

Glucocorticoids in the treatment of acute respiratory distress syndrome*

Les glucocorticoïdes dans le traitement du syndrome de détresse respiratoire aiguë

F. Roche-Campo · H. Aguirre-Bermeo · J. Mancebo

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Abstract Acute respiratory distress syndrome (ARDS) is characterized by local inflammation and an intense systemic inflammatory reaction. Glucocorticoid administration has been suggested due to their anti-inflammatory properties. However, results from the initial studies of glucocorticoids in ARDS, which evaluated high-dose and short-term treatments, were negative. More recent studies have evaluated the effect of lower doses of glucocorticoids administered over longer periods, but the results thus far have been inconclusive. **To cite this journal: *Réanimation* 21 (2012).**

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Résumé Le syndrome de détresse respiratoire aiguë (SDRA) est caractérisé par une inflammation locale et une réaction inflammatoire systémique intense. L'administration de glucocorticoïdes a été proposée en raison de leurs propriétés anti-inflammatoires. Cependant, les résultats des premières études concernant la prescription des glucocorticoïdes dans le SDRA, qui ont évalué de hautes doses avec des traitements de court terme, ont été négatifs. Des études plus récentes ont évalué des doses plus basses administrées sur des périodes plus longues, mais les résultats ont aussi été peu concluants. **Pour citer cette revue : *Réanimation* 21 (2012).**

Mots clés Glucocorticoïdes · Traitement · Syndrome de détresse respiratoire aiguë

Introduction

Acute respiratory distress syndrome (ARDS) has been one of the greatest challenges faced by intensive care physicians since it was first described in 1967 [1]. Mortality rates remain high (approximately 50%) [2], and sequelae in survivors can be severe and long-lasting [3]. ARDS is characterized by the sudden appearance of hypoxemia with radiographic evidence of bilateral lung infiltrates. ARDS is the physiological response of the lungs to numerous aggressions, both direct and indirect, which can lead to an increase in the permeability of the alveolocapillary membrane, secondary lung edema, and persistent inflammation [4]. This increased alveolocapillary permeability is central to the pathophysiology of the syndrome and distinguishes ARDS from cardiogenic pulmonary edema that occurs due to an increase in the pulmonary capillary vascular pressure [5].

Various pharmacological and nonpharmacological strategies have been tried in an attempt to prevent or attenuate this inflammatory process [6]. Protective ventilation with low tidal volume has been shown to reduce the inflammatory response [7] and improve survival [8]. Encouraging results have also been obtained with prone position ventilation [9] and ventilating with a positive end-expiratory pressure to a maximum plateau pressure of 30 cmH₂O [10,11]. Results from pharmacological interventions—including a variety of anti-inflammatory and immunomodulating drugs—have been disappointing [12]. Glucocorticoids (GCs) have shown some promising results in the past, so researchers have taken a renewed interest in this medication in recent years.

The use of GCs in intensive care dates back to the decade of the 1980s, when critical care clinicians began to better understand the role of inflammation in the pathogenesis of many diseases affecting critically ill patients. GCs were used to control or prevent inflammation in patients with ARDS or septic shock [13]. However, the high doses used proved to be more harmful than beneficial, and interest in these drugs waned over time [14–17]. Now that we better understand

F. Roche-Campo (✉) · H. Aguirre-Bermeo · J. Mancebo
Servei de Medicina Intensiva, Hospital de Sant Pau,
Barcelona, Espagne
e-mail : ferranroche@yahoo.es

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why these mega doses failed, and as more recent studies have shown that the use of more appropriate physiological doses yields improved results, interest in the use of these drugs has increased.

The aim of this review is to evaluate the biological effects of GCs and to discuss the most relevant published studies of GCs in the treatment of ARDS. Although GCs are also used to treat septic shock and community-acquired pneumonia, both of which are known causes of ARDS [18], these specific areas are not addressed directly in the present review.

