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Steroids in late ARDS?

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Expanded Abstract

Citation

Steinberg KP, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, Thompson BT, Ancukiewicz M: Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med 2006, 354:1671-1684 [1].

Background

Persistent acute respiratory distress syndrome (ARDS) is characterized by excessive fibroproliferation, ongoing inflammation, prolonged mechanical ventilation, and a substantial risk of death. Because previous reports suggested that corticosteroids may improve survival, the study authors performed a multicenter, randomized controlled trial of corticosteroids in patients with persistent ARDS.

Methods

Objective: To determine if low dose corticosteroids would improve survival among patients with persistent ARDS.

Design: Multicenter randomized controlled trial.

Setting: 25 hospitals in the United States that were part of the ARDS Clinical Trials Network.

Subjects: 180 mechanically ventilated patients with ARDS of at least seven days duration.

Intervention: Subjects were randomized to either intravenous methylprednisolone (steroid group) or placebo in a double-blind fashion. Those in the steroid group received 2 mg/kg loading dose followed by 0.5 mg/kg every 6 hours for 14 days, 0.5 mg/kg every 12 hours for 7 days, and then tapering of the dose over 2-4 days.

Measurements and mai n res ults: The primary end point was mortality at 60 days. Secondary end points included the number of ventilator-free days and organ-failure-free days, biochemical markers of inflammation and fibroproliferation, and infectious complications. At 60 days, the hospital mortality rate was 28.6 percent in the placebo group (95 percent confidence interval, 20.3 to 38.6 percent) and 29.2 percent in the methylprednisolone group (95 percent confidence interval, 20.8 to 39.4 percent; P=1.0); at 180 days, the rates were 31.9 percent (95 percent confidence interval, 23.2 to 42.0 percent) and 31.5 percent (95 percent confidence interval, 22.8 to 41.7 percent; P=1.0), respectively. Methylprednisolone was associated with significantly increased 60- and 180-day mortality rates among patients enrolled at least 14 days after the onset of ARDS. Methylprednisolone increased the number of ventilator-free and shock-free days during the first 28 days in association with an improvement in oxygenation, respiratory-system compliance, and blood pressure with fewer days of vasopressor therapy. As compared with placebo, methylprednisolone did not increase the rate of infectious complications but was associated with a higher rate of neuromuscular weakness.

Conclusion

These results do not support the routine use of methylprednisolone for persistent ARDS despite the improvement in cardiopulmonary physiology. In addition, starting methylprednisolone therapy more than two weeks after the onset of ARDS may increase the risk of death. (ClinicalTrials.gov number, NCT00295269.)

Commentary

ARDS is a condition characterized by excessive and protracted inflammation. The lung inflammation observed in ARDS can be precipitated by diverse disease processes, including both intrapulmonary ones (such as, infection or aspiration) and extrapulmonary ones (such as, shock or extensive trauma). In the early (<7 days) stages of ARDS,

an exudative inflammation is thought to predominate. In later stages (>7 days), a fibroproliferative phase may develop. Each of these two inflammatory phases has been considered potentially amenable to the anti-inflammatory effects of corticosteroid (steroid) therapy.

Short courses of high doses of steroids in ARDS are not beneficial [2,3]. More recently, it has been suggested that lower doses of steroid (1-2 mg/kg/day) for a more prolonged period might benefit the lung while reducing the potential for systemic side-effects. Recent data from a retrospective subgroup analysis of a clinical trial [4] and a small (n=91) prospective clinical trial [5] suggest that such an approach may improve outcomes, including mortality, in early ARDS. In late ARDS, initial observational studies also suggested benefit [6,7]. Subsequently, in 1998, Meduri and colleagues reported dramatically lower ICU (0% vs 62%, p=0.002) and hospital (12% vs 62%, p=0.03) mortality in a small (n=24) randomized study of low dose steroids in patients who had severe ARDS for 7 days [8].

