

Indications and practical use of replacement dose of corticosteroids in critical illness

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Purpose of review

Ongoing and severe systemic inflammation affecting critically ill patients may cause adrenal insufficiency and steroid resistance in target cells. As the appropriate diagnosis of this clinical entity remains a challenge, indication and practical use of corticosteroid replacement therapy in the critically ill is generally directed by clinical symptoms and features.

Recent findings

In the last 2 years, a series of clinical trials have been undertaken to investigate corticosteroid replacement therapy in critically ill patients with severe systemic inflammation of various origin. Improvements of morbidity have been demonstrated in some studies. The data of recent studies should lead to a restriction of corticosteroid replacement therapy in critically ill patients. The purpose of this review is to investigate indications and the best current practical use of corticosteroid replacement therapy in critically ill patients in the absence of accurate laboratory assessment of adrenal insufficiency.

Summary

Corticosteroid replacement therapy may improve morbidity and mortality in specific target groups of critically ill patients. The appropriate target groups remain to be refined. To demonstrate this, additional studies are required on endocrine disorder in critical illness and corticosteroid replacement therapy.

Keywords

adrenal insufficiency, corticosteroid replacement, critical illness, sepsis, shock

Introduction

In patients with septic shock, the Surviving Sepsis Campaign recommends the use of hydrocortisone at doses of 200–300 mg per day, for 7 days in three or four divided doses or by continuous infusion [1]. This recommendation is mainly based on one multiple-centre, randomized, controlled trial in patients with severe septic shock and relative adrenal insufficiency as defined by post-adrenocorticotrophic hormone (ACTH) cortisol increase of less than 9 µg/dl [2]. Two meta-analyses published 3 years ago concluded that corticosteroid replacement therapy in patients with septic shock reduces the duration of vasopressor therapy and improves 28-day survival [3,4]. This encouraged investigators to use corticosteroid replacement therapy in other diseases characterized by severe systemic inflammation such as acute respiratory distress syndrome (ARDS), pneumonia, cardiac surgery, acute pancreatitis, burns, or trauma [5^{••}–7^{••},8–12]. As laboratory assessment and accurate diagnosis of adrenal insufficiency in critically ill patients is still uncertain [13^{••}], the majority of investigators used clinical criteria to identify target groups at risk for cortisol deficiency.

Target groups in clinical trials

Critical illness is the result of stressful events such as tissue damage or infection inducing a systemic inflammatory syndrome. Severity and duration of systemic inflammation increases the risk of adrenal insufficiency or corticosteroid tissue resistance, respectively. Patients with overwhelming systemic inflammation unresponsive to volume and vasopressor therapy appear to be a target group that may have adrenal insufficiency and may respond to corticosteroid replacement therapy. The Annane *et al.* study [2] included a large number of such patients. Septic shock is without doubt the best known diagnosis for severe systemic inflammation with related distributive shock. Therefore, systemic inflammation and vasopressor dependency became the central inclusion criteria in many studies investigating corticosteroid replacement therapy.

Septic shock

Septic shock and corticosteroid replacement therapy has been extensively investigated during the last decade [2,14–19]. The main finding supported by all studies is that corticosteroid replacement therapy accelerates shock reversal. This is also supported by two recent trials: a single-centre study and the large European CORTICUS trial [18,19]. Improvement in physiology, however, did not result in improved survival in the latter trial.

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Abbreviations

ACTH adrenocorticotrophic hormone
ARDS acute respiratory distress syndrome
CPB cardiopulmonary bypass
IL interleukin

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Adjustment of the appropriate target group by means of ACTH testing did not make a difference as this has been found in the Annane *et al.* study [2,19]. The reasons for the differences found in the Annane *et al.* study and CORTICUS remain to be discussed. First analyses revealed that patients in the Annane *et al.* study were more severely ill, had higher vasopressor doses at inclusion, did not respond to volume therapy for at least 1 h, had more pneumonia as underlying infection and had a higher incidence of relative adrenal insufficiency. This suggests that only patients with septic shock unresponsive to fluid resuscitation and high-dose vasopressor therapy may benefit from hydrocortisone therapy. In addition it is noteworthy that patients in the Annane *et al.* study were treated with fludrocortisone in addition to hydrocortisone replacement therapy. Whether this makes a difference is the objective of an ongoing trial.

