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Corticosteroids in the management of brain-dead potential organ donors: a systematic review

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Editor's key points

- The evidential basis of the widespread use of corticosteroids in brain-dead organ donors was examined by the authors.
- The evidence base appeared to include considerable risk of confounding, and most randomized studies had neutral results.
- Observational studies appear to support the continued use of corticosteroids, but large, prospective studies of the use of corticosteroids in the management of organ donors are needed.

Summary. Current guidelines recommend the administration of hormonal combination therapy including immunosuppressive doses of corticosteroids to donors with low left ventricular ejection fractions and to consider hormonal therapy administration to all donors. However, these recommendations are largely based on observational data. The aim of this systematic review (SR) was to assess the clinical efficacy and safety of corticosteroids in brain-dead potential organ donors. MEDLINE and EMBASE were searched from the earliest accessible date up to March 2013 with a qualified librarian. Studies comparing the effects of any corticosteroid with those of placebo, standard treatment, or another active comparator were sought. Two independent reviewers evaluated each citation retrieved and selected studies independently and in duplicate. A third independent reviewer resolved any disagreement. Outcomes included donor haemodynamics and oxygenation, organ procurement, recipient survival, and graft survival. This review included 11 randomized controlled trials (RCTs) and 14 observational studies. The majority used methylprednisolone and often combined it with other hormonal therapies. Ten out of the 11 RCTs yielded neutral results. However, in observational studies, use of corticosteroids generally resulted in improved donor haemodynamics and oxygenation status, increased organ procurement, and improved recipient and graft survival. Overall quality of included studies was poor, as most of them presented high risks of confounding. This SR highlights the low quality and conflicting evidence supporting the routine use of corticosteroids in the management of organ donors. A large trial evaluating the effect of corticosteroids on outcomes such as organ recovery and graft survival is warranted.

Keywords: adrenal cortex hormones; brain death; human; systematic review; tissue and organ procurement; transplantation

Organ donation saves lives and can prolong the survival of patients with end-stage organ diseases. Unfortunately, the gap between the number of patients on transplantation waiting lists and the number of donors continues to widen.[1] In 2011, more than 113 000 candidates were waiting for an organ transplantation in the USA, while there were only 14 000 donors and a total of 28 500 transplantations.[1]

Brain death often induces a catecholamine storm followed by haemodynamic instability leading to cardiovascular collapse. Without aggressive intervention, clinical deterioration may account for donor loss.[2] Disruption of the hypothalamic–pituitary–adrenal axis may contribute to the observed haemodynamic instability in potential brain-dead organ donors. Although adrenal insufficiency was observed in some potential donors,[3–7] other reports have described normal or increased adrenal function after brain death.[8] Therefore, the administration of corticosteroids (CSs) to restore normal adrenal function remains a subject of debate. Brain death has also been identified as inducing cytokine release contributing to organ damage.[9 10] Theoretically, glucocorticoids could alleviate inflammatory neurogenic pulmonary oedema.[9 11]

Canadian guidelines recommend the administration of hormonal combination therapy consisting of vasopressin, methylprednisolone (MP), insulin, and thyroid hormones to donors with a low left ventricular ejection fraction and consideration in all donors, whereas MP is recommended to all potential

lung donors.[12] In contrast, American guidelines recommend administration of hormonal combination therapy to all donors.[13] However, these recommendations are based on few observational studies.[14–17] The aim of this systematic review (SR) was to assess the clinical efficacy (haemodynamics, oxygenation, organ procurement, graft survival, and function) and safety of CSs in the management of brain-dead potential organ donors compared with placebo, standard treatments, or active comparator.

Methods

Search strategy

Randomized controlled trials (RCTs) and observational studies were identified using electronic and manual search strategies. In March 2013, MEDLINE and EMBASE were searched from the earliest accessible date. A qualified librarian reviewed the final search strategy. Terms defining the study treatments (CSs) and the study population (brain death and tissue donor) were combined. No filters were used in the search but a limit to human was applied. The bibliographies of identified studies and reviews were manually searched for additional studies. The full MEDLINE search strategy is available in Supplementary Appendix S1.