Biological effects of glucocorticoids and basis for its use in ARDS

Inflammation is the body's reflex response to any type of aggression [19]. The inflammatory response consists of a series of integrated reactions, whose objective is to destroy the harmful agent and repair damaged tissues. As long as the inflammatory process remains circumscribed and controlled, it is beneficial. However, uncontrolled inflammation is harmful. In ARDS, the intense inflammatory reaction is both local (the lungs) and systemic [20]. The evolutionary onset of the syndrome depends on the level and duration of this inflammatory process [21]. Persistently elevated levels of proinflammatory cytokines are associated with unresolving ARDS and a sign of worse prognosis [22].

The hypothalamic-pituitary-adrenal axis regulates the production of endogenous GCs, which, in addition to their metabolic and cardiovascular effects, play an essential role in modulating and limiting the inflammatory response [23]. Endogenous GCs are the natural drugs that protect us from stress and enhance survival [19]. Thus, while the adrenal cortex secretes 20 mg/day of cortisol in basal conditions, secretion may increase to between 200 and 400 mg/day in inflammatory processes, and basal levels of plasmatic cortisol can increase by a multiple of 5 [24]. Elevated levels of cortisol are associated with more severe underlying disease and higher mortality [25,26].

More than 90% of circulating cortisol is bound to corticosteroid-binding globulin. The remaining 10%—the biologically active form—circulate freely [27]. During acute illness, the levels of corticosteroid-binding globulin can decrease by up to 50%, leading to a corresponding large increase in free cortisol [28]. The free cortisol has a high affinity for a specific cell receptor called receptor alpha (GR-alpha), which is expressed in virtually all cells. The cortisol-GR-alpha complex acts at the intracellular level through genomic and nongenomic mechanisms, thereby inducing the production of anti-inflammatory proteins while inhibiting the production of proinflammatory proteins. This complex also inhibits fibroblast proliferation and collagen deposits [20]. However, endogenous GCs are not always

able to modulate the inflammatory response, either because endogenous GC secretion is insufficient to overcome the inflammatory response (adrenal insufficiency) or because peripheral tissues become resistant (with or without adrenal insufficiency) [29]. This dynamic situation, defined as critical illness-related corticosteroid insufficiency (CIRCI), may be reversed through the administration of exogenous GCs [30]. Unfortunately, the diagnostic criteria for CIRCI still remain to be well-defined [29].

Experimental and clinical evidence show that administration of exogenous GCs regulates the inflammatory response, reduces markers of inflammation, and improves symptoms [30,31]. For this reason, GC therapy is considered biologically plausible in ARDS.

Comments on the most relevant clinical studies

The first randomized controlled studies (RCTs) of GC administration date back to the 1980s. The hypothesis at that time, based on experimental studies [32–35], was that the use of high-dose, short-term GC treatment (e.g., 120 mg/kg per day of methylprednisolone for 48 hours) could prevent the emergence of ARDS in at-risk septic patients and could also be used to treat early-stage ARDS [14–17]. However, studies that evaluated this hypothesis in ARDS or in septic shock patients found no benefits [36–38]. As we discuss in more detail below, it seems that harmful side effects caused by these high doses outweigh any beneficial effects of this therapy. In fact, recently published meta-analyses conclude that high doses of GCs not only fail to prevent ARDS in at-risk patients but may even hasten its onset [39].

Given the failure of this high-dose, short-term GC therapy, these drugs largely disappeared from the medical literature until they regained popularity nearly a decade later, when promising results were reported for GC therapy in meningitis [40] and *Pneumocystis carinii* pneumonia [41]. An important conceptual change, which transformed our understanding of appropriate dosing levels, had taken place. In 1991, Schneider and Voerman [42] described for the first time how septic shock could be reversed using “only” physiological doses of GCs. These results established the basis for new dosing strategies in ARDS, which Meduri et al. adopted in their seminal study published just a few years afterwards [43]. As a result, researchers have carried out new studies that abandoned the original high-dose, short-term approach in favor of low to moderate doses delivered over prolonged periods (Table 1).