Based on the promising results in late ARDS, the ARDS Clinical Trials Network conducted the current study, which was a multicenter randomized trial of low dose steroids in 180 patients with ARDS of at least 7 days duration [1]. In this study, the steroid treated group received intravenous methylprednisolone (2 mg/kg/day) for 14 days. The dose was then decreased to 1 mg/kg/day for 7 more days, and then tapered to zero over 2-4 days. Steroid treated subjects had significantly reduced lung inflammation, improved oxygenation, better respiratory-system compliance, and more ventilator-free and shock-free days during the first 28 days. However, 60 and 180 day mortality rates in each group were almost identical (29.2% vs. 28.6% and 31.5% vs. 31.9%, steroids vs. placebo). There were no differences in infectious complications, but there was a higher rate of neuromuscular weakness in the steroid group. In the subset of patients enrolled at least 14 days after the onset of ARDS, steroids were associated with significantly worse 60 and 180 day mortality. Yet, in those enrolled between 7 and 13 days of ARDS onset, mortality was non-significantly lower with steroids.

Although this was a large and well conducted study, a number of criticisms have been raised. The study was conducted over a period of time when there were substantial changes in ICU practice, including low tidal volume ventilation, tight blood glucose control, and steroids for refractory septic shock. Even so, the authors did not find an interaction between period of time or baseline tidal volume and outcome, suggesting that secular trends did not obscure a beneficial steroid effect. The study had a large number of exclusion criteria, which resulted in only 5% of otherwise eligible patients being enrolled. While this could affect the generalizability of the study, it is not uncommon in ICU-based clinical trials. The methylprednisolone was tapered relatively quickly (over 2-4 days), which might have led to rebound pulmonary inflammation [9]. This premise is supported by greater reintubation rates in steroid treated subjects (22% vs. 7%), though neuromyopathy could also be responsible for this latter finding. The treatment group contained a disproportionate number of females, and females have previously been shown to be less responsive to corticosteroid therapy [10], perhaps because of a greater capacity to metabolize methylprednisolone compared to males [11]. However, the interactions between gender, treatment assignment, and outcome were not significant.

It is perhaps surprising that while steroids had beneficial short-term effects, such as reduced inflammation and improved physiologic measures, this did not translate into improved mortality. Yet the literature is full of examples where short-term effects and surrogate endpoints fail to predict long-term clinical outcomes [12] (**table**).

Table: Surrogate vs. clinical outcomes

Intervention	Disease	Surrogate	Clinical Outcome
Growth hormone	Critical illness	↑ nitrogen balance	↑ mortality [13]
Milrinone	CHF	↑ exercise	↑ mortality [14,15]
Flecanide	Post-AMI	↓ arrhythmias	↑ mortality [16,17]
Transfusion	ICU anemia	↑ hematocrit	↑ mortality [18]
Inhaled nitric oxide	ARDS	↑ oxygenation	No mortality benefit [19]
Surfactant	ARDS	↑ oxygenation	No mortality benefit [20]

CHF = congestive heart failure; AMI = acute myocardial infarction; ICU = intensive care unit; ARDS = Acute respiratory distress syndrome

Such disparate findings do not indicate a failed clinical trial. In fact, protocol dictates that after *in vivo* biology has been demonstrated and efficacy inferred by improvements in surrogate measures, definitive studies should seek evidence of benefit using end points that measure important, patient-centered outcomes, including intermediate and longer term survival [21]. Clearly, the authors of the current study followed the established paradigm. Their findings should serve to remind us that while we may be eager to embrace the latest treatment advances, we should always maintain a skeptic's eye.

Recommendation

Prolonged low dose corticosteroids are not beneficial for the treatment of late ARDS and may be harmful for patients when initiated more than 14 days after the onset of ARDS. There may be a window of opportunity for further study of low dose steroids in late ARDS in patients who are within 7-13 days of disease onset. This distinction, however, is somewhat arbitrary and the optimum time to intervene might be better guided by as yet unidentified measures of pulmonary and systemic immune status.

Competing interests

The authors declare no competing interests.

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