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Effect and mechanism of hydrocortisone on organ function in patients with severe burns

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ABSTRACT

Introduction: In patients with severe burns, resuscitation with large volumes of fluid is needed, partly because of an increase in capillary leakage. Corticosteroids might be beneficial by diminishing capillary leakage. This study aimed to assess in severely burned nonseptic patients whether hydrocortisone (HC) improved outcome and diminished capillary leakage.
Methods: Retrospective analyses of a prospectively collected database were performed, including 39 patients (age 52 [35-62] years, 72% male). Patients were divided based on HC therapy. First, in patients in whom HC was started late, that is when deteriorating (late; 5-12 days postburn) data before and after start of HC were compared. Second, patients in whom HC was started day 0 or 1 postburn (upfront; within 48 hours) were compared with patients who did not receive HC (control). Outcome was assessed as organ dysfunction by Denver Multiple Organ Failure (MOF) score and Sequential Organ Failure Assessment (SOFA) score. As markers for capillary leakage and hydration state, proteinuria, B-type natriuretic peptide (BNP), and fluid administration were assessed. Follow-up was 20 days postburn. Possible adverse effects including mortality were recorded. Repeated measurement regression analyses were performed using MLwiN.
Results: In the late group, Denver MOF and SOFA scores significantly decreased after HC ($P < .001$). Proteinuria tended to decrease ($P = .13$), BNP increased on the days HC was used ($P < .001$), and amounts of fluids diminished ($P < .001$). In the upfront vs control group, Denver MOF and SOFA scores ($P < .001$) decreased more quickly. Proteinuria ($P = .006$) and administered fluids decreased more rapidly ($P < .001$).
Mortality rate, numbers of positive blood cultures, incidence of pneumonia, and graft loss were similar in all groups.
Conclusions: Hydrocortisone treatment in severe burned patients without sepsis might improve organ dysfunction possibly because of a reduction in capillary leakage, as reflected by a decrease of proteinuria, an increase of BNP, and diminished fluid resuscitation volumes.

1. Introduction

In clinical practice, resuscitation of patients with severe burns remains difficult because of an increased capillary leakage on the one hand, and the drawbacks of fluid overload on the other hand. An important feature of burn trauma is massive loss of plasma from the intravascular to the extravascular space because of systemic microvascular leakage, triggered by inflammatory mediators [1]. Because of this capillary leakage in combination with vasodilatation and alterations in cardiac function, resuscitation with large volumes is necessary, but too large volumes of fluid may have negative consequences, including compartment syndromes, conversion of superficial into deep burns, and worsening of burn edema [1,2]. Therefore, an intervention that can reduce capillary leakage is of great importance in burn care. Although controversial, in septic nonburn intensive care patients, treatment with corticosteroids reduces vasopressor dependency and may improve morbidity and mortality [3]. Two studies assessed corticosteroid treatment in septic burn patients [4,5]. Their results suggested that corticosteroids may improve hemodynamics in septic burn patients who were catecholamine-dependent. However, only 1 study was available describing the results of treatment with corticosteroids in nonseptic burn patients [6], until very recently, another randomized controlled trial (RCT) was published evaluating the use of glucocorticoid treatment in patients with burns more than 70% of their total body surface area [7]. This last study demonstrated a decrease of levels of proinflammatory cytokines and a decrease in the incidence of pulmonary infection and stress ulcer, resulting in a shorter length of hospital stay.

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Unfortunately, no further data are available on outcome measures or on possible mechanisms of this potentially beneficial effect of corticosteroids in burn patients. One of the proposed mechanisms is decrease of capillary leakage [8]. Proteinuria and especially microalbuminuria have been described as markers of endothelial dysfunction c.q. systemic capillary leakage [9,10]. B-type natriuretic peptide (BNP) is emerging as a potential marker of hydration state and has been suggested to increase if capillary leakage diminishes [11-14]. Furthermore, we and others showed that BNP levels increase with fluid resuscitation [11,13,15]. In several studies, high levels of BNP predict poor prognosis and this thus may be related to excessive resuscitation. In contrast, we found that patients with burns high levels of BNP were associated with better outcome if combined with low proteinuria and lower volumes of fluid resuscitation [11]. These data together thus suggest that lowering capillary leakage can be a favorable mechanism to be used to optimize fluid resuscitation: increasing volume when necessary, but preventing excessive volume administration.

Based on these data, we hypothesized that in severely burned nonseptic patients treatment with hydrocortisone (HC) improves outcome (ie, organ failure) as a result of less capillary leakage, as reflected by a decrease in proteinuria and an increase in BNP, and thereby diminished amounts of administered fluids.

2. Patients and methods

This study involved patients admitted to the burn center of the Martini Hospital between January 2002 and October 2009. Eligible were patients with severe burns, that is with a total body surface area (TBSA) burned of more than 20% or a TBSA of more than 15% and inhalation injury. Excluded were patients younger than 18 years of age, with a life expectancy of less than 24 hours or a history of renal disease (to exclude proteinuria from other causes).

