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Original article

Effects of glucocorticoids on serum amino acid levels during cardiac surgery in children

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SUMMARY

Background and aims: Children undergoing cardiac surgery with cardio pulmonary bypass often receive glucocorticoids to reduce the systemic inflammatory response. Glucocorticoids stimulate protein breakdown and increase amino acid availability. We studied whether glucocorticoid treatment influences the availability of amino acids, specifically those involved in the nitric oxide pathway.
Methods: We prospectively studied 49 children with congenital heart disease undergoing cardiac surgery. Serum cortisol and amino acid levels were measured in arterial blood sampled before surgery ($t = -5$ min), directly after surgery ($t = 0$ h) and at $t = 12$ h and $t = 24$ h after surgery. Serum cortisol and amino acid levels were compared between children who had received glucocorticoids (G+) and children who had not (G−).
Results: Of 49 patients included ((49% male, age 1.7 (0.5–8.7) y)), 33 (67%) received glucocorticoids. Baseline characteristics were not different between groups, except a higher weighted inotropic score in the G+ group. At $t = 0$ h, serum cortisol levels in the G+ group were significantly higher than in the G− group (7218 vs. 660 nmol/L; ($p < 0.05$)), but not different at the other time points. The levels of plasma amino acids had dropped after surgery. Compared to the G− group, in the G+ group the total amount of amino acids was significantly higher at $t = 12$ and $t = 24$; citrulline levels were higher at $t = 12$ and $t = 24$; and glutamine and arginine levels were higher at $t = 12$.
Conclusions: Glucocorticoid treatment during cardiac surgery in children preserves serum amino acid levels post-surgery. The preservation of glutamine, citrulline and arginine levels might have a beneficial effect on the related NO metabolism.

Introduction

The metabolic stress response to cardiac surgery with cardio pulmonary bypass (CPB) will induce catabolism [1]. In this state, protein turnover doubles; amino acids are redistributed in neonates [2]; and the production of urea cycle intermediates is lower in children [3]. In the postoperative period, arginine, citrulline, and nitric oxide (NO) metabolites are much less available [3]. As children with congenital heart disease (CHD) often have increased metabolic demands and decreased energy, they are at risk for a poor nutritional status [4]. Furthermore they are at risk for pulmonary hypertension related to a lower NO production [5]. The presence of pulmonary hypertension is a major cause of postoperative morbidity and death [6].

NO is one of the most potent vasodilators known and is essential to vascular homeostasis [7]. Amino acid metabolism is tightly related to the synthesis of NO. For instance, while the amino acid arginine is the sole precursor of NO [5,8], glutamine, *via* the intermediate citrulline, is an important precursor for arginine [9]. Decreased availability of glutamine, citrulline and arginine therefore might contribute to reduced availability of NO and thus lead to a higher risk of developing postoperative pulmonary hypertension [10].

Children undergoing CPB are often given peri-operative glucocorticoids to reduce the systemic inflammatory response. An

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important adverse effect of corticosteroids in general is muscle protein breakdown leading to protein catabolism [11]. Increased protein catabolism seems unfavorable, but alternatively may also increase the systemic availability of specific amino acids like glutamine, citrulline and arginine.

In this study we evaluated the effects of glucocorticoid treatment on peri-operative plasma amino acid levels in children with CHD undergoing CPB, with a focus on the amino acids involved in the NO pathway.

Materials and methods

Infants and children (aged 0–18 y) admitted to the pediatric intensive care unit of the Erasmus MC-Sophia's Children Hospital following elective cardiac surgery with CPB were eligible. Exclusion criteria were endocrine or chromosomal abnormalities or radiation/chemotherapy within the previous 6 months. The Medical Ethics Review Board of the Erasmus MC approved the study protocol and we obtained written informed consent from parents or legal representatives of all subjects.

Clinical parameters

We prospectively recorded general patient characteristics as well as anthropometric measurements one day before cardiac surgery, the duration of mechanical ventilation, lengths of intensive care unit (ICU) and hospital stays, and survival. Severity of illness was assessed with the risk adjustment for congenital heart surgery (RACHS) score [12], the pediatric risk of mortality (PRISM) score [13] and the pediatric logistic organ dysfunction (PELOD) score [14]. In addition, we recorded the presence of cyanotic heart disease, the duration of CPB, and the aorta cross-clamp time.

All children received standardized analgesia during and after surgery. For each individual patient, the attending anesthetist considered whether or not to administer glucocorticoids before surgery, thus regardless of the findings during surgery. Inotropes were administered by standardized protocol. A weighted inotropic score was calculated based on maximum inotropic support during surgery and (ICU) stay [15]. Weaning from the ventilator was protocolized.

