ donors. The GRADE assessment is definitely an added value as it will provide knowledge users with evaluations of the quality of evidence underlying the use of steroids in potential organ

donors. In doing so, our goal was to support guidelines for clinical care and to highlight areas for improving scientific rigor in this field. A primary limitation of this review was the inability to address differences in effect with different dosing regimens, or between organ types, based on the small number of studies to support such subgroup analyses.

Limitations of our study are largely those of the original studies and thus of the body of evidence to which they contribution. Applying GRADE methodology, the overall quality of evidence was rated down as a result of the risk of bias, indirectness of evidence, inconsistency and imprecision. While the risk of bias among five studies reported in the past 20 years was relatively low, the risk of bias was uncertain for six earlier studies, and may be high.[37] Risk of bias was related to lack of blinding and possible selection bias in the unexplained post-randomization exclusion of specific transplant recipients from some studies.[29, 31]

Another limitation is that studies did not take the clustering of organs within donors (a single donor can contribute up to 7 organs) into account in the analysis. To the extent that organs from some donors do systematically better than organs from other donors, the confidence intervals presented in the studies are narrower than would be the case in an analysis that took clustering into account.

Indirectness of evidence was another important reason for rating down the overall quality of evidence. Six studies combining all steroid interventions (but not control interventions) with other hormone therapies,[27,34] or with cyclophosphamide,[30-33] provide only indirect evidence of the potential treatment effects of corticosteroids alone. Variation in timing of randomization and subsequent administration of study intervention also have affected treatment effect presuming that later administration (i.e. 5-8 hours before organ recovery) may be less effective. Indirectness also comes into play when

evaluating studies of varied dosing regimens; it is conceivable that the apparent lack of effect overall is a result of assessing relatively helpful regimens alongside of those that are relatively harmful.

Finally, we also rated down the quality of evidence for two outcomes on the basis of imprecision. The small number of studies, patients within studies, and events among patients resulted not only in wide confidence intervals but also precluded subgroup analyses and assessment for publication bias. In summary, because the quality of evidence is low for at least two outcomes, this review cannot support strong recommendations for clinical care.

Inferences from this systematic review are also limited by varied outcomes of graft dysfunction; variable results across outcomes (apparent harm in number of organs recovered and apparent benefit in graft rejection; varied definitions for each specific term; and the inability to apply outcome definitions across organ groups, which is important in this field because one organ donor may donate kidneys, liver, lung, heart, and/or pancreas or small bowel. For example, outcomes of renal graft function across studies included graft failure,[25, 34] graft survival,[31, 32] and delayed graft function.[26] Even the measurement of renal 'graft failure' was problematic for pooling across studies: Chatterjee et al. defined graft failure as a composite outcome of kidney removal after transplantation, return to hemodialysis or death,[25] while Soulillou et al. defined graft failure as any requirement for hemodialysis or a serum creatinine level (threshold not specified) after transplantation.[34] Unified outcome measures for specific organs, and potentially generic outcome measures across organ groups, would help to advance the science of organ donor management.

Our results are similar to those previously reported.[16, 38] However, we went beyond prior reviews in conducting meta-analyses and using the GRADE approach for rating the quality of evidence. Unfortunately, the moderate or low quality of evidence does not allow strong inferences about the use of steroids in these populations.[15, 39]

Although observational studies frequently overestimate treatment effects, and these might have been confounded by surgical interventions, organ preservation techniques and transplant recipient characteristics, evidence from the current RCTs is also limited in quality. In a recent European multicentre observational study (n = 259), administration of corticosteroids to deceased organ donors with a neurological determination of death was associated with a lower dose of norepinephrine (steroid group [SG] = 1.18 +/- 0.92 mg/h vs control group [CG] =1.49 +/- 1.29 mg/h, p = 0.03) and shorter duration of vasopressor support (SG = 874 min vs CG = 1160 min., p < 0.0001).[40] The incidence of delayed graft function among recipients was similar between the two groups (SG = 30.8% vs CG = 26.6%, p=0.14). These findings are consistent with expected effects regarding the impact of corticosteroid therapy in potential organ donors.

This systematic review highlights three challenges of research addressing the medical management of deceased organ donors: the scarcity of donors, practical challenges of studying therapeutic interventions and subsequent outcomes among very separate study populations, (i.e., organ donors and transplant recipients), and the complexity of definitions of graft function. These challenges will only be met through research collaborations, recruiting all eligible patients into clinical trials, and possibly with models of consent that are adapted to the reality of organ donation.

CONCLUSION

Current clinical trials do not identify benefits of corticosteroid therapy for deceased organ donors or their transplant recipients. The quality of this evidence is insufficient, however, to rule out the possibility of benefits or harms with respect to donation rates or transplant outcomes for any organ. In light of these results, there is no imperative to modify current recommendations for clinical care, based on observational studies, to consider corticosteroid therapy in the management of organ donors.

ACKNOWLEDGEMENTS

None

SOURCE OF FUNDING

None

FIGURE LEGEND

Figure 1: Flow Diagram

Figure 2: Risk of Bias across the Included Studies

Figure 3: The Effect of Corticosteroids on Vasopressor Requirement

Figure 4: The Effect of Corticosteroids on Successful Donation of More Than One Organ

Figure 5: The Effect of Corticosteroids on Acute Graft Rejection at Three Months

Figure 6: Forest Plot of the Effect of Corticosteroids on Graft Dysfunction

STATEMENT

All authors have made material contributions to this manuscript according to the rules of authorship of ICMJE. Specifically, here are the contributions of each author:

F D'Aragon: Conception of the design, acquisition of data,analysis and interpretation of the data, draft and revised the manuscript, approved the final version to be published;

E Belley Cote: Conception of the design, acquisition of data,analysis and interpretation of the data, draft and revised the manuscript and approved final version to be published;

A Argawal: Conception of the design,acquisition and analysis of the data, draft and revised the manuscript, approved final version to be published;

AJ Frenette: Conception of the design, acquisition and analysis of the data, draft and revised manuscript and approved the final version to be published;

F Lamontagne: Conception of the design, acquisition and analysis of the data, draft and revised mansucript and approved the final version to be published;

G Guyatt: Conception of the design, acquisition and analysis of the data, draft and revised the manuscript and approved the final version to be published;

S Dhanani: Conception of the design, acquisition and analysis of the data, draft and revised the manuscript and approved the final version to be published;

M Meade: Conception of the design, data acquisition and analysis, draft and revised the manuscript and approved the final version to be published.