Eligibility criteria

Studies evaluating brain-dead potential organ donor patients, without age restrictions, comparing the effects of the systemic administration of any CS with those of placebo, standard treatment, or another active comparator were sought. Animal studies and case series presenting only descriptive data or lacking any comparison were excluded. Studies evaluating CS efficacy on any clinical primary or secondary outcome measures, safety, or both were included. Clinical outcomes could be evaluated on donors, recipients, or both. Studies evaluating only biochemical markers or hormone levels were excluded. There was no restriction for date and language of publication. Reasons for exclusions were documented.

Study selection

Two independent reviewers (A.J.F. and D.R.W.) screened all citations based on titles and abstracts. Full articles of selected citations were then retrieved for eligibility assessment. Disagreements were resolved by consensus.

Data extraction and validity assessment

Each study was evaluated independently and in duplicate (J.-A.A., S.D., M.D., or Z.T. and D.R.W., A.J.F., M.M.P., or K.S.). The information was collected using a pretested standardized form. A third independent reviewer (S.D. or A.J.F.) resolved any disagreement. Descriptive variables for each study (language of publication, source of funding, sample size, and study objectives) were collected.

Information regarding the study population characteristics (donors and recipients when appropriate), pharmacological interventions, and outcome measures were collected and analysed. The number of organs successfully recovered and transplanted or mortality, morbidity, or both of the recipient were considered as high-impact clinical outcomes. Lower impact clinical outcomes included echocardiographic or haemodynamic changes (left ventricular ejection fraction, cardiac output, blood pressure, vasopressor, or inotrope requirements) and oxygenation status ($Pa_{O_2}/F_{I_{O_2}}$ ratio) in the donor. Information on all reported side effects was also collected. The risks of hyperglycaemia in the donor and HLA mismatching between the donor and the recipient were specifically evaluated.[18 19]

Methodological quality was assessed using the Downs and Black scale for observational studies and the rating instrument developed by the Cochrane Handbook for Systematic Reviews of Interventions for RCTs.[20 21] Power rating in the Downs and Black scale was not assessed because of a lack of reporting of power calculation in studies. Information regarding safety assessment method in individual studies was also collected. It was considered appropriate if side effects were prospectively collected or if they were a study endpoint. The method of assessing side effects had to be provided and its timing clinically relevant.[22] This SR was performed according to the preferred reporting items for systematic reviews and meta-analyses statement (PRISMA).[23]

Data synthesis

Sensitivity analyses were planned to evaluate the potential effect of the following subgroups on efficacy: children *vs* adults (16 yr of age or older), type of CS, concomitant active study treatment (vasopressin, liothyronine, or other), and year of publication. However, pooled estimates of outcome measures were not calculated because of study clinical and methodological heterogeneity.

Results

Included studies

The MEDLINE and EMBASE search strategies identified 1089 citations after duplicate removal. An additional, 15 records were identified through manual search and screened. From these, 56 full-text articles were assessed for eligibility. The SR included 11 RCTs[24–34] and 14 were observational studies.[14–17 35–44] Reasons for exclusion are listed in Figure 1. Patient characteristics of studies are listed in Tables 1 and 2. Financial sponsorship, when declared, was mainly from non-profit organizations or institutes. Ten of the studies declared financial sponsorship,[14 15 24 25 27 30 32–34 40] with only one of them being from a private company.[24] One study declared having received no financial support[43] and no information on financial support was provided in the remaining studies.[16 17 26 28 29 31 35–39 41 42 44]

Study population

The number of included donors in each study varied widely, and studies that measured recipient outcomes did not always report the number of donors. Patient characteristics of study population can be found in Tables 1 and 2. Of note, variation in patient characteristics was an important source of clinical heterogeneity. Although not reported in every