In 1998, Meduri et al. reported the results of a small randomized multicenter study that included 26 patients with ARDS of 7 days duration or more [44]. This study could be considered the first study of GCs in ARDS of the “modern era”. Patients were randomized to receive either 2 mg/kg

Table 1 Randomized studies focused on the prolonged use of low–moderate doses of glucocorticoids (GCs) in acute lung lesions and ARDS

Study	Methodology	Patient population	Number of patients	Timing of inclusion	Treatment	Duration of treatment, days
Meduri et al. (1998)	Prospective	ARDS	24	Late	Methylprednisolone 2 mg/kg	Up to 32
Confalonieri et al. (2005)	Prospective	Severe pneumonia	46	Early	Hydrocortisone 240 mg/d	7
Steinberg et al. (2006)	Prospective	ARDS	180	Late	Methylprednisolone 2 mg/kg	Up to 25
Annane et al. (2006)	Retrospective	Sepsis and ARDS	177	Early	Hydrocortisone 200 mg/d	7
Meduri et al. (2007)	Prospective	ARDS	91	Early	Methylprednisolone 1 mg/kg	Up to 28

ARDS: acute respiratory distress syndrome; ICU: intensive care unit; LIS: lung injury score; Early (<6 days) versus late (>7 days).

per day of methylprednisolone (16 patients) or placebo (8 patients) for 32 days. The main outcome measures were lung function and mortality, with patients in the treatment group showing significant improvement in both measures. Consequently, the authors concluded that prolonged administration of methylprednisolone in patients with unresolving ARDS is associated with improved lung function and reduced mortality. The main limitations of that study were its small sample size and crossover design, which permitted patients in the placebo group who showed no improvement after 10 days of GC treatment (4 patients). Moreover, the study was stopped early after an intermediate analysis of efficacy; as a result, it is possible that the treatment effect was overestimated.

Nevertheless, these encouraging results prompted other investigators to undertake additional studies in the early 2000s, although no results were published until several years later.

The multicentric RCT published by Confalonieri et al. in 2005 [45] has been included in some meta-analyses, even though the primary focus was on patients with severe pneumonia rather than ARDS. These authors evaluated 46 patients who had been admitted to the Intensive Care Unit (ICU) for severe community-acquired pneumonia. Patients were randomized to receive 240 mg/day of continuous hydrocortisone infusion or placebo for 7 days. The main objectives were to improve oxygenation, reduce the number of organ failures at day 8, and decrease the number of days in shock. Patients in the treatment group showed significant improvement in oxygenation, lung mechanics, and shock-free days; and they also showed a decrease in hospital mortality. The main limitation of the study (from the perspective of the present review) was the inclusion criteria: severe pneumonia rather than ARDS.

In 2006, the ARDS Network [46] published the largest study to date of GC therapy for ARDS. A total of 180 patients with a recent ARDS diagnosis (from 7 to 28 days following onset) were randomized to receive either 2 mg/kg per day of methylprednisolone or placebo for 25 days. The GCs were withdrawn after 2–4 days. The primary endpoint was mortality at day 60. Secondary endpoint included days free from mechanical ventilation, changes in biochemical markers, and the number of infectious complications. No differences in death rates at day 60 (29% in both groups) or day 180 (32% in both) were observed. However, the treatment group required fewer days of mechanical ventilation (7 vs. 11 days, $p < 0.001$) and fewer days in the ICU (6 vs. 9 days, $p = 0.006$) during the first 28 days, as well as fewer days of shock, better oxygenation, and better lung mechanics. Treatment was also associated with a reduction in nosocomial infections without an increase in muscular weakness. *Post hoc* analysis showed higher death rates at day 60 and 180 for the 48 patients in whom GC treatment was initiated