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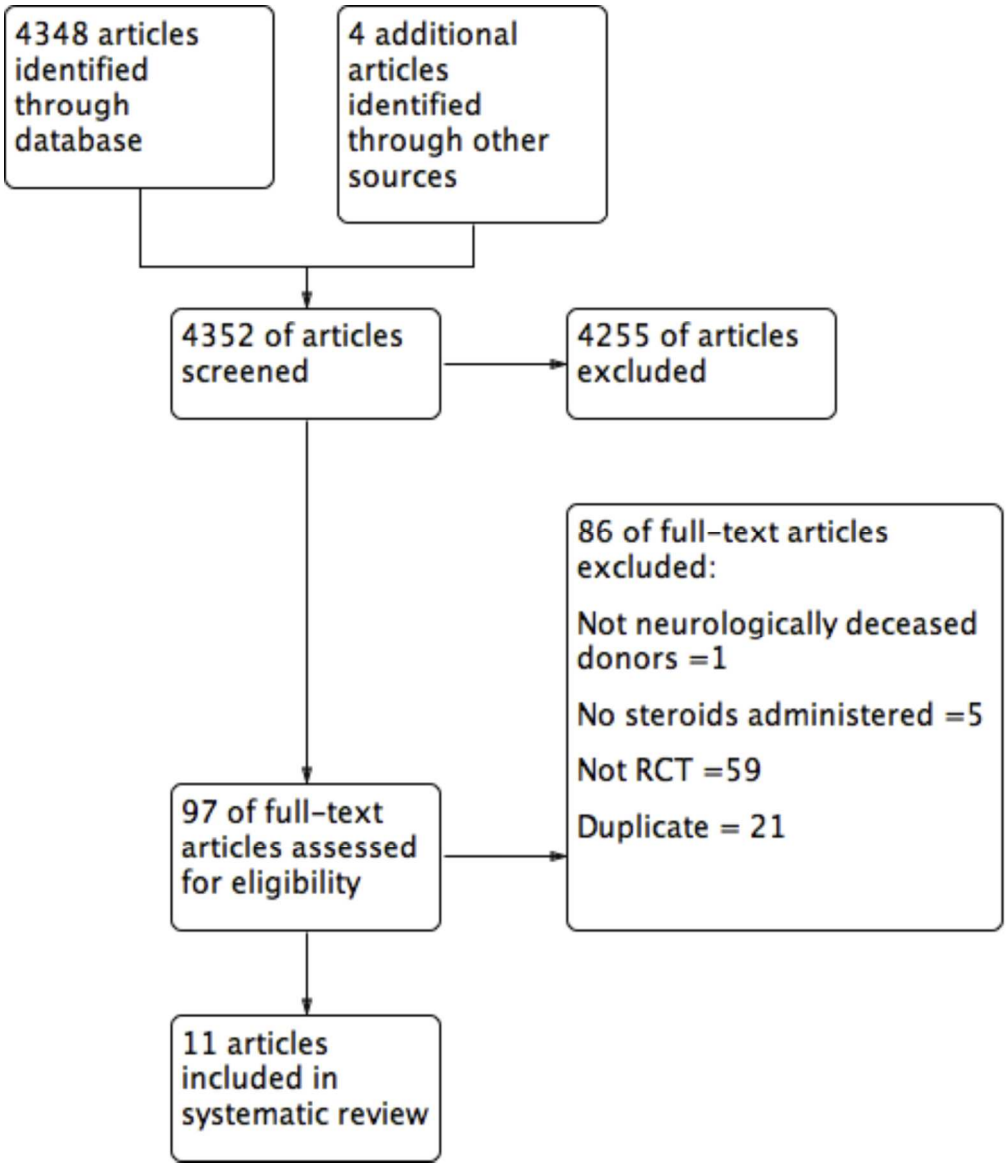

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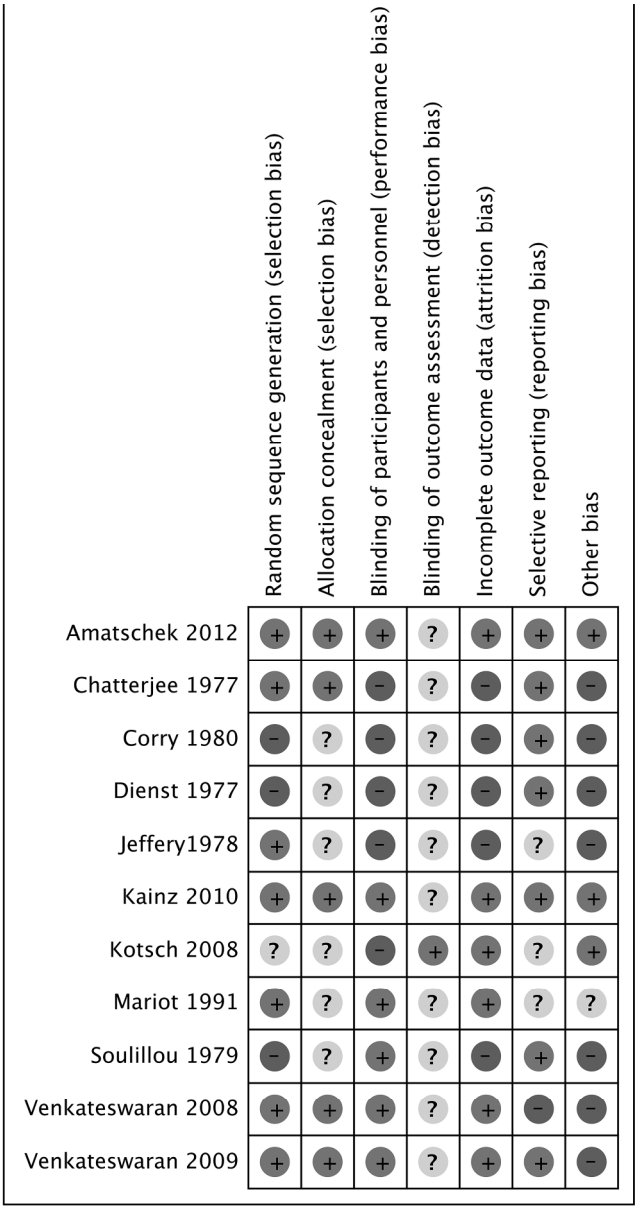

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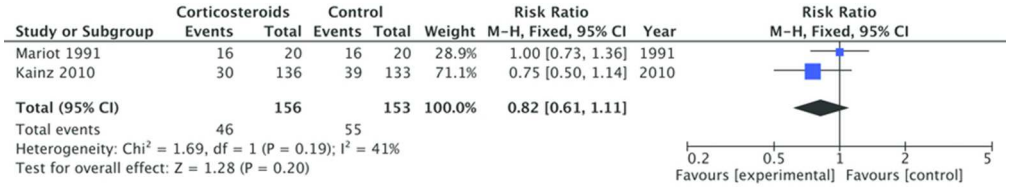

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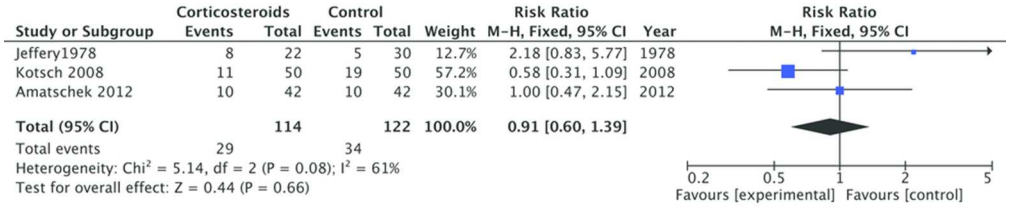

