Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: a systematic review and meta-analysis

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CRD summary
The authors concluded that use of low-dose corticosteroids in patients with acute lung injury and acute respiratory distress syndrome was associated with improved mortality and morbidity outcomes without increased adverse events. The authors' conclusions reflected the evidence presented, but incomplete reporting of review methods made the reliability of the authors' conclusions unclear.

Authors' objectives
To determine the effect of low dose corticosteroids on mortality and morbidity of acute lung injury or acute respiratory distress syndrome (ARDS).

Searching
MEDLINE, EMBASE, Current Contents, DARE, Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews were searched without language restrictions from January 1967 to September 2007. Search terms were reported. Reference lists of included studies were searched.

Study selection
Eligible for inclusion in the review were randomised controlled trials (RCTs) or cohort studies that used low dose methylprednisolone (0.5 to 2.5mg/kg/day of methylprednisolone or equivalent) and enrolled adult patients (aged 18 or older) with acute lung injury or ARDS. The primary outcome of interest was hospital mortality. Other outcomes of interest included: length of mechanical ventilation; length of intensive care unit stay; Multiple Organ Dysfunction Syndrome (MODS) score; lung injury score; oxygen saturation (PaO$_2$/FiO$_2$ ratios); and adverse events (infection, neuromyopathic complications, gastrointestinal bleeding, hyperglycaemia, arrhythmia, psychiatric disorder and organ failure).

Studies were excluded if they did not use a control group, used high dose corticosteroids (30mg/kg/day of methylprednisolone or equivalent) or enrolled patients with other systemic inflammatory disease such as Pneumocystis carinii or idiopathic pulmonary fibrosis.

Included studies were conducted in Europe, South Korea and USA. Dose equivalent (methylprednisolone 48mg/day to 100 to 250mg/day), stage of ARDS (early, persistent, late), duration of acute lung injury/ARDS (zero to 15 days), length of treatment (seven to 32 days), presence of sepsis (0% to 100%) and mean age of patients (43 years to 67 years) all varied between studies. There were significantly more male than female patients (median male: female ratio of 2.3).

The authors did not state how many reviewers performed study selection.

Assessment of study quality
RCT study quality was assessed using criteria of method of randomisation, allocation concealment, blinding of outcome assessment and completeness of follow-up. Cohort study quality were assessed using baseline comparability of treatment group against control group, adjustment for confounders, blind outcome assessment and completeness of follow-up.

The authors did not state how many reviewers performed study quality assessment.

Data extraction
Data were extracted in order to calculate risk ratios (RR) and 95% confidence intervals (CI) for dichotomous outcomes and mean differences (MD) or standardised mean differences (SMD) and their associated 95% CI for continuous
outcomes.

Two reviewers independently extracted data. Any disagreements were resolved by consensus.

**Methods of synthesis**
Risk ratios, mean differences or standardised mean differences were combined in a meta-analysis using a random-effects model. Heterogeneity was assessed using Cochran's Q statistic and the $I^2$ test. Heterogeneity was explored using subgroup analyses and meta-regression analyses using pre-planned variables. Number needed to treat was calculated.

**Results of the review**
Nine studies (n=648 patients) were included in the review: four RCTs (n=341 patients) and five cohort studies (n=307). The authors stated that study quality was fair in most studies. RCTs provided 75% of the quality assessment items and cohort studies provided 82%.

**Mortality**: There was no statistically significant difference in mortality between corticosteroids and control for RCTs alone (RR 0.51, 95% CI 0.24 to 1.09; four studies) or for cohort studies alone (RR 0.66, 95% CI 0.43 to 1.02; five studies). When cohort studies and RCTs were combined, use of corticosteroids was shown to be associated with a statistically significant reduction in mortality (RR 0.62, 95% CI 0.43 to 0.91; nine studies). There was evidence of statistically significant heterogeneity ($I^2$=51%).

**Mechanical ventilation**: Corticosteroids were associated with a statistically significant reduction in mechanical ventilation duration (MD -4.84, 95% CI -9.28 to -0.39; three RCTs and one cohort study). There was evidence of statistically significant heterogeneity ($I^2$=86%).

**Multiple Organ Dysfunction Syndrome (MODS) score**: Corticosteroids were associated with a statistically significant reduction in MODS score (MD -0.76, 95% CI -1.10 to -0.42; three RCTs and two cohort studies). No significant heterogeneity was found.

**Oxygen saturation (PaO$_2$/FiO$_2$ ratios)**: Corticosteroids were associated with statistically significant greater oxygen saturation (SMD 0.64, 95% CI 0.15 to 1.13; four RCTs and two cohort studies). There was evidence of statistically significant heterogeneity ($I^2$=78%).

There was no statistically significant difference between corticosteroids and control for length of intensive care stay, lung injury score, infection, neuromyopathy and all major adverse events. Results of additional adverse events were provided in a table. Results of subgroup analyses and meta-regression were reported.

**Authors' conclusions**
Use of low-dose corticosteroids was associated with improved mortality and morbidity outcomes without increased adverse events in patients with acute lung injury/ARDS.

**CRD commentary**
The review addressed a clear research question. The search was adequate. There were no language restrictions, which reduced the risk of language bias. There were no apparent attempts to locate unpublished material, so publication bias could not be ruled out. Study quality was assessed using appropriate criteria; however, the assessment for each study was not reported. Numbers of reviewers involved in study selection and study quality assessment were not reported, so it was unclear whether these review processes were at risk of reviewer error and bias. Overall, sufficient study details were provided; however, no information was provided on the controls used. Pooling of RCTs and cohort studies seemed inappropriate, but studies were also analysed according to study design. Potential reasons for heterogeneity were examined and discussed.

The authors' conclusions reflected the evidence presented. However, incomplete reporting of review methods made the reliability of the authors' conclusions unclear.
Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that future RCTs should use a standardised regimen of timing, dosage and formulations, duration and length of tapering. Trial enrolment should include stratified subgroups to determine the effect of corticosteroids on non responders versus responders to corticotrophin stimulation. Mortality benefits in early ARDS should be confirmed by an adequately powered randomised trials.

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