13 or more days after the onset of ARDS. Another *post hoc* analysis evaluated the levels of type III procollagen peptide in bronchoalveolar lavage fluid taken from 91 patients during their admission. In these patients, the authors found that in the 46 patients with the lowest peptide values (<50th percentile)—a group that included most of the patients treated after day 13—mortality at day 60 was higher for patients in the treatment group (23 cases) compared to the placebo group (35% vs. 8%, $p = 0.03$). Conversely, in the 45 patients with the highest peptide values (>50th percentile), mortality at day 60 was lower in the treatment group (23 cases) than the placebo group (4% vs. 19%, $p = 0.10$). The authors concluded that the evidence did not support the use of methylprednisolone for persistent ARDS, despite the observed improvement in cardiopulmonary physiology. Moreover, they noted that mortality rates may actually increase when GC treatment is initiated more than 13 days after ARDS onset. Among the more notable limitations of the ARDS Network study is the early termination due to low enrollment (only 180 patients from 25 hospitals were included in a 6-year period). Likewise, a high percentage of patients in the treatment group required reintubation (20 vs. 6; $p = 0.008$). It has been hypothesized that this outcome could be explained by the abrupt discontinuation of the GC treatment, which may lead to renewed pulmonary inflammation (the mechanisms by which abrupt discontinuation can be harmful are discussed in more detail below). Finally, there were several nonsignificant differences in the baseline characteristics of the small subgroup of patients who were randomized 13 or more days following onset, thus making comparison between these subgroups difficult.

In the same year (2006) that the ARDS Network study was published, Annane et al. [47] reported a *post hoc* analysis that evaluated a subgroup of patients from a larger clinical trial. The original study assessed low-dose GCs in 300 patients with septic shock. Of these original 300 cases, the authors analyzed the 177 patients who had a diagnosis of ARDS at the time of admission. Of these, 85 patients had received hydrocortisone (200 mg/d) for 7 days, while the remaining cases (92) received placebo. In their analysis, the authors differentiated between responders and non-responders by a rapid corticotrophin stimulation test. These researchers found that treatment with GCs was associated with lower mortality rates in patients with septic shock who did not respond to the corticotrophin test but not in the responder group nor in the group with septic shock without ARDS. Unfortunately, causal relations cannot be established due to the retrospective nature of the analysis.

In 2007, Meduri et al. [48] reported results of their second multicentric randomized study. This is the only RCT to date specifically focused on early ARDS (<7 days). A total of 91 patients were randomized within the first 72 hours of ARDS onset to receive 1 mg/kg per day of methylprednisolone

($n = 63$) or placebo ($n = 28$) for 28 days. The main end points were lung injury scores and successful extubation at day 7. Patients in the treatment group showed a significant improvement in these measures in addition to a lower ICU mortality rate (21% vs. 43%; $p = 0.03$). This study had several limitations, including a low recruitment rate per center (five centers and a 10-year enrollment period) and the use of a crossover design (most patients in the placebo group who still required mechanical ventilation at day 9 were treated with GCs), a strategy that makes interpretation of results difficult. In the placebo group, 45% of the patients required vasopressor support at the time of admission, so they did not receive GC therapy. Thus, this fact could be considered detrimental to the most severely ill patients [49]. In addition, the authors used the same sequential design as in their first study, in which measures of treatment effects influenced the decision to stop the study [50].

Comment on meta-analyses

Five meta-analyses or systematic reviews (but only few original, optimal papers) have been published since 2007. Despite variations among these five reviews in terms of methodology and study selection, the conclusions are generally similar.

- Agarwal et al. [51] evaluated two observational studies and four RCTs and concluded that current evidence does not support the use of GCs in the management of early or late ARDS ;
- Meduri et al. [52] evaluated five RCTs, including the studies by Confalonieri et al. and Annane et al. They concluded that prolonged administration of GCs started before day 14 improved prognosis ;
- Tang et al. [53] assessed five observational studies and four RCTs of ARDS patients treated with low to moderate doses of GCs (including the Confalonieri study). The authors concluded that low doses are associated with less morbidity and mortality without an increase in side effects. They recommended that a new, rigorous trial be performed to confirm these findings in early ARDS ;
- Peter et al. [39] used a rigorous statistical approach to carry out a meta-analysis of a group of highly heterogeneous studies. They evaluated nine RCTs, four of which were studies of ARDS prevention. The other five studies were RCTs for the treatment of persistent ARDS; of these, one evaluated high-dose treatment and another was the aforementioned study by Annane et al. This meta-analysis found that while GC treatment seems to yield positive results, no definitive conclusions can be made at present. The authors did, however, rule out the use of GC for preventive measures ;