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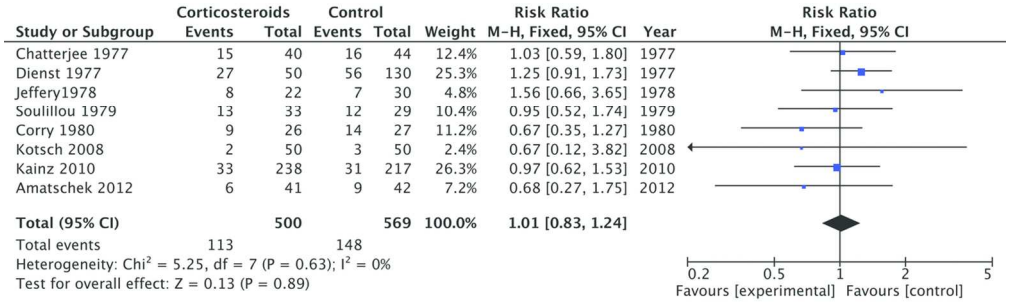

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APPENDIX 1: Search Strategy Medline

1. steroids/ or steroids, brominated/ or steroids, chlorinated/ or beclomethasone/ or chlormadinone acetate/ or cyproterone/ or cyproterone acetate/ or steroids, fluorinated/ or betamethasone/ or betamethasone 17-valerate/ or clobetasol/ or dexamethasone/ or desoximetasone/ or dexamethasone isonicotinate/ or flumethasone/ or fluocinolone acetonide/ or fluocinonide/ or fluocortolone/ or diflucortolone/ or fluorometholone/ or fluoxymesterone/ or fluprednisolone/ or flurandrenolone/ or flurogestone acetate/ or paramethasone/ or triamcinolone/ or triamcinolone acetonide/ or steroids, heterocyclic/ or azasteroids/ or finasteride/
2. glucocorticoids/ or beclomethasone/ or betamethasone/ or betamethasone 17-valerate/ or budesonide/ or clobetasol/ or desoximetasone/ or dexamethasone/ or dexamethasone isonicotinate/ or diflucortolone/ or flumethasone/ or fluocinolone acetonide/ or fluocinonide/ or fluocortolone/ or fluorometholone/ or fluprednisolone/ or flurandrenolone/ or melengestrol acetate/ or methylprednisolone/ or methylprednisolone hemisuccinate/ or paramethasone/ or prednisolone/ or prednisone/ or triamcinolone/ or triamcinolone acetonide/
3. anti-inflammatory agents/ or algestone acetophenide/ or beclomethasone/ or benzydamine/ or betamethasone/ or betamethasone 17-valerate/ or budesonide/ or clobetasol/ or corticosterone/ or cortisone/ or desonide/ or desoximetasone/ or dexamethasone/ or dexamethasone isonicotinate/ or diflucortolone/ or fludrocortisone/ or flufenamic acid/ or flumethasone/ or fluocinolone acetonide/ or fluocinonide/ or fluocortolone/ or fluorometholone/ or fluprednisolone/ or flurandrenolone/ or hydrocortisone/ or methylprednisolone/ or methylprednisolone hemisuccinate/ or nedocromil/ or paramethasone/ or prednisolone/ or prednisone/ or tilorone/ or triamcinolone/ or triamcinolone acetonide/
4. glucocorticoid*.ti,ab.
5. methylprednisolone.ti,ab.
6. hydrocortisone.ti,ab.
7. dexamethasone.ti,ab.
8. corticosteroid.ti,ab.
9. medrol.mp.
10. or/1-9
11. " "tissue and organ procurement"/ or directed tissue donation/ or donor selection/
12. Transplantation/ or unrelated donors/
13. Organ transplantation/ or heart transplantation/ or heart-lung transplantation/ or kidney transplantation/ or liver transplantation/ or lung transplantation/or pancreas transplantation
14. donor management.mp
15. " tissue and organ harvesting "/or donor selection/
16. organ harvesting.mp.
17. donor pretreatment.mp
18. organ donor.mp
19. organ donation.mp.
20. organ donation*.ti,ab.

21. organ transplantation/
22. or/11-21
23. brain death/
24. (brain adj1 (death or dead or deads)).mp.
25. irreversible coma.mp
26. coma depasse.mp
27. (neurologic*adj1 (death or Dead or deads)).mp.
28. deceased.mp
29. or/23-28
30.10 and 22 and 29
31.brain Dead donor*.mp.
32.deceased donor*.mp.
33.31 or 32
34.10 and 33
35.30 and 34
36.(retrieval adj3.donor*).mp.
37.organ harvesting.mp.
38.organ donation.ti,ab.
39.organ donor*.mp.
40.(potential adj3 donors*).mp.
41.or/36-40
42.10 and 41
43.30 or 34 aor 42
44.Animals/
45.Humans/
46.44 not (44 and 45)
47.43 not 46
48.Methylprednisolone Therapy in Deceased Donors Reduces.m_titl.
49.Early donor management increases the retrieval rate of lungs.m_titl.
50.Steroid pretreatment of organ donors to prevent postischemic.m_titl.
51.The haemodynamic effects of adjunctive hormone therapy in potential heart.m_titl.
52.or/ 8-51
53.43 or 52

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	S2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

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Effect of Corticosteroid Administration on Neurologically Deceased Organ Donors and Transplant Recipients : A Systematic Review and Meta-Analysis

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EFFECT OF CORTICOSTEROID ADMINISTRATION ON NEUROLOGICALLY DECEASED ORGAN DONORS AND TRANSPLANT RECIPIENTS : A SYSTEMATIC REVIEW AND META-ANALYSIS

My manuscript is submitted as an original works:

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ABSTRACT

Objectives : This review investigates the impact of corticosteroids on donation rates and transplant outcomes in light of findings from randomized controlled trials (RCTs) and to highlight the sources of uncertainty in this unresolved donor management issue.

Data Sources : We searched electronic databases, trial registries, and conference proceedings for RCTs evaluating corticosteroid therapy in neurologically deceased donors.

Study Selection & Data Extraction : Independent reviewers assessed eligibility, evaluated risk of bias, and abstracted data, including donor hemodynamic data, number of organs recovered, and transplant outcomes. Where possible, we pooled results. For each outcome we assessed the overall quality of evidence using GRADE methodology.

Data Synthesis: Eleven RCTs with different corticosteroid regimens were included. Most trials assessed a once-daily infusion of methylprednisolone. Aside from one study showing improved liver graft function, no individual study or pooled analysis showed benefit of corticosteroids for any outcome: vasopressor use (3 trials; relative risk [RR] 0.96; 95% confidence interval [CI] 0.89 to 1.05), multiple organs recovered (2 trials; RR

0.82; 95% CI 0.61 to 1.11), acute graft rejection (3 trials; RR 0.91; 95% CI 0.60 to 1.39) or graft dysfunction (8 trials; RR 1.01; 95% CI 0.83 to 1.24). Two trials investigated adverse effects and found similar rates between groups. Quality of evidence was moderate or low for all outcomes.

