Hydrocortisone treatment and organ donor management: a randomized placebo controlled trial

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Abstract

In brain death patients pituitary-adrenal hormonal dysfunctions are common. It is suggested, that these patients get hormonal replacement therapy to counteract haemodynamic instability and electrolyte disorders. Corticoid treatment is recommended as a part of hormonal therapy. We performed a randomized, double-blind, placebo controlled study to investigate the effects of hydrocortisone on the need of norpepinephrine in brain death patients.

Methods

Adult patients, who were treated in Kuopio and Tampere University Hospitals only due to potential organ donation or were diagnosed brain death were eliglible for the study. Exclusion criteria were consent from legal representative, age under 18, pregnancy, known pituitary or adrenal insufficiency, etomidate use during the last seven days or any corticoid therapy. The patients were randomized to receive either hydrocortisone (50mg x4) or placebo. The sample size was calculated based on the assumption from studies is septic shock, that corticoid treatment could decrease norepinephrine doses by 50%. We used an alpha value of 0.05 and beta value of 0.8. With this assumption 40 patients would have been needed. Additionally baseline serum cortisol and adrenocorticotropic hormone levels were determined.

Results

During 18.5.2008 to 16.08.2011 35 patients were recruited with the mean age of 56 ± 12. The mean dose of hydrocortisone was150 ±74 mg. The median time from study start to organ donation was 344 (275-602) min in the placebo group and 775 (377-1502) min in the hydrocortisone group (p=0.14). There was no difference in the median dose (p=0.9) or length of norepinephrine infusion (p=0.07) between study groups. No difference was seen in the time of systolic blood pressure <100mmHg (p=0.1), mean minimal central venous pressure (p=0.15), or amounts of fluids given (p=0.21).

Conclusions

Hydrocortisone treatment did not reduce the amount of length of norepinephrine infusion in brain dead organ donors.

Introduction

Brain death patients may suffer from hormonal insufficiencies [1].These may be due to pituitary and/or adrenal insufficiency which may cause hemodynamic instability and can lead to high dose usage of vasoactive drugs. Vasoactive drugs may worsen the quality of donated organs [1]. This has led to the recommendation to use protocolized hormonal replacement therapy [2, 3] to increase hemodynamic stability and to increase the number and quality of donated organs.

Traditionally high dose corticoid therapy has been used for brain death organ donors to treat corticoid insufficiency and to achieve hemodynamic stability. In septic patients low dose corticoids have been shown to be effective in reversing shock [4] . In brain dead patients low dose corticoid infusion or boluses have been shown to be hemodynamically effective as well [5, 6](ref). However, in these studies, hormonal replacement therapy was commenced always after the diagnosis of brain death and no blinding for corticoid therapy was used.

In this double blind, randomized trial our aim was to show whether low dose corticoid treatment (hydrocortisone 50 mg x 4/d) would result in less use of norepinephrine.

Methods

All patients >18 years old and who had subarachnoid haemorrhage and/or brain injury or intracerebral haemorrhage and who were treated only for possible organ donation, were included. Consent from the legal representative was obtained at the time of asking permission for possible organ donation. Thus, the study start time could have been also before diagnosing brain death, but the treatment in the ICU was only due to possible organ transplantation. Exclusion criteria were no consent from legal representative, age under 18, pregnancy, known pituitary or adrenal insufficiency, etomidate use during the last seven days or corticoid therapy. Institutional ethics board approved the study protocol in Tampere and Kuopio University Hospitals, Finland. Additionally the Finnish Medicines Agency (Fimea) approved the study.

Brain death was determined according to the Finnish law. After excluding for potential confounding factor like sedative drugs and hypothermia brain death was diagnosed with no response to pain stimuli, no brain stem reflexes and no more spontaneous breathing diagnosed with apnea test.