- Finally, Lamontagne et al. [54] evaluated 12 RCTs of patients with severe pneumonia, acute lung injury, or ARDS. These authors also found that prolonged GC treatment (at least 7 days) given before day 14 of onset seems to yield positive results. However, they too were unable to reach any firm conclusions.

Factors that affect the response to treatment with glucocorticoids

ARDS criteria and etiology

- Most ARDS studies use diagnostic criteria described in 1994 [55], a definition that, though straightforward, is not perfect: postmortem studies showed that 25% of lungs diagnosed with ARDS failed to meet the pathological criteria [56];
- Many of these ARDS cases are secondary to septic shock and pneumonia [18]. The specific effects of GCs on both pathologies may be a confounding factor in the association between GCs and ARDS. The same can be said for etomidate, a drug which may induce transitory adrenal insufficiency and promote the overexpression of the inflammatory response [57];
- Many of the studies of GCs for ARDS were designed before the clinical benefits of protective ventilation were described in the year 2000 [8]. Protective ventilation using low tidal volumes and limited airway pressures have proven to be less proinflammatory and less damaging than ventilation without volume limits [58]. If the volutrauma is reduced, the beneficial effects of GCs may be less than reported.

The individual variability of each patient

To believe that proinflammatory and anti-inflammatory processes occur at the same time and counterbalance each other in the same way in all patients is illusory. The course of these processes varies between individuals and depends both on the severity of the pathology as well as genetic factors and

individual susceptibility. Biomarkers of lung inflammation may be useful to individualize therapy [59].

Treatment strategies

Administration of low doses of GCs, the usual strategy in septic shock, is quite different from the immunosuppressive doses that were used in the first studies of ARDS or in the more recent CRASH trial of patients with cranial trauma [60]. Much confusion persists in terms of the action of GCs with respect to the type of molecule used (either hydrocortisone or methylprednisolone) and the dose (low or moderate). In septic shock, perhaps it is best to use molecules with a mineralocorticoid and GC effect at doses that replace the adrenal insufficiency, while in ARDS, perhaps it would be better to use molecules whose effect is purely GC at anti-inflammatory doses (Table 2). In addition, we must determine when to initiate GC treatment with respect to ARDS onset (preventative, early, or late), the delivery method (intermittent bolus or continuous perfusion), treatment duration (short or prolonged), and the appropriate discontinuation method (abrupt or progressive).

The future development of new, selective GCs that mimic the beneficial effects of natural GCs without their detrimental side effects seems likely.

Adverse effects

The efficacy of GCs in alleviating inflammatory disorders is due to the different actions of the glucocorticoid receptor on multiple signaling pathways. Because there are multiple pathways involved, there is no selectivity, which in turn implies a high risk of adverse effects. Thus, it is essential that we employ strategies to prevent GC-related complications in order to minimize the adverse effects of treatment while maximizing the beneficial effects. The following measures have been proposed [61]:

- Perform systematic microbiological infection surveillance for early detection of nosocomial infections in patients who may have a blunted febrile response. Recent studies of low to moderate doses of GCs have not found a higher incidence of nosocomial infection [39,53]. At these doses,

Glucocorticoids	Equivalent doses in mg	Mineralocorticoid activity	Biological half life (h)
Hydrocortisone	20	Average	8–12
Prednisone	5	Low	12–36
Methylprednisolone	4	None	12–36
Dexamethasone	0.75	None	36–72

GCs may reduce the incidence of ventilator-associated pneumonia (VAP) in selected populations [62]. However, retrospective studies in patients with ARDS secondary to the A/H1N1 influenza virus show an association between the use of GCs and VAP and an increase in mortality [63,64];