Conclusion : Current clinical trials are limited in numbers and size to identify benefits or harms of corticosteroid therapy for deceased organ donors. In the face of these results, administering or withholding steroids both appear reasonable courses of action.

STRENGTHS AND LIMITATIONS

An exhaustive search strategy and strict adherence to systematic review methodology make this review the most rigorous on the topic.

Our comprehensive GRADE approach improves the transparency regarding the quality of the available evidence on the effect of steroids in potential organ donors.

Available data only allows for limited inference on the effects of steroid on graft outcome due to varied definitions of graft outcomes.

The clinical relevance of our results is limited by the inability to assess for differences in steroid effects associated with variations in dose or timing of administration.

INTRODUCTION

For patients with end-stage organ dysfunction, transplantation is a life-saving intervention. Universally, organs available for transplantation are insufficient to meet population needs.[1] Optimal medical management of deceased organ donors may help to address this shortage.[2, 3]

In the process that culminates in neurological death, cerebral herniation can induce a catecholamine storm that, when severe, leads to cardiovascular collapse. Hemodynamic instability of any degree threatens the viability of potentially recoverable organs[4] and disturbances in the hypothalamo-pituitary-adrenal axis can be an important contributor.[5] Though the prevalence of adrenal insufficiency among neurologically deceased organ donors is uncertain,[6-9] corticosteroid therapy may alleviate hemodynamic collapse during cerebral herniation.

Cerebral herniation also activates a systemic inflammatory response; thus, anti-inflammatory properties of corticosteroid offer another potential mechanism of benefit.[10, 11] Intuitively, inflammation will jeopardize the suitability of organs for transplantation, but prospective cohort studies have generated conflicting results.[12-14]

In theory, treatment of potential organ donors with corticosteroids could improve their hemodynamic status, improve organ suitability and attenuate post-transplant organ dysfunction. The *Society of Critical Care Medicine*, the *American College of Chest Physicians*, and the *Association of Organ Procurement Organizations*, recommend high-dose corticosteroid for organ donation following neurological death.[15] One recent systematic review addressing this topic concluded that existing research neither confirms nor refutes the efficacy of corticosteroid therapy for neurologically deceased donors.[16] To advance this field, we applied GRADE methodology to further define the

quality of current evidence, the specific limitations of previously reported trials, and future research needed to clarify the effects of systemic corticosteroid therapy in neurologically deceased donors.[17]

METHODS

This manuscript was drafted in accordance with the PRISMA guidelines on reporting of systematics review and meta-analyses.[18]

Eligibility Criteria

We included published and unpublished randomized controlled trials (RCTs) enrolling of children and adults neurologically deceased potential organ donors and comparing corticosteroids to placebo, to no administration of corticosteroids, or to other active treatments. We focused on the following outcomes: 1) vasopressor requirement among donors; 2) organ recovery from donors; 3) recipient graft rejection; 4) recipient graft dysfunction (using individual study definitions); and 5) adverse effects of corticosteroids in donors and recipients.

Search Strategy

With the assistance of a medical librarian we searched MEDLINE, EMBASE and Cochrane Central from their inception to January 2017. The MEDLINE search strategy is found in Appendix 1. We searched conference proceedings from the *International Society of Organ Donation and Procurement, American Transplant Congress*, the *Canadian Society of Transplantation*, the *Society of Critical Care Medicine*, and the *Canadian Critical Care Forum* over five years, as well as clinical trial registries, and we screened the reference lists of all relevant articles.

Eligibility Review and Data Abstraction

Two reviewers independently screened citations and evaluated the full text of potentially eligible studies in duplicate, then abstracted data onto customized, pre-tested forms. Disagreements between reviewers were resolved through discussion or third party adjudication. We abstracted data pertaining to study characteristics and design, population, intervention, comparison and all clinical outcomes. We clarified missing data through email correspondence with the study author.

Assessment of Risk of Bias (single studies) and Quality of Evidence (entire body of evidence)

For each study two reviewers evaluated the risk of bias using the Cochrane Collaboration tool for RCTs.[19] The risk of bias was judge to be at low risk, high risk or unclear risk with the following domains: treatment allocation, sequence generation and concealment, blinding, completeness of follow-up, selective outcome reporting and other potential sources of bias.

For each outcome, using GRADE methodology, we evaluated the quality of the entire body of evidence as high, moderate, low or very low,[17] The GRADE system considers each of the following: overall risk of bias,[20] imprecision in estimates of effect,[21] inconsistency in findings across studies,[22] indirectness (the extent to which individual study populations, interventions, and outcome measurements deviate from those of interest to this review)[23] and publication bias.[24]

Statistical Analyses

We calculated chance-corrected agreement for eligibility decisions using the kappa statistic.[19] Dichotomous outcomes are reported as relative risks (RR) with their respective 95% confidence interval (CI) for a two-sided comparison. For pooled analyses, using Revman software version 5.2 (Copenhagen), we chose a fixed effect

rather than a random effect model because estimates of between-study variability are necessary for random effects estimates and are uncertain when, as in this context, there are few studies.[19] If graft outcomes were measured at more than one interval we used the shortest one, assuming that steroid effects, if any, would manifest early. Heterogeneity was measured using the chi square test for homogeneity and the Cochrane I^2.[19] I^2 greater than 50% was considered significant heterogeneity. The Egger test to address publication bias was not performed as less than 10 studies were identified.

RESULTS

Study selection

From 4352 citations, 11 were eligible (Figure 1).[25-35] Between-reviewer agreement at the level of full text review was perfect (kappa = 1). Ten studies were published in English[25, 26, 28-35] and one in French.[27]

Study characteristics

Five out of 11 studies explicitly mentioned Ethics Review Board approval, and fewer detailed the approach to research consent.[26, 28-30, 35] Four publications with a focus on recipient outcomes reported separately for different organs from the same donors. Specifically, one trial was reported in two distinct publications addressing outcome related to the kidney[26] and to the liver respectively.[30] A second trial of a single donor cohort reported separately on outcomes related to lung[36] and heart.[28]

Four publications did not state the number of donors enrolled, because recipient outcomes were the focus.[16, 31-34] When reported, the number of donors ranged from 40 to 269, and baseline characteristics were similar between study groups.[26, 28-30, 35] The

mean donor age varied from 30 to 40 years. The most common cause for neurological death was vascular injury (e.g. stroke, subarachnoid hemorrhage), followed by traumatic brain injury.[26, 28, 35]

Participants in these studies also included transplant recipients in the eight trials reporting on transplant outcomes, of whom there were 885 kidney recipients and 183 liver recipients.[25, 26, 29-34] Their baseline characteristics were reported in only three publications.[26, 29, 30] Groups were similar and liver recipients had favourable prognosis at baseline with a mean Model For End-Stage Liver Disease (MELD) score between 14 and 16.[29, 30] Two studies measured graft outcome only among patients transplanted in the participating organ donation centre and excluded all recipients transplanted in other facilities.[29, 31]

