

WHAT IS ALREADY KNOWN ON THIS TOPIC

Studies have found that the spot protein:creatinine ratio compares favourably with 24 hour urinary protein estimation, the traditional comparator for measuring proteinuria in pregnancy. Many cut-off points for detection of proteinuria of 0.3 g/day or more have been published.

WHAT THIS STUDY ADDS

The 24 hour urine collection should not be the standard against which new measures of proteinuria or albuminuria are compared in pregnancy.

The spot urinary protein:creatinine ratio is a reasonable "rule-out" test for significant proteinuria of 0.3 g/day or more in pregnancy.

Information about the spot urinary albumin:creatinine ratio is insufficient to suggest a cut-off point for diagnosis of significant proteinuria in pregnancy.

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Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis

John Victor Peter,¹ Preeti John,² Petra L Graham,³ John L Moran,⁴ Ige Abraham George,⁵ Andrew Bersten⁶

EDITORIAL by Adhikari and Scales

¹Department of Medical Intensive Care, Christian Medical College and Hospital, Vellore, India 632 004

²Department of Surgical Critical Care and Anaesthesia, Christian Medical College and Hospital, Vellore, India

³Department of Statistics, Division of Economic and Financial Studies, Macquarie University, Sydney, NSW, Australia

⁴Department of Intensive Care, Queen Elizabeth Hospital, Woodville, SA, Australia 5011

⁵Department of Medicine, Christian Medical College and Hospital, Vellore, India

⁶Department of Critical Care Medicine, Flinders Medical Centre and School of Medicine, Flinders University, Bedford Park, SA, Australia

Correspondence to: J L Moran john.moran@adelaide.edu.au

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ABSTRACT

Objective To systematically review the efficacy of steroids in the prevention of acute respiratory distress syndrome (ARDS) in critically ill adults, and in treatment for established ARDS.

Data sources Search of randomised controlled trials (1966-April 2007) of PubMed, Cochrane central register of controlled trials, Cochrane database of systematic reviews, American College of Physicians Journal Club, health technology assessment database, and database of abstracts of reviews of effects.

Data extraction Two investigators independently assessed trials for inclusion and extracted data into standardised forms; differences were resolved by consensus.

Data synthesis Steroid efficacy was assessed through a Bayesian hierarchical model for comparing the odds of developing ARDS and mortality (both expressed as odds ratio with 95% credible interval) and duration of ventilator free days, assessed as mean difference. Bayesian outcome probabilities were calculated as the probability that the odds ratio would be ≥ 1 or the probability that the mean difference would be ≥ 0 . Nine randomised trials using variable dose and duration of steroids were identified. Preventive steroids (four studies) were associated with a trend to increase both the odds of patients developing ARDS (odds ratio 1.55, 95% credible interval 0.58 to 4.05; P(odds

ratio ≥ 1)=86.6%), and the risk of mortality in those who subsequently developed ARDS (three studies, odds ratio 1.52, 95% credible interval 0.30 to 5.94; P(odds ratio ≥ 1)=72.8%). Steroid administration after onset of ARDS (five studies) was associated with a trend towards reduction in mortality (odds ratio 0.62, 95% credible interval 0.23 to 1.26; P(odds ratio ≥ 1)=6.8%). Steroid therapy increased the number of ventilator free days compared with controls (three studies, mean difference 4.05 days, 95% credible interval 0.22 to 8.71; P(mean difference ≥ 0)=97.9%). Steroids were not associated with increase in risk of infection.

Conclusions A definitive role of corticosteroids in the treatment of ARDS in adults is not established. A possibility of reduced mortality and increased ventilator free days with steroids started after the onset of ARDS was suggested. Preventive steroids possibly increase the incidence of ARDS in critically ill adults.

INTRODUCTION

It would seem logical to use corticosteroids to treat acute respiratory distress syndrome (ARDS), with its protracted inflammation. Clinical outcomes in trials on the role of steroids in ARDS^{w1-w5} have varied, however, and two recent overviews on the efficacy of steroids in ARDS reached opposite conclusions.^{1,2} We assessed whether steroids are associated with mortality benefit in adults with ARDS. We also determined the effect of

steroids on infections and ventilator free days and their role in preventing the development of ARDS in critically ill adults.