We distinguished 3 groups of patients based on the HC treatment they had received. The first group consisted of patients with severe burns who started with HC when deteriorating, that is *late*, defined as day 3 postburn or later (late group, n = 7). In this group, data were compared before and after the start of HC. Based on positive clinical observations from these patients, in more recent years, patients started receiving hydrocortisone almost immediately (within 48 hours after admission). These patients formed the upfront group (n = 15). To study the effects of HC in this group, a *control group* was defined (n = 17) with patients conform the in- and exclusion criteria specified, but in whom HC was not administered. In total, 39 patients were included. Baseline characteristics for the 3 groups are shown in Table 1. This retrospective study was approved by the Medical Ethics Committee of the Martini Hospital (No. 2009-39). Patients were coded and data analyzed anonymously. The Medical Ethics Committee waived the need for informed consent.

2.1. Treatment

Resuscitation during the first 48 hours consisted of hyperosmotic fluid (60 mL saline bicarbonate 8.4% in 1 L NaCl 0.9%). For the first 8 hours, the amount of fluid was 1.5 mL × body weight × %TBSA; the next 16 hours, 1.5 mL × body weight × %TBSA; the following 24 hours, 1.5 mL × body weight × %TBSA. In addition, patients received 2500 mL oral fluids or intravenously (0.45% glucose and 0.45% NaCl). After 48 hours, the fluid requirement was calculated by 1.25 mL × %TBSA × body weight plus standard fluids, but adjusted according to urine production and clinical signs.

The HC stress protocol treatment started with 300 mg per 24 hours based on previous studies [16,17]. Dosage was tapered after 2 to 3 days to 150 mg per 24 hours for 5 days, and when the patient was clinically stable as judged from hemodynamics and diuresis, the dose was reduced further by 25 mg per 24 hours each day.

Apart from HC treatment, the same standard protocols for operative and supportive therapy were followed in all patients. Deep partial thickness burns, showing no reepithelialization after 12 to 14 days, were debrided 14 to 21 days after injury and grafted with split skin grafts. In extensive full thickness wounds, excision would be performed weekly, beginning 6 to 10 days after injury. During each surgery, approximately 10% to 15% TBSA would be excised and covered with split skin grafts or Meek-Wall grafts. All patients were treated with cerium-silver-sulfadiazine and selective decontamination of the digestive tract. Furthermore, strict infection control measures were in place, including cohort nursing, strict aseptic techniques for changing dressings, timely closure of the burn wounds, and laminar airflow techniques.

2.2. Methods

Retrospective analyses of a prospectively collected database for research purposes were performed. Data were collected from the day of admission until day 20 postburn. The following demographic and burn injury characteristics were recorded: sex, age, weight, percentage TBSA burned, percentage body surface area of full thickness burns, presence of inhalation injury (as confirmed by bronchoscopy), and comorbidity.

Outcome was assessed first of all as organ dysfunction, by calculating the Denver Multiple Organ Failure (Denver Multiple Organ Failure [MOF]) scores [18], as this score has very recently been used as benchmark outcome in patients with severe burns [19]. Variables used to calculate the Denver MOF scores included use and dosage of catecholamines, heart rate, fraction of expired oxygen, renal creatinine, and hepatic total bilirubin and were extracted on admission and everyday at 6 AM. These variables were also used to calculate Sequential Organ Failure Assessment (SOFA) score [20].

As marker for capillary leakage and hydration state, proteinuria and BNP were assessed, respectively. Proteinuria and BNP levels were taken from laboratory databases. Proteinuria was assessed in urine, with a

Table 1
Characteristics of patients included in 3 groups.

	Late HC[a] (n = 7)	Upfront HC[a] (n = 15)	Controls (n = 17)
Age, y	57 (52-64)	43 (33-58)	43 (33-58)
Male, n (%)	5 (71%)	13 (87%)	10 (59%)
Weight, kg	112 (75-125)	88 (74-100)	75 (66-86)*
TBSA, %	35 (29-53)	37 (30-47)	37 (25-45)
TBSA >20%, n (%)	7 (100%)	14 (93%)	17 (100%)
	3 with inhalation	10 with inhalation	4 with inhalation**
TBSA 15%-20% + inhalation, n (%)	0	1 (7%)	0
Intubation, n (%)	6 (86%)	14 (93%)	6 (35%)**
Abbreviated Burn Severity Index	9 (8-11)	9 (7-10)	8 (8, 9)
Creatinine clearance, mL/min	150 (76-250)	150 (113-200)	176 (102-200)

Data are presented as median (interquartile range).
[a] Late hydrocortisone group: hydrocortisone started 5 to 12 days postburn. Upfront is hydrocortisone started within 48 hours postburn.
* $P < .05$ controls vs upfront.
** $P < .01$ controls vs upfront.