- Avoid the concomitant use of muscle relaxants. When used alone, GCs do not seem to increase muscle weakness [65]. However, combined use of GCs and muscle relaxants in asthmatic patients has been associated with a significant increase in muscle weakness [66]. Recently, the use of muscle relaxants during the first 48 hours after ARDS onset has been shown to reduce mortality without increasing muscle weakness [67]. In that study, 55% of patients received GCs for varying reasons at some time during treatment;
- Avoid premature and abrupt discontinuation. As we have already discussed, this is the main critique of the ARDS Network study. Administration of exogenous GCs may induce adrenal insufficiency through inhibition of cellular receptors and/or negative feedback from the hypothalamic-pituitary-adrenal axis. Once exogenous GCs are stopped, the receptors need time to recover (the precise time in ARDS patients is not well-known, but is estimated to range from 1 to 2 weeks) [68]. In experimental acute lung injury, prolonged GCs administration decreased edema and lung collagen formation, whereas early withdrawal rapidly negated the positive effects of therapy [33–35]. In unresolving ARDS, early discontinuation of GC treatment was associated with physiological deterioration that improved following reinstatement of treatment [59,69]. Untreated adrenal insufficiency is associated with prolonged weaning [70]. In patients with septic shock, premature discontinuation of GCs may be associated with a spike in markers of inflammation and a worsening of hemodynamic parameters [71];
- Continuous perfusion rather than intermittent bolus administration may reduce glycemia variability and improve its control [72]. Marked oscillations in glycemia levels increase oxidative stress [73] and may be a marker of poor prognosis in critically ill patients [74].

Conclusion

The various studies and meta-analyses on the prolonged use of low to moderate doses of GCs in ARDS suggest the possibility that this medication may provide some benefits with a manageable risk profile (Table 3). Indeed, the use of GCs was actively recommended at a recent consensus conference of the American College of Critical Care Medicine: “Moderate-dose GC should be considered in the management strategy of patients with early severe ARDS and before day 14 in patients with unresolving ARDS. The role of GC

Table 3 Reasons to administer or not (advantages vs. disadvantages) glucocorticoids (GCs) in acute respiratory distress syndrome (ARDS)

Advantages

- Several studies show beneficial results for many secondary endpoints Mortality should not be the only argument to evaluate a therapeutic approach
- Few side effects are observed when GCs are properly administered at appropriate dosages
- Some beneficial results in related pathologies, such as community-acquired bacterial pneumonia
- Cheap and easily accessible

Disadvantages

- Limitations in biological knowledge
- Serious methodological problems in several studies, a fact that also brings into question the validity of the meta-analyses
- The largest and best-designed study to date had negative results in its primary endpoint
- Early administration in patients with ARDS secondary to the A/H1N1 influenza virus could be dangerous
- New studies, promoted by authors that currently defend the use of GCs, are currently underway

treatment in acute lung injury and less severe ARDS is less clear” [29]. The first *Surviving Sepsis* campaign reached a similar conclusion regarding the use of GCs for septic shock [75]. Nevertheless, given the difficulties of achieving consistently reproducible results thus far [76], the recommendation levels provided by recently published clinical guidelines have been lowered from previous guidelines [77]. Even so, several authors [78–82] have expressed their disagreement with these recommendations for two main reasons:

- Most of the studies that the meta-analyses have evaluated were carried out by enthusiastic supporters of GC therapy, and these are the same people who have authored the American recommendations;
- The primary endpoint of the ARDS Network trial, which is considered to be the most rigorous study to date, was negative.

In order to resolve some of the uncertainties, a new study focused on low to moderate prolonged doses of methylprednisolone in early ARDS is being planned (the CARS trial, sponsored by the Clinical Trial Group of the European Society of Intensive Care Medicine).

Until new results become available, current evidence does not support the use of GCs for ARDS and, therefore, we do not recommend their use for the treatment of ARDS at this time.

Conflit d’intérêt : les auteurs déclarent ne pas avoir de conflit d’intérêt.

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