After received consent blood samples for plasma Adrenocorticothrophic (ACTH) hormone and plasma cortisol were drawn. An ACTH level <5 pmol/l and/or baseline cortisol level <415 mmol/l was considered as secondary adrenal insufficiency (AI).

Patients were randomized to receive intravenously either 1ml normal saline in 2ml syringes or 50 mg of hydrocortisone in 2ml syringes in six hours interval. Randomization was performed with sealed, opaque envelopes. Only unblinded nurses were allowed to randomize and to give study drugs. Unblinded nurses did not treat patients at the ICU during the study.

For serum cortisol measurements electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany) was used. For serum ACTH measurements immunoluminometric assay (IMMULITE; Diagnostic Products Corporation, Los Angeles, CA) was used.

All patients were tracheally intubated and ventilated with controlled mode with keeping peep 6-8 cmH2o and plateau airway pressures under 30 mmHg and with tidal volumes 6-8 ml/kg. All patients had invasive arterial pressure monitoring and central venous catheters.

Fluid was administered to achieve a central venous pressure (CVP) of >4 mmHg and a mean arterial pressure (MAP) of >60 and a systolic blood pressure (SAP) >100 mmHg. A haemoglobin level of >100 g/l was aimed. Serum potassium and sodium levels were kept normal. If diuresis was 300 ml/h more than two hours, desmopressin was administered.

Distribution of the parameters was assessed by the Shapiro Wilkins test. For normally distributed parameters, student's *t*-tests were used to compare the means of different groups. The Mann-Whitney U test was used for nonparametric testing between the groups. Chi-square test or Fisher's exact test was used to test dichotomized and categorical independent variables. Spearman or Pearson correlations were calculated. SPSS 19.0 software (SPSS, Chicago, IL) was used to perform the analyses..

The sample size was calculated based on the assumption from studies is septic shock [7] that corticoid treatment could decrease norepinephrine doses by 50%. We used an alpha value of 0.05 and beta value of 0.8. With this assumption, 40 patients would have been needed.

Results

During 18.5.2008 to 16.08.2011 35 patients were recruited to the study. The demographics of the patients are shown in table 1.

The mean hydrocortisone dose was 150 ±74 mg. The median time from study start to organ donation was 344 (275-602) min in the placebo group and 775 (377-1502) min in the hydrocortisone group (p=0.14). In 22 patients the study treatment started already before brain death diagnosis.

The median time from study start to brain death was 55 (86-206) min in the placebo group (11 patients) and 393(-1044-139) min in the hydrocortisone group (11 patients) (p=0.49). If the study was started after brain death the median time from brain death diagnosis to study start was 338(255-341) min in the placebo group (6 patients) and 334(205-545) min in the hydrocortisone group (7 patients) (p=0,75).

In the placebo group the mean minimal central venous pressure was 2±3 mmHg and 0±3 in the hydrocortisone group (p=0,15).

The median diuresis was 170 (51-285) ml/h in the placebo group and 208 (79-262) ml/h in hydrocortisone group (p=0,68).

Baseline ACTH and cortisol values are expressed in table 1. Four patients in the placebo group and two in the hydrocortisone group had ACTH levels below 5 pmol/l. There was no difference in the median dose (p=0.9) or length of norepinephrine infusion (p=0.07) between these groups. There was no correlation with the ACTH-concentration and norepinephrine dose or length of infusion (p=0.15 and 0.06 respectively).

Five patients in the hydrocortisone group and three patients in the placebo group had baseline cortisol levels < 415 nmol/l. One baseline cortisol measurement is missing. In two patients both ACTH and cortisol concentrations were indicating AI.

Discussion

To our knowledge, this is the first randomised placebo controlled study investigating the effects of low dose hydrocortisone treatment to reduce requirements for norepinephrine in patients treated for organ donation. In this study hydrocortisone, treatment did not reduce the total amount or the length of norepinephrine treatment.

Hormonal replacement therapy has been recommended for brain-dead organ donors although this recommendation is mostly based on observational studies [8] .