Acute respiratory distress syndrome

In the last decade, ongoing systemic inflammation induced by excessive fibroproliferation in persistent ARDS has been proposed as another indication for corticosteroid therapy. Methylprednisolone treatment exceeding the dose of corticosteroid replacement therapy by a factor of two improved pulmonary function and reduced multiple organ dysfunctions by profound immunomodulation of the persistent inflammatory process [20,21]. A recently published, large-scale trial of the ARDS network does not support this intervention [5^{••}]. Despite significant improvements in cardiopulmonary physiology associated with a higher number of ventilator-free days and ICU-free days at day 28, the use of corticosteroids did not result in a lower mortality at day 60 after randomization. An increased rate of return to assistant breathing associated with muscle weakness has been discussed as the main reason why improved physiology did not translate into improved outcome. A post-hoc analysis revealed that patients with ARDS of over 14 days duration had even increased 60-day mortality when they were assigned to the corticosteroid group whereas a trend to improved survival was seen in the group recruited between day 7 and 13 after onset of ARDS [5^{••}]. This raises the question of whether there is an optimal time window for corticosteroid therapy in late ARDS.

Two recent publications investigated the effect of corticosteroid replacement therapy in early ARDS [6^{••},7^{••}]. The first paper is a post-hoc analysis of a multicentre randomized double-blind study on patients with severe septic shock [6^{••}]. Treatment with hydrocortisone and fludrocortisone was associated with a significant decrease in 28-day mortality, ICU mortality and hospital mortality in patients with early ARDS and relative adrenal insufficiency (as defined by post-ACTH cortisol increase of less than 9 µg/dl) but not in patients without relative adrenal insufficiency or without early ARDS. In contrast to the

ARDS network study in late ARDS, improvements in physiology were translated in decreased mortality, but only in patients with relative adrenal insufficiency. The second paper was published by Meduri and coworkers [7^{••}]. It is the first prospective randomized controlled trial investigating low-dose methylprednisolone (1 mg/kg/day) in early ARDS. Patients were treated for 28 days with decreasing doses of methylprednisolone starting 15 days after enrolment. Significant improvements in pulmonary and extrapulmonary organ dysfunctions were found with reduction of duration of mechanical ventilation and length of stay in the ICU. Unfortunately, the study was not powered to demonstrate a survival benefit (63 treated and 28 control patients). It is noteworthy that investigators used a lower dose of methylprednisolone for a long period of time (4 weeks) irrespective of early resolution of organ dysfunction. In the ARDS network study of late ARDS, investigators tapered down study drug within 2 days, if patients were able to breath without assistance for a period of 48 h, which may account for the high number of reintubations (9% versus 28%) in this study [5^{••},7^{••}].

Community-acquired pneumonia

Recently, corticosteroid replacement therapy in pneumonia has been investigated. In a multicentre trial conducted from 2000 to 2003 46 patients with community-acquired pneumonia were randomized to receive either a continuous infusion of hydrocortisone at a dose of 10 mg/h for 7 days or placebo [8]. Primary endpoints were the evolution of organ dysfunctions by day 8. In this study of corticosteroid replacement early in the course of community-acquired pneumonia, patients in the hydrocortisone group showed favourable improvements in lung physiology and inflammatory markers such as C-reactive protein. Most important, no patient in the hydrocortisone group developed septic shock or other adverse effects in the course of the study. As no patient in the hydrocortisone group died but two patients in the placebo group, a significant difference in mortality could be observed. The authors discuss that this study was not powered to demonstrate treatment effects on mortality and outline other imbalances at inclusion. In conclusion, they recommend a confirmative large-scale trial.