Table 1 presents the study corticosteroid regimens. A single intravenous dose of methylprednisolone was the most common regimen, ranging in dose from 1 gram to 5 grams. Three trials tested corticosteroid therapy in isolation;[26, 29, 30] two others evaluated corticosteroids in a factorial design with liothyronine,[28, 35] one as part of combined hormonal therapy with liothyronine[27] and five placebo-controlled trials administered corticosteroids in combination with cyclophosphamide.[25, 31-34] The timing of corticosteroid therapy also varied across studies. Corticosteroids were administered 30 to 60 minutes after death declaration in one study,[27] immediately after consent for organ donation in three studies,[28, 29, 35] and three to eight hours before surgery in seven studies.[25, 26, 30-34] In most studies, methylprednisolone was dosed every 24 hours.[25, 26, 28, 30-35]

Table 1: Prospective Randomized Trials of Steroids Administration in Neurologically Dead Donors- Summary of the Studies

Author, Year	Donors/ Recipients (n)	Organs Recovered	Experimental Intervention	Control intervention
Parallel Design				
Chatterjee, 1977 [25]	50 84	Kidney	MTP 5 g IV single dose after brain death confirmation	Usual care
Dienst, 1977 [32]	NR 106	Kidney	MTP 3 g IV + Cy 3 g IV single doses 5-8 hrs. before organ recovery	Usual care
	NR 45		MTP 5 g IV + Cy 3 g IV single doses 5-8 hrs. before organ recovery	Usual care
	NR 29		MTP 5 g IV + Cy 5 g IV single doses 5-8 hrs. before organ recovery	Placebo
Jeffery, 1978 [33]	NR 52	Kidney	MTP 5 g IV +Cy 7 g IV single doses ≥ 4 hrs. before organ recovery	Usual care
Soulillou, 1979 [34]	NR 62	Kidney	MTP 5 g IV + Cy 5 g IV single doses ≥ 5 hrs. before organ recovery	Placebo
Corry, 1980 [31]	NR 52	Kidney	MTP 60 mg/kg IV +Cy 80 mg/kg IV single doses ≥ 5 hrs. before organ recovery	Usual care
Mariot, 1980 [27]	40 NR	Multi-organs	Hydrocortisone 100 mg IV+ T_3 2 mcg IV after brain death confirmation q.30-60 min. until stable CVP and SBP	Placebo
Kotsch, 2008 [29]	100 100	Liver	MTP 250 mg IV + 100 mg/h IV after brain death confirmation	Usual care
Kainz, 2010 [26]	269 455	Kidney	MTP 1 g single dose ≥ 3 hrs. before organ recovery	Placebo
Amatschek,2012 [30]	8390 83	Liver	MTP 1 g single dose ≥ 3 hrs. before organ recovery	Placebo
Factorial Design				
Venkateswaran, 2008 [35]	60 NR	Lung	MTP 1 g IV single dose+/- T_3 0.8 ug/kg +0.113 ug/kg/hr IV after brain death confirmation	Placebo
Venkateswaran , 2009 [28]	80 NR	Heart	MTP 1 g IV single dose +/- T_3 0.8 ug/kg +0.113 ug/kg/hr IV after brain death confirmation	Placebo

Legend : CVP= Central Venous Pressure, Cy = Cyclophosphamide, MTP = Methylprednisolone, NR = Not Reported, SBP = Systolic Blood Pressure, T_3 = Liothyronin

Risk of bias of individual studies

Using the Cochrane tool,[19] four RCTs published after 1995 had low risk of bias.[26-30, 35] Earlier trials reported insufficient information to evaluate risk of bias (Figure 2).[25, 31-34]

Results of individual studies and pooled results

Vasopressor requirement

The three studies (n = 452 donors) that reported on vasopressor administration most commonly used norepinephrine.[26, 29, 30] Individually and when pooled, corticosteroid did not influence the rate of vasopressor use in these studies (pooled RR 0.96; 95% CI 0.89 to 1.05; moderate quality) (Figure 3). The GRADE quality of evidence was rated down to moderate quality primarily because this outcome was relatively susceptible to lack of blinding (Table 2).

Organ recovery

Four trials evaluated organ recovery rates, but these data were analysed and reported differently across the four trials. None of the individual trials reported results suggesting increased organ recovery with steroids. Two trials (n = 309 donors) reported on the number of donors that provided multiple organs,[26, 27] and the pooled estimate suggested no effect of corticosteroids but with a very wide confidence interval including substantial benefit (RR 0.82; 95% CI 0.61 to 1.11; moderate quality) (Figure 4). Similarly, in a factorial RCT, investigators did not demonstrate a significant increase in the number of hearts recovered or suitable for transplantation.[28] In a *post hoc* analysis, Venkateswaran observed a decrease in the extravascular lung water index with the administration of corticosteroids; this could potentially increase the number of lungs suitable for transplantation if taken into consideration during donor care. (35) For this

group of outcomes, we rated down the quality of evidence to moderate because of imprecision (wide confidence intervals) (Table 2).

Table 2: GRADE Profile

Quality assessment							Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	
3	RCT	serious[a]	not serious	not serious	not serious	none	⊕⊕⊕ MODERATE
2	RCT	not serious	not serious	not serious	serious[b]	none	⊕⊕⊕ MODERATE
3	RCT	not serious	serious[c]	not serious	serious[b]	none	⊕⊕ LOW
8	RCT	serious[d]	not serious	serious[e,f,g]	not serious	none	⊕⊕ LOW

RCT= Randomized Clinical Trial, RR= Relative Risk
a =Lack of blinding, *b* = Wide confidence interval suggesting appreciable harm or benefit, *c* = Large variation in effect, I2 large, *d* = Selection bias.
e = Different definition of the same outcome, *f* = Surrogate outcomes used to describe graft function, *g* = Co intervention.

Transplant outcomes (acute graft rejection and graft function)

Three trials (n = 235 recipients) studied acute graft rejection.[29, 30, 33] Trials on acute liver rejection reported conflicting results.[29, 30] Amatschek et al. reported similar risks of acute rejection as measured from routine biopsy specimens at three months.[30] However, Kotsch et al. obtained a lower rate of acute rejection, in the corticosteroid group, on routine biopsies within the first six months.[29] Jeffery et al. did not find a reduction in the number of acute kidney rejection with corticosteroids within the first year.[33] Episodes of rejection were diagnosed on the basis of an increase in serum creatinine of more than 0.2 mg/100ml, clinical findings and absence of alternative diagnosis explaining worsening renal function. Pooled estimates do not suggest that corticosteroids reduce the risk of acute graft rejection (RR 0.91; 95% CI 0.60 to 1.39; low confidence) (Figure 5). For this group of outcomes, we rated down the overall quality of evidence to low because of inconsistency (large variation in effect between studies) and imprecision (Table 2).

