Glucocorticoid therapy in acute respiratory distress syndrome

Acute respiratory distress syndrome is an important cause of mortality and morbidity in the critically ill. Despite advances in ventilation strategies and organ support, mortality remains at around 30%. Persistent functional disability and neuropsychiatric disorders, such as cognitive dysfunction and depression, can exert a profound effect on quality of life in the months or years following discharge in patients diagnosed with the syndrome.

Glucocorticoids are a cheap and widely available therapy used for over 20 years in the management of acute respiratory distress syndrome. Glucocorticoid therapy has remained controversial as steroid use is associated with significant morbidity.

Early evidence suggested a mortality benefit in patients with persistent acute respiratory distress syndrome and most subsequent research has focused on this sub-group. More recently trials have suggested a possible role for glucocorticoids in patients with early acute respiratory distress syndrome and those with acute respiratory distress syndrome and septic shock.

Glucocorticoids should be used

The only high quality, multi-centre randomized controlled trial without crossover design to determine the efficacy and safety of glucocorticoids in patients with persistent acute respiratory distress syndrome was conducted by the ARDS Clinical Trials Network (Steinberg et al, 2006). Significant improvements in oxygenation, plateau pressures and lung compliance were seen in those treated with methylprednisolone, as well as significantly more shock-free and ventilator-free days.

A post-hoc analysis of a randomized controlled trial of low-dose corticosteroids in septic shock suggested that patients with septic shock and acute respiratory distress syndrome treated with corticosteroids had significantly reduced mortality, with increased days alive and ventilator-free (Annane et al, 2006). There was no significant difference in super-infection, gastrointestinal bleeding or psychiatric disorders between the treatment group and placebo.

Most trials of low or moderate dose glucocorticoids in acute respiratory distress syndrome show no difference or a reduced incidence of super-infection. Two trials by Meduri et al (1998, 2007) suggested a decreased risk of secondary infection in acute respiratory distress syndrome following rigorous infection surveillance.

Much of the concern about glucocorticoid therapy in acute respiratory distress syndrome has resulted from the ARDS Clinical Trials Network which suggested harm when glucocorticoids were initiated after 14 days. Large imbalances in baseline characteristics between the treatment and control groups (the trial was probably underpowered because enrolment was slow) contributed to an unusually low mortality in the control group, so interpretation of these results should be guarded.

Meta-analysis of data from this and other trials suggests that glucocorticoids started before day 14 significantly reduce mortality and days mechanically ventilated. The Society of Critical Care Medicine (Marik et al, 2008) consensus recommends consideration of moderate-dose glucocorticoids in the management of patients with early severe acute respiratory distress syndrome and before day 14 in patients with unresolving acute respiratory distress syndrome.

Glucocorticoids should not be used

Randomized controlled trials in the 1980s showed that using high-dose (30 mg/kg) methylprednisolone to prevent acute respiratory distress syndrome does not improve mortality rates, and may increase the likelihood of acute respiratory distress syndrome and secondary infection.

The ARDS Clinical Trials Network trial did not find any mortality benefit from moderate-dose methylprednisolone. In the pre-specified subgroup of patients enrolled at least 14 days after the onset of acute respiratory distress syndrome, methylprednisolone treatment was associated with a fourfold increase in mortality.

Meta-analysis of several trials of low- and moderate-dose glucocorticoid therapy suggests a benefit when it is started before 14 days (Meduri et al, 2007). However, a proportion of the positive data in this meta-analysis comes from the aforementioned trials by Meduri et al which used a crossover design. This confounds outcomes from conventional intention to treat analysis.

Conclusions

Glucocorticoids cannot be recommended for routine use in acute respiratory distress syndrome. High-dose glucocorticoid therapy is of no benefit to treat early acute respiratory distress syndrome or to prevent it in high-risk patients. Moderate-dose glucocorticoids in both early and late acute respiratory distress syndrome significantly improve cardiovascular and respiratory physiological indices but a long-term survival benefit has not been seen. **BJHM**

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Annane D, Sébille V, Bellissant E, Ger-Inf-05 Study Group (2006) Effect of low doses of corticosteroids in septic shock patients with or without early acute respiratory distress syndrome. *Crit Care Med* **34:** 22–30

Marik PE, Pastores SM, Annane D et al (2008) Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: Consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med* **36**(6): 1937–49

Meduri GU, Headley AS, Golden E et al (1998) Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. *JAMA* **280:** 159–65

Meduri GU, Golden E, Freire AX et al (2007) Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. *Chest* **131:** 954–63

Meduri GU, Marik PE, Chrousos GP et al (2008) Steroid treatment in ARDS: a critical appraisal of the ARDS network trial and the recent literature. *Intensive Care Med* **34**(1): 61–9

Steinberg KP, Hudson LD, Goodman RB et al (2006) Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* **354:** 1671–84

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