Cardiac surgery

Cardiac surgery with cardiopulmonary bypass (CPB) is characterized by a postoperative systemic inflammatory response, which is well reproducible in the course of events. A recent study investigated different doses of corticosteroid replacement therapy while inhibiting endogenous steroidogenesis with etomidate. In the control group, the authors found that total cortisol peaks at 4 h after termination of the surgical procedure with a mean peak cortisol level of 43.8 µg/dl. In the groups of patients receiving etomidate and corticosteroid replacement

therapy, similar plasma concentrations have been reached by replacement of hydrocortisone at a dose of 4 µg/kg/min. Compared with control this dose was sufficient to suppress interleukin (IL)-6. Increasing the dose of hydrocortisone did not change the response of IL-6 [22].

Some patients undergoing cardiac surgery with CPB develop severe systemic inflammation, associated with significant hypotension due to vasodilation, which requires high-dose vasopressor treatment. A recent study revealed that vasodilatory syndrome (VDS) after cardiac surgery was associated with a higher incidence of postoperative renal failure, a longer duration of ventilation, a greater need for red cell transfusion and a longer length of stay in the ICU. Vasopressor dependence could be predicted from a combination of factors, including preoperative ejection fraction under 40%, CPB lasting over 97 min, and postoperative IL-6 over 837 pg/ml [23[•]]. As VDS after cardiac surgery shares many features with vasopressor-dependent septic shock or the hemodynamics in Addisonian crisis, we have investigated corticosteroid replacement therapy in this specific target group. Treatment with hydrocortisone by continuous infusion of 10 mg/h on the day of surgery resulted in lower concentrations of IL-6, lower need for vasopressors and assisted mechanical ventilation and a shorter length of stay in the ICU and in the hospital [9] and was also associated with improved health-related quality of life outcomes in one small study [24[•]]. It is important to emphasize that corticosteroid replacement therapy was allocated to patients with compromised cardiac performance undergoing long CPB which represented 27% of patients undergoing cardiac surgery in our institution.

Replacement of hydrocortisone after cardiac surgery may also reduce the incidence of atrial fibrillation. A double-blind, randomized multicentre trial of 241 consecutive patients without prior atrial fibrillation or flutter and scheduled to undergo coronary artery bypass graft surgery demonstrated that a 3-day course of 300 mg hydrocortisone per day divided in three doses significantly reduced the incidence of postoperative atrial fibrillation (30% versus 48%, number needed to treat, 5.6).

Hydrocortisone treatment was not associated with higher rates of superficial or deep wound infections, or other major complications [25^{••}].

Other indications

Vasopressor-dependent shock associated with severe systemic inflammation of various origin such as trauma, acute pancreatitis and burns inspired investigators to use corticosteroid replacement therapy. Severe trauma with hemorrhagic shock may induce abnormal vascular reactivity leading to sustained hypotension despite fluid resuscitation. Hoen *et al.* [10] could demonstrate that

hydrocortisone increased the vascular sensitivity to α_1 -adrenoreceptor stimulation in fully resuscitated trauma patients requiring vasopressor infusion. In severe acute pancreatitis and shock hydrocortisone reduced time and amount of norepinephrine therapy in the first 48 h of treatment. In addition, significant differences in fluid balances with less need of fluids in the hydrocortisone group were observed [11]. A recent study [26] on endogenous cortisol metabolism in patients with acute pancreatitis showed that patients with the more severe form of necrotizing pancreatitis are at risk to develop adrenal insufficiency in the course of the disease. Whether this subgroup of patients represents a target group for corticosteroid replacement therapy in the early vulnerable phase of acute pancreatitis remains to be elucidated.