Of the eight RCTs (n = 1068 recipients) that evaluated graft outcomes,[25, 26, 29-34] two trials provided conflicting results on liver graft function. Kotsch et al. reported a reduction in transaminase levels within the ten days after transplantation among patients receiving corticosteroid therapy.[29] In contrast, Amatschek et al. obtained similar transaminase levels within seven days.[30] Six studies compared a composite risk of one or more of the following data: creatinine level, creatinine clearance, dialysis, listed for kidney transplantation or death at different time interval.[25, 26, 31-34] Pooled estimates, suggest no effect of corticosteroids on graft function (RR 1.01; 95% CI 0.83 to 1.24; low confidence) (Figure 6). Individual studies had high risk of bias, (lack of blinding and loss to follow up) and also provided only indirect evidence because they combined steroids

with cyclophosphamide in the experimental groups. Therefore, we rated the quality of evidence for this outcome as low (Table 2).

Adverse effects

Only two studies evaluated steroid-related adverse events. Investigators reported no effect on infection rates among donors.[29] Bile duct complications and hepatitis C virus reinfection following liver transplantation were similar between groups.[29, 30]

DISCUSSION

We systematically reviewed 11 RCTs evaluating the efficacy of corticosteroid therapy in potential organ donors with respect to clinically important outcomes among both donors and recipients. Individual studies applied a variety of dosing strategies and study outcomes, and very few suggested any difference between corticosteroid and control groups. When two or more studies measured the same outcome, pooled results did not support a treatment effect for hemodynamic stability, the number of organs recovered, or transplant function. The overall quality of evidence was moderate or low for these outcomes, limiting our confidence in the results.

Strengths of our study include a comprehensive search, independent duplicate assessments of study eligibility, risk of bias, and data abstraction, and the pooling of results across studies where possible. Most importantly, we applied the GRADE system to rate the quality of evidence for each outcome that was addressed by more than one study. It provides a transparent assessment of our confidence in the estimates of the effect of steroids on key clinical outcomes in potential organ donors. The GRADE assessment is definitely an added value as it will provide knowledge users with evaluations of the quality of evidence underlying the use of steroids in potential organ

donors. In doing so, our goal was to support guidelines for clinical care and to highlight areas for improving scientific rigor in this field. A primary limitation of this review was the inability to address differences in effect with different dosing regimens, or between organ types, based on the small number of studies to support such subgroup analyses.

Limitations of our study are largely those of the original studies and thus of the body of evidence to which they contribution. Applying GRADE methodology, the overall quality of evidence was rated down as a result of the risk of bias, indirectness of evidence, inconsistency and imprecision. While the risk of bias among five studies reported in the past 20 years was relatively low, the risk of bias was uncertain for six earlier studies, and may be high.[37] Risk of bias was related to lack of blinding and possible selection bias in the unexplained post-randomization exclusion of specific transplant recipients from some studies.[29, 31]

Another limitation is that studies did not take the clustering of organs within donors (a single donor can contribute up to 7 organs) into account in the analysis. To the extent that organs from some donors do systematically better than organs from other donors, the confidence intervals presented in the studies are narrower than would be the case in an analysis that took clustering into account.

Indirectness of evidence was another important reason for rating down the overall quality of evidence. Six studies combining all steroid interventions (but not control interventions) with other hormone therapies,[27,34] or with cyclophosphamide,[30-33] provide only indirect evidence of the potential treatment effects of corticosteroids alone. Variation in timing of randomization and subsequent administration of study intervention also have affected treatment effect presuming that later administration (i.e. 5-8 hours before organ recovery) may be less effective. Indirectness also comes into play when

evaluating studies of varied dosing regimens; it is conceivable that the apparent lack of effect overall is a result of assessing relatively helpful regimens alongside of those that are relatively harmful.

Finally, we also rated down the quality of evidence for two outcomes on the basis of imprecision. The small number of studies, patients within studies, and events among patients resulted not only in wide confidence intervals but also precluded subgroup analyses and assessment for publication bias. In summary, because the quality of evidence is low for at least two outcomes, this review cannot support strong recommendations for clinical care.

Inferences from this systematic review are also limited by varied outcomes of graft dysfunction; variable results across outcomes (apparent harm in number of organs recovered and apparent benefit in graft rejection; varied definitions for each specific term; and the inability to apply outcome definitions across organ groups, which is important in this field because one organ donor may donate kidneys, liver, lung, heart, and/or pancreas or small bowel. For example, outcomes of renal graft function across studies included graft failure,[25, 34] graft survival,[31, 32] and delayed graft function.[26] Even the measurement of renal 'graft failure' was problematic for pooling across studies: Chatterjee et al. defined graft failure as a composite outcome of kidney removal after transplantation, return to hemodialysis or death,[25] while Soulillou et al. defined graft failure as any requirement for hemodialysis or a serum creatinine level (threshold not specified) after transplantation.[34] Unified outcome measures for specific organs, and potentially generic outcome measures across organ groups, would help to advance the science of organ donor management.

Our results are similar to those previously reported.[16, 38] However, we went beyond prior reviews in conducting meta-analyses and using the GRADE approach for rating the quality of evidence. Unfortunately, the moderate or low quality of evidence does not allow strong inferences about the use of steroids in these populations.[15, 39]

Although observational studies frequently overestimate treatment effects, and these might have been confounded by surgical interventions, organ preservation techniques and transplant recipient characteristics, evidence from the current RCTs is also limited in quality. In a recent European multicentre observational study (n = 259), administration of corticosteroids to deceased organ donors with a neurological determination of death was associated with a lower dose of norepinephrine (steroid group [SG] = 1.18 +/- 0.92 mg/h vs control group [CG] =1.49 +/- 1.29 mg/h, p = 0.03) and shorter duration of vasopressor support (SG = 874 min vs CG = 1160 min., p < 0.0001).[40] The incidence of delayed graft function among recipients was similar between the two groups (SG = 30.8% vs CG = 26.6%, p=0.14). These findings are consistent with expected effects regarding the impact of corticosteroid therapy in potential organ donors.

This systematic review highlights three types of challenges to research addressing the medical management of deceased organ donors: the scarcity of donors; practical challenges of studying therapeutic interventions and subsequent outcomes among very separate study populations, (i.e., organ donors and transplant recipients); and the complexity of definitions of graft function. To better guide clinical management of deceased donors will require strong research collaborations among donation and transplantation communities at a national or even international level. Scientifically sound, large clinical trials ideally will enrol consecutive eligible deceased donors, administer a single experimental steroid therapy in a blinded fashion, and measure

outcomes not only among donors but also transplant recipients in a manner that allows the integration of transplant outcomes across organ groups. To achieve these goals may even require modification of current health services in donation and transplantation.

CONCLUSION

Current clinical trials do not identify benefits of corticosteroid therapy for deceased organ donors or their transplant recipients. The quality of this evidence is insufficient, however, to rule out the possibility of benefits or harms with respect to donation rates or transplant outcomes for any organ. In light of these results, there is no imperative to modify current recommendations for clinical care, based on observational studies, to consider corticosteroid therapy in the management of organ donors.

