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Comparison of high- and low-dose corticosteroid regimens for organ donor management

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Abstract

Purpose: Corticosteroids are used to promote hemodynamic stability and reduce inflammatory organ injury after brain death. High-dose (HD) methylprednisolone has become the standard regimen based on comparisons to untreated/historical controls. However, this protocol may exacerbate hyperglycemia. Our objective was to compare a lower-dose (LD) steroid protocol (adequate for hemodynamic stabilization in adrenal insufficiency and sepsis) to the traditional HD regimen in the management of brain-dead organ donors.

Methods: We evaluated 132 consecutive brain-dead donors managed before and after changing the steroid protocol from 15 mg/kg methylprednisolone (HD) to 300 mg hydrocortisone (LD). Primary outcome measures were glycemic control, oxygenation, hemodynamic stability, and organs transplanted.

Results: Groups were balanced except for nonsignificantly higher baseline Pao_2 in the LD cohort. Final Pao_2 remained higher (394 mm Hg LD vs 333 mm Hg HD, $P=.03$); but improvement in oxygenation was comparable (+37 mm Hg LD vs +28 mm Hg HD, $P=.43$), as was the proportion able to come off vasopressor support (39% LD vs 47% HD, $P=.38$). Similar proportions of lungs (44% vs 33%) and hearts (31% vs 27%) were transplanted in both groups. After excluding diabetics, median glucose values at 4 hours (170 mmol/L vs 188 mmol/L, $P=.06$) and final insulin requirements (2.9 U/h vs 8.4 U/h, $P=.01$) were lower with LD steroids; and more patients were off insulin infusions (74% LD vs 53% HD, $P=.02$).

Conclusions: A lower-dose corticosteroid protocol did not result in worsened donor pulmonary or cardiac function, with comparable organs transplanted compared with the traditional HD regimen. Insulin requirements and glycemic control were improved. High-dose methylprednisolone may not be required to support brain-dead donors.

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1. Introduction

Brain death triggers a systemic inflammatory response that may contribute to organ injury and graft dysfunction [1-3]. Hemodynamic instability, which may be related to neurohormonal dysregulation, is common and can further compromise viability of organs for transplantation [4]. Hormonal resuscitation is recommended to stabilize donor function and ensure maximal recovery of suitable organs for transplantation [5]. Corticosteroids are given to both attenuate inflammatory injury and maintain hemodynamics in the face of secondary adrenal insufficiency [6]; the regimen most frequently used involves large doses of intravenous methylprednisolone. The evidence for this practice comes from poorly controlled retrospective studies (using historical controls and/or comparing methylprednisolone to no steroids) that suggested greater thoracic organ procurement rates and improved oxygenation [7-10]. However, there is concern that such megadoses of steroids may worsen hyperglycemia, which itself may be detrimental to organ function [11]. Much lower corticosteroid doses (eg, hydrocortisone ≤ 200-300 mg/d, at approximately 20× lower potency) have been shown to stabilize shock associated with sepsis and are routinely used to support states of adrenal insufficiency [12-14]. Such doses may also be adequate to inhibit inflammatory cytokine propagation [14,15].

Coupling the theoretical rationale and preliminary evidence supporting steroid treatment of brain-dead organ donors with the concerns and uncertainty over whether megadoses are truly required for their beneficial effects (balanced against potential harm), the Critical Care Committee at Mid-America Transplant Services advised a lowering of the steroid dose used after brain death. The primary safety aim of this study was to ensure that this protocol change did not result in any reduction in thoracic organ function or transplantation yield. Specifically, we hypothesized that lower-dose steroids would be comparable in terms of oxygenation, hemodynamic stability, and heart and lung recovery for transplantation, as well as 1-year graft function. Furthermore, we wanted to evaluate whether glycemic control and insulin requirements were improved with lower-dose steroids.

2. Methods

We extracted records on consecutive consented brain-dead organ donors from a prospectively collected database for our donor-service area 7 months before and after the change in steroid protocol (February 2009). The high-dose (HD) group comprised those donors who received the traditional regimen of 15 mg/kg of intravenous (IV) methylprednisolone(with a repeat dose given at 24 hours if necessary), whereas the lower-dose (LD) group included those who, after the protocol change, received hydrocortisone 300 mg IV followed by 100 mg every 8 hours (given its shorter half-life) until organ procurement. We excluded children (age < 14 years/considered too small to receive the full dose of steroids) and those older than 65 years (who traditionally are not candidates for lung donation, an outcome of primary safety concern given the belief that high-dose steroids preserve lung function and procurement) [7]. Informed consent for donation and associated research was obtained from donor families, whereas study approval was provided by the executive committee at Mid-America Transplant Services.

2.1. Donor management

A standardized protocol for donor optimization was followed by all case coordinators over the entire period of study. The only change in this protocol was the dose/type of steroid given after brain death. All patients are monitored with continuous electrocardiogram, arterial blood pressure, central venous pressure (CVP), hourly urine output, and temperature. Serum electrolytes, arterial blood gases, and tests of renal function are performed every 4 hours. Management is targeted at attaining key physiologic metrics: vasopressors are titrated to the lowest dose required to achieve systolic blood pressure of at least 100 mm Hg, and IV fluid rate is titrated to urine output of at least 0.5 ml/kg/h and CVP 5 to 10 mm Hg. Intravenous and enteral fluids are adjusted to maintain serum sodium to less than 160 mEq/L. Diabetes insipidus is treated with vasopressin infusion (rate of 0.5-2 U/h), titrated to normalize urine output. Temperature is maintained between 36°C and 38°C, with heating/cooling blankets if necessary. Glucose levels between 65 and 140 mg/dL are targeted, aggressively titrating insulin infusions as required. An infusion of intravenous levothyroxine (T_4) is started on each donor and titrated down if hypertension develops. Echocardiography is performed in potential heart donors once hemodynamics have stabilized, at least 8 hours after T_4 initiation; results are all read by a single transplant cardiologist. Ventilator settings are adjusted to normalize pH and maintain oxygen saturation at greater than 90%. All donors undergo bronchoscopy to clear any mucous plugging and obtain sputum specimen for Gram stain and culture. Tidal volumes are kept at roughly 10 mL/kg while maintaining plateau pressures at less than 30 cm H_2O. Atelectasis and secretions are treated using a chest percussion vest and repeat bronchoscopy as needed. Other lung recruitment maneuvers such as increasing positive end-expiratory pressure or manual bagging with inspiratory holds are used if hypoxemia persists. Inspiratory:Expiratory time may be adjusted between 1:3 and 1:1. Infiltrates associated with high CVP are treated with diuretics. Chest radiographs are repeated every 4 hours as needed. Arterial blood gases are obtained on fraction of inspired oxygen (FiO2) of 100% and positive end-expiratory pressure of 5 cm H_2O with goal Pa_{O_2} of at least 300 mm Hg.