Burns associated with vasopressor-dependant shock do not appear to benefit from corticosteroid replacement therapy. Interesting data on this topic date back to the 1950s when an explosion and fire on the aircraft carrier Bennington severely injured 26 naval soldiers. The burns were largely second degree and half of the patients were assigned to the corticosteroid replacement group. No relevant differences could be observed between the groups either in endogenous cortisol metabolism or outcome between the groups [27]. A recent uncontrolled study on burned patients showed that hydrocortisone infusion does not reduce either vasopressor or fluid requirements in the patients under study. Survivors, however, responded well in contrast to nonsurvivors [12]. The sparse data on corticosteroid replacement therapy in patients with burns do not agree with other studies in critically ill patients with overwhelming systemic inflammation and vasopressor dependency.

Long-term corticosteroid therapy and surgical stress

For more than 50 years, it has been known that long-term corticosteroid therapy may cause adrenal insufficiency. The degree of adrenal insufficiency is difficult to diagnose and does not correlate with the dosage or the duration of corticosteroid therapy [28]. Therefore, corticosteroid replacement is recommended during every surgical procedure to prevent hemodynamic instability and refractory shock, respectively. It is recommended that dose and duration of corticosteroid replacement should be adjusted to degree and duration of surgical stress [29,30].

Appropriate replacement doses and duration of treatment

As depicted in Table 1 various doses and different time periods are used for corticosteroid replacement therapy during stressful events. The dose for corticosteroid replacement therapy is mainly directed by endogenous cortisol production rates, which have been measured in specific

Table 1 Clinical trials on low-dose corticosteroids in the treatment of diseases associated with overwhelming systemic inflammation

Indication	Year	Type of study	Patient number	Endpoints	Duration of treatment	Corticosteroid taper	Total dose (mg) (HC or equivalents)
Septic shock	2005	RCT, double-blind	42	Shock reversal, LOV, cytokine response	6 days	Yes	Approximately 900
Septic shock	2007	RCT, double-blind	499	28-day mortality	11 days	Yes	1450
Early ARDS and septic shock	2006	RCT, double-blind	177	28-day mortality	7 days	No	1400
Early ARDS	2007	RCT, double-blind	91	1-point reduction in LIS or extubation by day 7	28 days	Yes	Approximately 6600
Late ARDS	2006	RCT, double-blind	180	60-day mortality	25 days	Yes	Approximately 13 000
Pneumonia	2005	RCT, double-blind	46	LOS: hospital	7 days	No	1880
Cardiac surgery	2006	RCT, double-blind	60	Cytokine response	6 h	No	10–200
Cardiac surgery	2003	RCT, nonblinded	91	Shock reversal, LOV, LOS: ICU, hospital	4 days	Yes	550

ARDS, acute respiratory distress syndrome; HC, hydrocortisone; LIS, lung injury score; LOS, length of stay; LOV, length of mechanical ventilation; RCT, randomized controlled trial.

stressful conditions. Healthy patients undergoing major surgical procedures show production rates of 50–150 mg/day with peak cortisol secretion of 10 mg/h shortly after extubation [29,30]. Patients suffering from infections increase cortisol secretion up to 90 mg per day [31]. After administration of 40 Units ACTH healthy persons or patients with pulmonary asthma achieve cortisol secretion rates between 135 and 310 mg per day [32]. In many studies, the maximum secretion rate in healthy persons results in plasma cortisol concentrations between 40 and 50 µg/dl [13,22]. It is interesting to note that cortisol secretion during surgical procedures is maintained by continuous rather than pulsatile ACTH secretion [33].