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None

FIGURE LEGEND

Figure 1: Flow Diagram

Figure 2: Risk of Bias across the Included Studies

Figure 3: The Effect of Corticosteroids on Vasopressor Requirement

Figure 4: The Effect of Corticosteroids on Successful Donation of More Than One Organ

Figure 5: The Effect of Corticosteroids on Acute Graft Rejection at Three Months

Figure 6: Forest Plot of the Effect of Corticosteroids on Graft Dysfunction

STATEMENT

All authors have made material contributions to this manuscript according to the rules of authorship of ICMJE. Specifically, here are the contributions of each author:

F D'Aragon: Conception of the design, acquisition of data,analysis and interpretation of the data, draft and revised the manuscript, approved the final version to be published;

E Belley Cote: Conception of the design, acquisition of data,analysis and interpretation of the data, draft and revised the manuscript and approved final version to be published;

A Argawal: Conception of the design,acquisition and analysis of the data, draft and revised the manuscript, approved final version to be published;

AJ Frenette: Conception of the design, acquisition and analysis of the data, draft and revised manuscript and approved the final version to be published;

F Lamontagne: Conception of the design, acquisition and analysis of the data, draft and revised mansucript and approved the final version to be published;

G Guyatt: Conception of the design, acquisition and analysis of the data, draft and revised the manuscript and approved the final version to be published;

S Dhanani: Conception of the design, acquisition and analysis of the data, draft and revised the manuscript and approved the final version to be published;

M Meade: Conception of the design, data acquisition and analysis, draft and revised the manuscript and approved the final version to be published.

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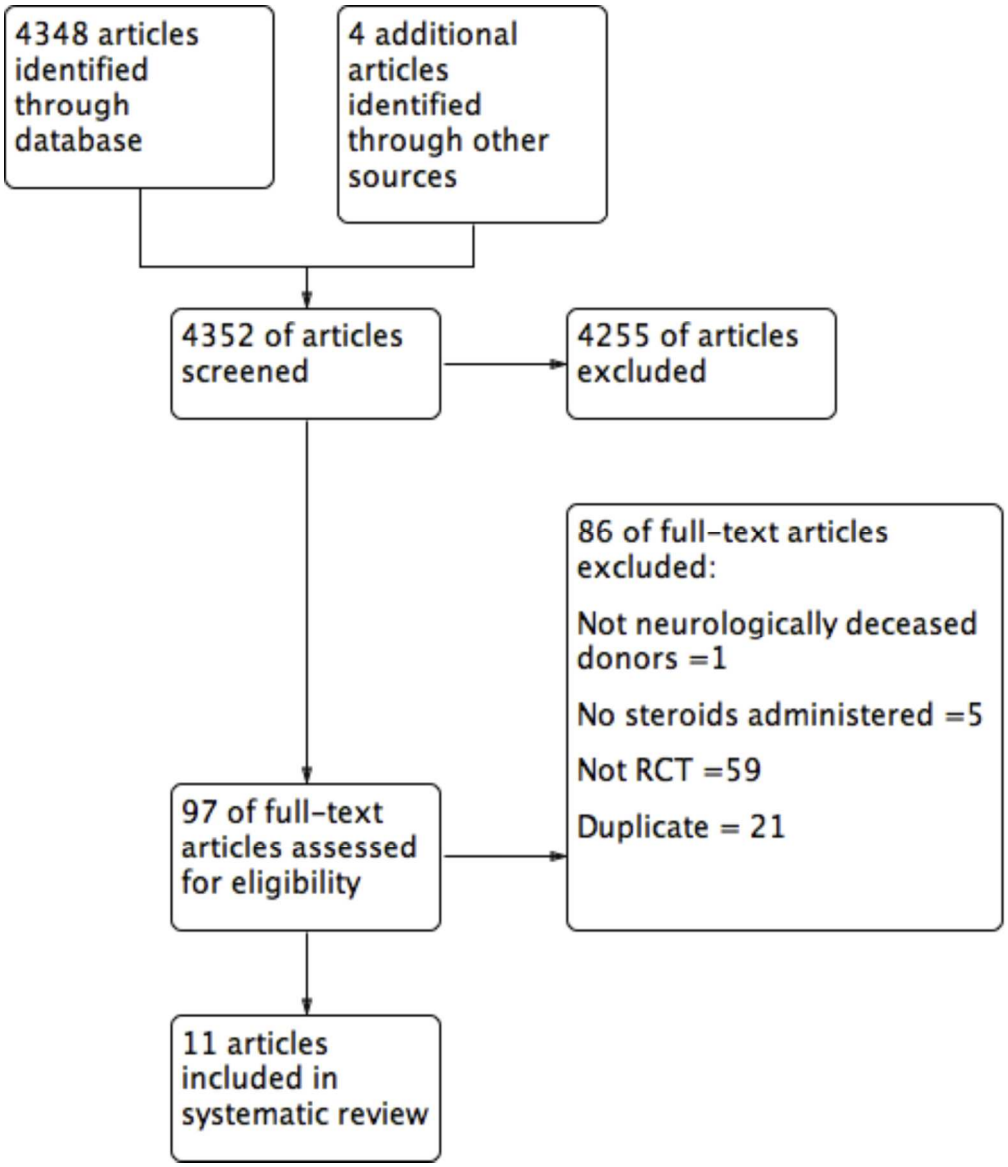

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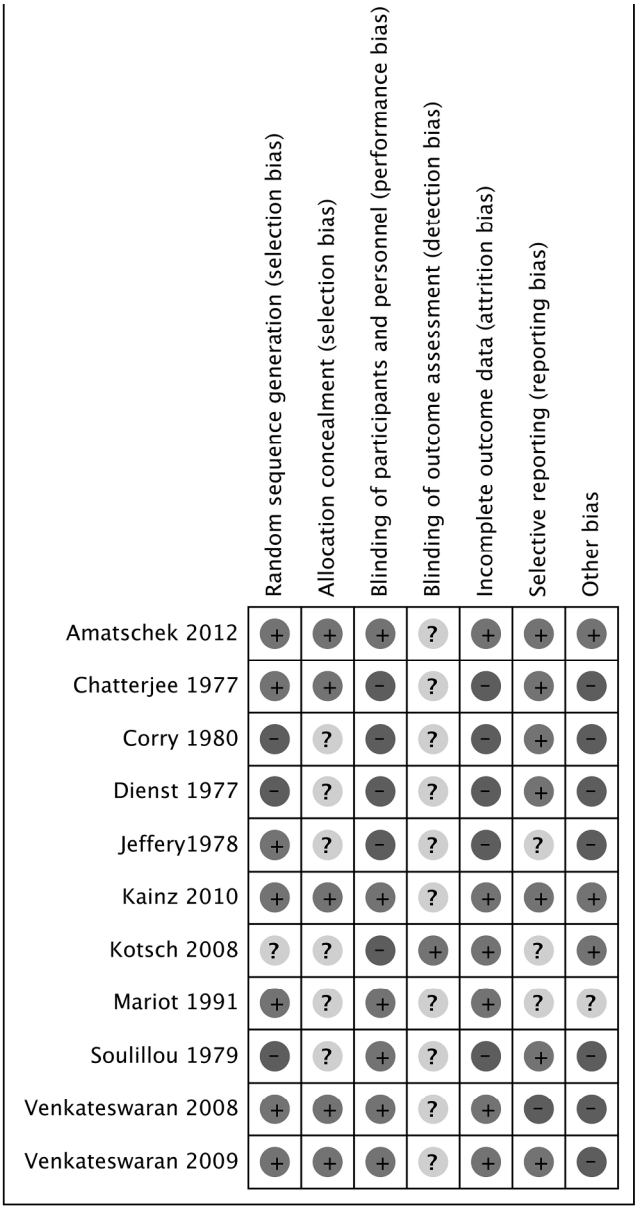