METHODS

We selected randomised controlled trials in critically ill patients that evaluated steroid treatment compared with no steroid treatment to reduce the incidence of ARDS or to improve the outcome from ARDS. Only trials reporting mortality, incidence of ARDS, or data on ventilation were included. We classified trials as preventive treatment in critically ill patients when used to decrease the risk of development of ARDS, and therapeutic when started after the onset of ARDS.

We did an electronic search and retrieved trials on steroids in ARDS and sepsis (see bmj.com). Predefined data were extracted from included studies. Quality assessment of these studies was done unblinded using a modified 10 point scoring system.³

The primary outcome was hospital mortality or survival to hospital discharge. We chose the odds ratio as an appropriate metric for the mortality effect (see bmj.com). Because of selection bias in trial reporting, assessable secondary end points were incidence of ARDS in critically ill patients after treatment with steroids, number of patients developing new infections or pneumonia, number of ventilator free days, and year of study completion.

ARDS was defined after the 1994 American-European consensus definition.⁴ The duration of ventilator free days was the number of days patients were breathing without assistance during the 28 days after onset of ARDS, presented in the studies as mean (standard deviation) days.

Statistical analysis

We used Bayesian random effects models⁵ to assess the effect of steroids compared with control on mortality, proportion of patients who developed ARDS, new infections, and pneumonia, expressed as odds ratios with 95% credible intervals. We used a model for summary statistics to assess the overall mean difference (steroid treatment minus placebo) in number of ventilator free days. We calculated Bayesian outcome probabilities as the probability that the odds ratio was 1 or more or the mean difference was 0 or more. A probability of 50% suggests a null effect whereas a probability of at least 90% signifies harm for the odds ratio analyses, but benefit (increase in ventilator free days) for the mean difference analysis; and a probability of less than 10% indicates benefit for the odds ratio analyses and harm (decrease in ventilator free days) for the mean difference analysis. We also used Bayesian metaregression⁵ to determine the relation between the odds of mortality and time to treatment in ARDS, total dose of steroids, and year of study completion. The slope (β) with 95% credible intervals and the probability that β was 0 or more are presented. We present heterogeneity as the standard deviation between studies. For all analyses a standard deviation close to 0 indicates little heterogeneity,

whereas for the odds ratio meta-analyses a standard deviation of more than 1 reflects substantial heterogeneity. Similarly, for the mean difference analysis, a standard deviation greater than, for example, 10 indicates substantial heterogeneity. Publication bias was not formally assessed, as the two subgroups each had fewer than 10 studies.⁶

We analysed the data with WinBUGS⁷ using three simultaneous runs of the program with disparate starting values. The first 100 000 iterations were discarded and results were reported as posterior medians and intervals on the basis of a further 100 000 iterations. We used various diagnostics available in the package Bayesian Output Analysis to assess convergence.⁸ We used diffuse priors as described in Warn et al⁵ for the odds ratio models and the meta-regressions. Mathematically diffuse priors aim to have about equal probability over all plausible values of the variable. For the mean difference model we placed a non-informative normal prior distribution with mean 0 and variance 10^5 on the overall mean difference. A normal distribution with mean 0 and variance of 13.5 and truncated below 0 was placed on the parameter for standard deviation between studies.⁹ Such a distribution was derived from the notion that the median difference between any two studies was about four days and that a difference of more than 11 days would be extremely unlikely. To determine the influence on the overall results we also undertook a sensitivity analysis in which the priors were made even less informative.

RESULTS

Nine of 62 articles retrieved on use of steroids in ARDS or sepsis were eligible. Four evaluated preventive therapy in critically ill patients^{w13-w16} and five assessed the role of steroids after the onset of ARDS.^{w1-w5} The treatment and control arms had similar baseline characteristics (see bmj.com). The reporting of mortality varied. The steroid dose ranged from methylprednisolone 1-120 mg/kg/day (or equivalent of hydrocortisone or dexamethasone) administered from four hours to 30 days (see bmj.com).