Recently, three studies have compared hydrocortisone treatment in brain-death organ donors [5, 6, 9]. Dhar et al. [5] compared in a before after setting the effects of low vs. high dose corticoid treatment on hemodynamic stability, glycemic control and organs transplanted. They concluded, that high dose corticoids were not superior to low dose corticoids when it comes to hemodynamic stability.

Nicolas-Robin et al. [6] performed a study in which a single dose of 50 mg hydrocortisone was given to brain-dead organ donors. Their hypothesis was that brain-dead organ donors would have more stable hemodynamics after corticoid supplementation. A single dose of hydrocortisone enhanced systemic hemodynamics by reducing the dose of norepinephrine.

In the most recent study of Pinsard et al. they compared low-dose steroid administration without steroid administration. The probability for norepinephrine weaning was higher in the corticoid group and the duration and dose of norepinephrine was less than in the control group.

All three studies [5, 6, 9] are in contrast to our study. We did not show any benefit in any hemodynamic parameter if patients received hydrocortisone or not. Neither the dose nor time on norepinephrine was different in the active treatment group compared to the placebo group. Thus, reduction in catecholamine doses could be beneficial. In a recent systematic review, it has been shown that many studies of corticoid therapy in organ donor patients are of low quality and give conflicting results [8].

Adrenal insufficiency with major hemodynamic instability is common in brain-dead organ donors [10]. It may be primary due to adrenal gland dysfunction or secondary due to hypothalamo-pituitary-adrenal dysfunction. It is a well-known fact, that corticoid treatment reduces need for catecholamine treatment in hemodynamically unstable septic patients (ref) and corticoids sensitise the norepinephrine receptors in the vasculature (ref). In the

study of Nicolas-Robin et al. [6] they found, that 87% of patients had secondary adrenal insufficiency and only a quarter of patients did not respond to an ACTH-stimulation test. In our study, the incidence on AI was lower than in those studies of Nicolas-Robin et al [6, 10].

There are some limitations in our study. We did not assess the function of transplanted organs. Previously it has been shown, that vasopressors may be an independent risk factor for delayed graft function [11]. Moreover, we did not perform an ACTH-stimulation test. However, Nicolas-Robin et al. have shown that a baseline total cortisol measurement is sufficient to diagnose AI even compared to stimulated free cortisol measurement [10].

We conclude that in this randomized, double-blinded, placebo-controlled trial, hydrocortisone treatment did not reduce the amount of norepinephrine in organ donation patients.

Table 1. Basic characteristics and hormonal levels of the patients. Expressed as mean ±SD or medians (25^{th} and 75^{TH} percentiles).

	Placebo(n=17)	Hydrocortisone(n=18)	p-value
Age	58±12	54±12	0,04
Gender male	11	13	0,73
Hydrocortisone dose(mg)	0	150±74	
LOS ICU(h)	0,7(0,5:1,2)	30(1:2,2)	<0,001
Study time (min)	344 (274:602)	774 (348:1504)	0,14
SAPS	62(59:68)	60(52:64)	0,17
APACHE II	30±12	29±8	0,7
ACTH pmol/l	13 (6:35)	12(8:24)	0.97
Serum cortisol nmol/l	785(467:896)	745(367.887)	0,7

Table 2. Haemodynamic variables of the patients.

	Placebo	Hydrocortisone	p-value
time MAP<60mmHg(min)	25±51	0(0-2)	0,1
Time SAP<100mmHG	17(12-60)	8(0-24)	0,1
Time HR<60/min	0(0-4,5)	0(0-32)	0,76
Number of patients needed norepin.	16	13	0,09
Norepinephrine median u/kg	0,05(0,03-0,08)	0,04(0-0.09)	0,34
Norepinephrine time (min)	291(155-476)	490(0-756)	0,54
total amount of fluids (ml)	3200±2200	4300±3000	0,21

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