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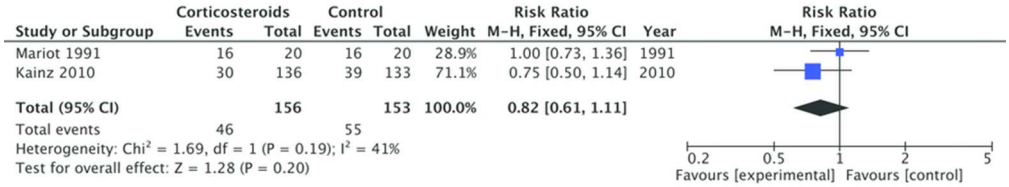

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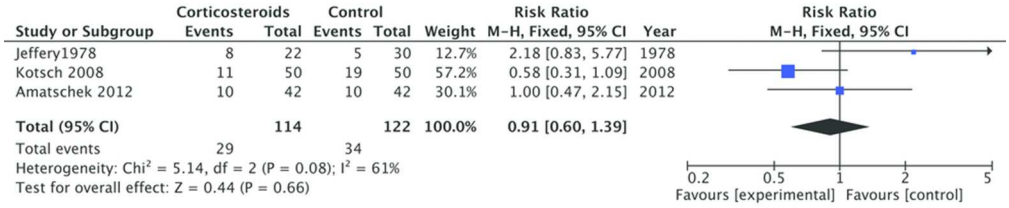

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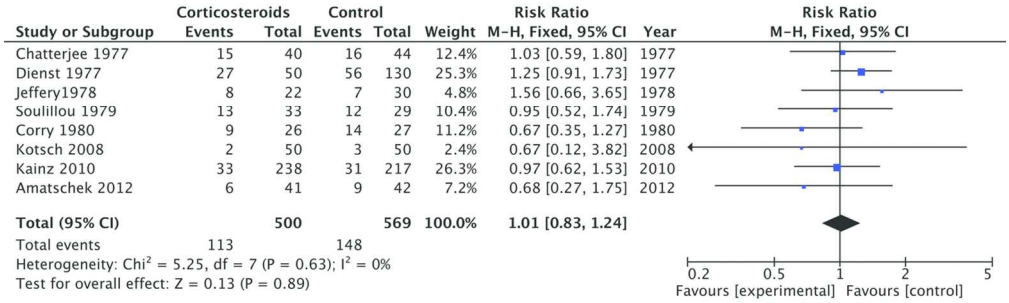

59x18mm (600 x 600 DPI)

APPENDIX 1: Search Strategy Medline

1. steroids/ or steroids, brominated/ or steroids, chlorinated/ or beclomethasone/ or chlormadinone acetate/ or cyproterone/ or cyproterone acetate/ or steroids, fluorinated/ or betamethasone/ or betamethasone 17-valerate/ or clobetasol/ or dexamethasone/ or desoximetasone/ or dexamethasone isonicotinate/ or flumethasone/ or fluocinolone acetonide/ or fluocinonide/ or fluocortolone/ or diflucortolone/ or fluorometholone/ or fluoxymesterone/ or fluprednisolone/ or flurandrenolone/ or flurogestone acetate/ or paramethasone/ or triamcinolone/ or triamcinolone acetonide/ or steroids, heterocyclic/ or azasteroids/ or finasteride/
2. glucocorticoids/ or beclomethasone/ or betamethasone/ or betamethasone 17-valerate/ or budesonide/ or clobetasol/ or desoximetasone/ or dexamethasone/ or dexamethasone isonicotinate/ or diflucortolone/ or flumethasone/ or fluocinolone acetonide/ or fluocinonide/ or fluocortolone/ or fluorometholone/ or fluprednisolone/ or flurandrenolone/ or melengestrol acetate/ or methylprednisolone/ or methylprednisolone hemisuccinate/ or paramethasone/ or prednisolone/ or prednisone/ or triamcinolone/ or triamcinolone acetonide/
3. anti-inflammatory agents/ or algestone acetophenide/ or beclomethasone/ or benzydamine/ or betamethasone/ or betamethasone 17-valerate/ or budesonide/ or clobetasol/ or corticosterone/ or cortisone/ or desonide/ or desoximetasone/ or dexamethasone/ or dexamethasone isonicotinate/ or diflucortolone/ or fludrocortisone/ or flufenamic acid/ or flumethasone/ or fluocinolone acetonide/ or fluocinonide/ or fluocortolone/ or fluorometholone/ or fluprednisolone/ or flurandrenolone/ or hydrocortisone/ or methylprednisolone/ or methylprednisolone hemisuccinate/ or nedocromil/ or paramethasone/ or prednisolone/ or prednisone/ or tilorone/ or triamcinolone/ or triamcinolone acetonide/
4. glucocorticoid*.ti,ab.
5. methylprednisolone.ti,ab.
6. hydrocortisone.ti,ab.
7. dexamethasone.ti,ab.
8. corticosteroid.ti,ab.
9. medrol.mp.
10. or/1-9
11. " "tissue and organ procurement"/ or directed tissue donation/ or donor selection/
12. Transplantation/ or unrelated donors/
13. Organ transplantation/ or heart transplantation/ or heart-lung transplantation/ or kidney transplantation/ or liver transplantation/ or lung transplantation/or pancreas transplantation
14. donor management.mp
15. " tissue and organ harvesting "/or donor selection/
16. organ harvesting.mp.
17. donor pretreatment.mp
18. organ donor.mp
19. organ donation.mp.
20. organ donation*.ti,ab.

21. organ transplantation/
22. or/11-21
23. brain death/
24. (brain adj1 (death or dead or deads)).mp.
25. irreversible coma.mp
26. coma depasse.mp
27. (neurologic*adj1 (death or Dead or deads)).mp.
28. deceased.mp
29. or/23-28
30.10 and 22 and 29
31.brain Dead donor*.mp.
32.deceased donor*.mp.
33.31 or 32
34.10 and 33
35.30 and 34
36.(retrieval adj3.donor*).mp.
37.organ harvesting.mp.
38.organ donation.ti,ab.
39.organ donor*.mp.
40.(potential adj3 donors*).mp.
41.or/36-40
42.10 and 41
43.30 or 34 aor 42
44.Animals/
45.Humans/
46.44 not (44 and 45)
47.43 not 46
48.Methylprednisolone Therapy in Deceased Donors Reduces.m_titl.
49.Early donor management increases the retrieval rate of lungs.m_titl.
50.Steroid pretreatment of organ donors to prevent postischemic.m_titl.
51.The haemodynamic effects of adjunctive hormone therapy in potential heart.m_titl.
52.or/ 8-51
53.43 or 52

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	S2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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