The credible interval for preventive therapy in critically ill patients included 1, so a null effect could not be ruled out. The $P(\text{odds ratio} \geq 1)$ was 86.6% suggesting some evidence of an association between steroid therapy and the development of ARDS: four studies, odds ratio 1.55, (95% credible interval 0.58 to 4.05); SD 0.58 for variability between studies (table and bmj.com). Similarly, the probability suggested a weakly increased risk of death associated with steroid therapy in patients who developed ARDS: $P(\text{odds ratio} \geq 1)=72.8\%$ (table and bmj.com), although the credible interval included 1.

In the five therapeutic studies the probability that the odds ratio was one or more was small indicating that giving corticosteroids after the onset of ARDS was associated with a trend (table and see bmj.com) to reduced mortality (overall odds ratio 0.62, 95% credible interval 0.23 to 1.26, $P(\text{odds ratio} \geq 1)=6.8\%$), although the credible interval included 1. Some heterogeneity was

evident between studies. Steroid therapy was associated with substantially more ventilator free days (three studies) compared with controls (mean difference 4.05 days, 95% credible interval 0.22 to 8.71, $P(\text{mean difference} \geq 0) = 97.9\%$, SD 2.39). When the effect of moderators (time or dose of steroid therapy, year of study completion) on outcomes was explored in the five therapeutic studies, no evidence was found of an association between odds of mortality and time to treatment (see [bmj.com](#)).

Definitions for secondary infection varied (see [bmj.com](#)). Steroid therapy was not associated with an increase in the number of patients developing new infections or pneumonia (table and see [bmj.com](#)). Meta regression showed a trend towards an increased number of patients developing new infections as steroid dose increased; seven studies (two preventive, five therapeutic), $\beta = 0.08$ (95% credible interval -0.12 to 0.28), $P(\beta \geq 0) = 81.2\%$.

Sensitivity analysis was undertaken in which the prior for variability between studies was made increasingly less informative. In all cases the point estimates remained stable, the credible interval became wider, and probability changed slightly. This did not affect any of the interpretations of the results except for ventilator free days, with the credible interval including zero.

DISCUSSION

This systematic review failed to show a convincing treatment effect of steroids in acute respiratory distress syndrome (ARDS), although trends were found for treatment. Although preventive steroid therapy in critically ill patients may have been associated with detrimental effects on the incidence of ARDS and subsequent mortality, a trend was found to benefit when steroids were given after the onset of ARDS; particularly a reduction in odds of mortality (probability of reduction 93.2%). The review, however, showed no discernible time or dose effect of steroids on mortality with therapeutic use of steroids. Although steroids did not

increase overall infection risk, a latent dose dependent effect of steroid therapy on infection rates seemed to exist.

Key proinflammatory mediators have been implicated in the pathophysiology of sepsis, the most common cause of ARDS.¹⁰ In clinical studies, inhibition of these proinflammatory mediators has not improved outcome.¹¹ Preventive steroids may not only impede normal homeostatic response by inhibiting cytokine production,¹² but also contribute to the pathogenesis of ARDS by stimulating the release of macrophage migration inhibiting factor, a proinflammatory cytokine.¹³ This latter effect remains speculative as release of macrophage migration inhibiting factor by glucocorticoids seems to have a biphasic dose dependency,¹³⁻¹⁵ and protective effects have also been described.¹⁶ In addition the high doses of methylprednisolone given to the preventive group may have contributed to an increased risk of infection and poorer outcomes. Steroid therapy after the onset of ARDS may, however, have a different effect by modifying the persistent and protracted inflammation that exacerbates lung injury.

The implications of time to starting therapeutic steroids after onset of ARDS are of some importance and have been highlighted in the recent National Heart, Lung, and Blood Institute ARDS clinical trials network report,^{w5} where an interaction between time and treatment 14 days after the onset of ARDS was found to be significant. In the individual trials included in the current meta-analysis, the start of steroid therapy ranged from within 72 hours^{w4} to four weeks^{w5} after ARDS onset. Metaregression with initiation time of treatment as a moderator (see [bmj.com](#)) failed to show any influence on mortality.