A study by Udelsman *et al.* [34] investigated different replacement doses in adrenalectomized monkeys undergoing cholecystectomy (a moderate surgical stress). Replacement doses equivalent to the daily unstressed cortisol production rate were sufficient to allow homeostatic mechanisms to function during surgery, whereas subphysiological doses led to marked cardiovascular compromise. The conclusions of this review prompted the recommendation to adapt replacement dose to the degree of surgical stress with 25 mg hydrocortisone equivalent for minor surgery, 50–75 hydrocortisone equivalents for moderate surgical stress and 100–150 mg of hydrocortisone equivalents for major surgical stress such as major thoracic or abdominal surgery, or cardiac surgery involving CPB [29]. A recent study by Yeager *et al.* [22] used IL-6 response as a criterion to investigate appropriate corticosteroid replacement doses. The authors suppressed endogenous steroidogenesis by two etomidate boluses (0.3 and 0.15 mg/kg body weight) at induction of anesthesia and prior to the start of CPB. They found that hydrocortisone at infusion rate of 4 µg/kg/min (but not 0.4 µg/kg/min) is sufficient to control IL-6 response and to achieve similar physiologic cortisol concentrations as measured in a control group [22]. These concentrations are considered to be sufficient for control of surgical stress [34]. It is noteworthy that the dose of hydrocortisone used by Yeager *et al.* corresponds to approximately 400 mg/day in a person of 70 kg body weight, which exceeds the current recommendation for corticosteroid replacement therapy in patients undergoing cardiac surgery [22,29].

The data on cortisol concentrations during corticosteroid replacement therapy are sparse. In septic shock, a continuous infusion of 10 mg/h resulted in plasma cortisol levels of 85 or 125 µg/dl, respectively [35,36]. Interestingly, despite continuous infusion, cortisol concentrations decreased over time indicating an accelerated clearance of cortisol in the course of treatment [35]. In patients undergoing cardiac surgery, the infusion rate of hydrocortisone generates cortisol concentrations of approximately

50 µg/dl (own data). This indicates that cortisol concentration during corticosteroid replacement therapy depends on both the administered dosage of hydrocortisone and the actual clearance of cortisol. As depicted in Table 1, different durations for corticosteroid replacement therapy have been proposed. Today, the duration is mainly determined by the clinical dynamics of the underlying disease with the shortest duration for cardiac patients and longest for patients with late ARDS.

New approaches for corticosteroid replacement therapy

A recent study by Vanhorebeek *et al.* [37] reported five-fold higher total cortisol levels and nine-fold higher levels of calculated free cortisol in patients with relative adrenal insufficiency and corticosteroid replacement therapy. Extremely high concentrations of free serum cortisol are typically found in the postoperative period of cardiac surgery also in patients without corticosteroid replacement therapy [38]. Looking at free cortisol, it appears, however, that the current doses recommended for corticosteroid replacement therapy in relative adrenal insufficiency results in free cortisol fractions up to 30% thereby exceeding the needs of target tissues. Therefore, a reevaluation of doses used for corticosteroid replacement therapy is warranted [38–40]. Immunological data suggest that a target-controlled infusion of hydrocortisone to reach total cortisol concentration between 35 and 40 µg/dl would be sufficient to attenuate systemic inflammation and could help to adapt dose to the actual requirements of the effector cells [22,35]. A recent study by Ho *et al.* [41*] suggested that free cortisol is likely to reflect more accurately corticosteroid replacement therapy when compared with total cortisol because it corresponds more closely and rapidly to the severity of illness. Free cortisol levels decrease promptly with resolution of septic shock whereas total cortisol remains elevated. In addition, the authors could show that calculation of free cortisol by Coolens' method is accurate by adjustment of Coolens' equation constant *N* on varying albumin concentrations [41*]. New data suggest that free cortisol determination may also be superior to pharmacological tests of the adrenal reserve as proposed in recent papers [42–44].

Conclusion

In critically ill patients, various disease processes induce an overwhelming systemic inflammatory response, which may cause adrenal insufficiency and corticosteroid resistance in effector cells. As the exact diagnosis of adrenal insufficiency in these patients is affected by methodological problems and the lack of definitions, many authors investigated corticosteroid replacement therapy in critically ill patients with suspected or drug-induced cortisol deficiency. Dose and duration of the appropriate corticosteroid replacement therapy were adapted to the dynamics of the underlying condition. With respect to the current

data, corticosteroid replacement therapy should be restricted to specific target groups such as patients with septic shock requiring high-dose vasopressor therapy for more than 1 h despite adequate fluid resuscitation. In addition, it appears that the dose of corticosteroid replacement therapy could be reduced.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 457).

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