Blood sampling and analysis

Arterial blood samples were collected from an indwelling arterial catheter at $t = -5$ min (preoperatively directly after anesthetic induction), $t = 0$ h (end of surgery after closure of sternum), $t = 12$ h and $t = 24$ h post-surgery and immediately put on ice. After processing, plasma was stored at −80 °C and analyzed as described before [10,16].

Statistical analysis

Data were analyzed using SPSS (19.0) for Windows (SPSS Inc, Chicago, IL). The results are presented as median (interquartile range), unless specified otherwise. We used Mann–Whitney *U* test for group comparison. Significance of differences between measurement moments was tested with two-way ANOVA. Two-tailed p-values <0.05 were considered statistically significant.

Results

Baseline characteristics

In total 49 children were included. Baseline characteristics are presented in Table 1. For the purpose of this study, we created two groups: those treated with glucocorticoids (G+; n = 33) and those not treated with glucocorticoids (G−; n = 16). Cardioplegic arrest was initiated in 45 children, who all survived. Of the other four children, three were in the G− group and one in the G+ group. All but one child received mild hypothermia (median, 31 °C) during surgery; one child (age 16.6 years) received deep hypothermia (22.5 °C). Glucocorticoid treatment consisted of methylprednisolone (30 mg/kg) except for one child who received hydrocortisone (2 mg/kg).

Table 1
Baseline characteristics.

Variable	Glucocorticoids (n = 33)	No Glucocorticoids (n = 16)
Demographic data		
Age: years	1.4 (0.2–5.2)	3.1 (0.6–13.8)
Sex F (%)	18/33 (55%)	6/16 (38%)
Weight: kg	8.0 (6.0–17.8)	14.1 (6.7–44.6)
Z score weight for age	−1.1 (−2.1 to 0.3)	−1.2 (−2.0 to 0.5)
Z score BMI or age	−1.21 (−2.0 to 1.6)	−0.6 (−1.89 to 0.3)
Illness severity		
Cyanotic disease	11/33 (33%)	5/16 (31%)
Operative course		
CPB time: min	88.5 (59–128)	64 (45–111)
Aortic crossclamp time: min (range)	47 (31–88)	34 (18–42)
Hypothermia: °C	29.3 (28.6–31.7)	32.5 (30–34.2)
Postoperative course		
Ventilation duration: h	10 (7–26)	7 (6–11)
Inotropes (%)	22/33 (67%)	8/16 (50%)
RACHS-1 score	3 (2–3)	2.5 (1–3)
PRISM score	13 (10–15)	12 (10–14)
PELOD score	11 (1–11)	10 (1–11)
WI score*	38 (22–54)	1.4 (0–24)
Length of ICU stay: days	1.0 (0.9–1.1)	1.0 (0.95–1.0)
Length of hospital stay: days	8 (7–8.5)	7 (7–8)

Types of surgery were: ventricular septal defect (n = 10), atrial septal defect (n = 9) correction of tetralogy of Fallot (n = 10) re-implantation of anomalous left coronary artery from the pulmonary artery with patch closure of the aortopulmonary window (n = 1). Univentricular heart: cavopulmonary connection, partial (n = 4), total (n = 2). Left ventricular outflow tract obstruction: enucleation (n = 5), pulmonary autograft (n = 2), allograft aortic root replacement (n = 1). Right ventricular outflow tract obstruction: infundibulectomy (n = 2), pulmonary allograft (n = 1). Mitral valve insufficiency, mitral valve annuloplasty (n = 2).
Data are expressed as median (interquartile range) or numbers (percentage).
RACHS score risk adjustment for congenital heart surgery, *PRISM score* pediatric risk of mortality score, *PELOD score* pediatric logistic organ dysfunction score, *WI score* weighted inotropic score based on maximum inotropic support during surgery and ICU stay, *CPB* cardiopulmonary bypass, *ICU* intensive care unit.
*Marks a significant difference ($p < 0.05$) between the glucocorticoid and no glucocorticoids group.
Table 1 is an overview of all baseline patient characteristics divided in demographic data, Illness severity, operative, and postoperative course. 33 children received glucocorticoids and 16 did not.

None of the baseline characteristics (Table 1) was significantly different between the G+ and G− groups, except for the weighted inotropics score, which was significantly higher in the G− group.

General

Table 2 and Fig. 1 show the total amount of amino acids, cortisol, citrulline, arginine and glutamine levels from the start of surgery to 24 h after surgery. The total amount of amino acids decreased over time in both groups, reaching the lowest level at $t = 12$ h (significant compared to $t = -5$; $p < 0.001$). At $t = 24$ h, the difference with pre-surgery levels was no longer significant. At $t = 12$ h and $t = 24$ h, the total amount of amino acids was significantly higher in the G+ group compared to the G− group. At $t = -5$ min, both cortisol levels and total amounts of amino acid levels did not differ, but at $t = 0$ h serum cortisol levels were significantly higher in the G+ group.