Steroids did not seem to have any adverse effect on overall infection rates, including pneumonia, but a trend was found towards increased risk of infection with increasing steroid dose. The variation in the steroid dosages¹⁷ was primarily because studies in the 1980s used high dose (120 mg/kg/day methylprednisolone) short duration (24-48 hours) steroids as immunomodulatory therapy whereas prolonged

Summary of outcomes in included studies of steroids compared with placebo in prevention and treatment of adults with acute respiratory distress syndrome (ARDS)

Outcome variable	No of studies	No of patients*		Odds ratio† (95% CrI)	P (odds ratio ≥ 1) (%)	SD‡
		Control group	Steroid group			
Mortality:						
Therapeutic use	5	268	303	0.62 (0.23 to 1.26)	6.8	0.53
Preventive use	3	66	88	1.52 (0.30 to 5.94)	72.8	0.97
Proportion developing ARDS	4	244	258	1.55 (0.58 to 4.05)	86.6	0.58
New infections§:						
Therapeutic use	5	268	303	0.78 (0.41 to 1.69)	20.9	0.37
Preventive use	2	79	77	1.18 (0.19 to 5.99)	59.6	0.88
Pneumonia (therapeutic use)	4	219	253	0.59 (0.14 to 2.82)	23.1	1.34

CrI=credible interval.

*Number included in analysis.

†Odds ratio for steroids versus placebo.

‡Standard deviation between studies.

§Only number of patients with this outcome taken and not number of episodes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Corticosteroids as either immunomodulatory or anti-inflammatory agents have potential as therapy in ARDS

A small number of randomised trials and recent systematic reviews have tackled this theory

WHAT THIS STUDY ADDS

No convincing treatment effect of steroids in ARDS was evident; the optimal dose, timing, and duration of steroid therapy is not established

Meta-analyses based on a small number of trials with sparse data must be cognisant of limitations in estimation of treatment effects; Bayesian estimation would seem suitable

(2-4 weeks) low dose (1 mg/kg/day methylprednisolone) anti-inflammatory therapy has been more recently advocated.¹⁸ Given the complications of high dose steroids, current use is limited to specific (acute) immunological diseases, with little evidence supporting high dose steroids in ARDS.¹⁹

Secondary outcomes such as lung injury score could not be systematically evaluated because of publication bias within studies.²⁰ Although the steroid effect on ventilator free days was favourable, only three studies reported this outcome, and in the sensitivity analysis the credible interval included 0 suggesting the possibility of a null effect.

Strengths and weaknesses of the review

The number of trials and number of patients randomised to receive steroids (n=561) was relatively small, compounded by stratification into two subgroups; preventive and therapeutic. A previous meta-analysis¹ found odds ratios of 0.57 (95% confidence interval 0.25 to 1.32) in “early” ARDS and 0.58 (0.22 to 1.53) in “late” ARDS, but the conclusions of this meta-analysis are problematic (see bmj.com). Another study² used fixed effects estimation of the pooled mortality treatment effect with the relative risk metric (0.76, 95% confidence interval 0.62 to 0.93) and included the randomised trial²¹ on steroids in severe community acquired pneumonia, but did not consider an early trial of steroids in ARDS.^{w2} The principal concern was heterogeneity and its influence on the pooled mortality estimate.²

We judge aspects of the analyses in these two reviews as problematic and suggest that a Bayesian perspective is both apposite and, unlike conventional frequentist random effects estimation,²² able to accommodate heterogeneity, and an odds ratio metric is preferred.²³

Conclusions

Some evidence exists for the efficacy of steroid use after the onset of ARDS, without notable side effects such as new infection. We cannot, however, dismiss a null effect. Furthermore, we were unable to accurately define the optimal dose, timing, and duration of steroid

therapy. Meta-analyses on the basis of a small number of trials with sparse data must be cognisant of limitations in estimation of treatment effects.

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