DEM Journal Club

Article Appraisal

Article: Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

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Background and Study Objective(s):

Septic shock is a life-threatening condition with a high mortality, estimated in the short-term between 45-50%, and high morbidity with up to 50% of survivors experiencing long-term cognitive decline. Unfortunately, outside of early hemodynamic and respiratory support as well as antibiotic therapy, there are limited, well-established adjunctive therapies available. One such therapy is corticosteroid use for septic shock which has had both positive and negative results. This has led to widespread variability in practice for physicians managing septic shock.

For some background, multiple RCTs have examined the role for steroid therapy in septic shock in recent years. In 2002, Annane et al, the authors of this current study, published an RCT in JAMA of 299 patients with septic shock in French ICUs. These patients were randomized to receive either bolused doses of hydrocortisone and fludrocortisone or placebo and they found that the addition of steroids reduced mortality at 28d in pts in septic shock with those with relative adrenal insufficiency.

Subsequent to that, 3 studies were published which found the opposite. The first of these was CORTICUS, an RCT of 499 patients published in 2008. In this study steroids hastened reversal of shock but there was no mortality benefit. However, patients in CORTICUS were enrolled, on average, 72h after onset compared to 8h in the Annane et al 2002 study. Additionally, the patients in the Annane study were sicker. In 2016 HYPRESS was published which was an RCT of 380 patients with severe sepsis but without shock. They found that corticosteroids did not prevent the progression to shock at 14d. Finally, in 2018 ADRENAL was published which was a large RCT of 3,658 patients from 69 international sites (mostly Australia, New Zealand and UK). It compared hydrocortisone infusion to placebo in patients with septic shock on vasopressors and mechanical ventilation. They found no difference in their primary outcome of mortality at 90d, although the hydrocortisone group did have faster reversal of shock, shorter intubation times and shorter time to discharge from ICU.

The purpose of this current study was to examine whether hydrocortisone and fludrocortisone therapy or activated protein C (Xigris) would improve outcomes for patients with septic shock. As Xigris was removed from the market, this became a null point, and the question focused on whether there was a 90d mortality benefit for patients on hydrocortisone and fludrocortisone therapy with septic shock.

Study Design:

Publicly-funded randomized, multi-centre, double-blind, placebo-controlled trial in 34 French ICUs of n=1241 patients.

This study was originally designed to have 4 parallel groups in a 2 by 2 factorial design, with a combination of placebos for both corticosteroids and Xigris. When Xigris was removed this was adjusted and instead there were 2 parallel groups looking at corticosteroids vs placebo. The corticosteroids administered were hydrocortisone 50mg IV q6h and fludrocortisone 50mcg NG OD for 7d with no taper.

Inclusion criteria included: probable or indisputable septic shock for less than 24h, patients needed to be SOFA of 3 or greater for at least 2 organ systems for at least 6h and on pressors for at least 6h.

This was an intention-to-treat analysis. The primary outcome was all-cause mortality at 90d. There were several secondary outcomes including all-cause mortality at ICU discharge, hospital discharge, day 28 and day 180; time to wean off pressors and mechanical ventilation.

Results:

The primary outcome of 90d all-cause mortality was 43% in the steroid group vs 49.1% in the placebo group (6.1% absolute difference; p=0.03), yielding a relative risk reduction of death of 88% in favour of the steroid group.

In Table 1 we see the baseline characteristics were similar between the two groups. Most patients were male (66%), aged 66y with a SOFA score of 12. Most sites of infection were the lungs followed by the urinary tract then abdomen. Most patients did not have positive blood cultures and 97% of patients received adequate antimicrobial therapy.

Table 2 summarizes the primary and secondary outcomes. In short, there were significant differences ($p<0.05$) for the primary outcome, death at ICU discharge (35% vs 41%; p=0.04), death at hospital discharge (39% vs 45%; p=0.02), death at day 180 (47% vs 53%; p=0.04), vasopressor-free days to day 28 (17d vs 15d; $p<0.001$) and organ failure-free days (14d vs 12d; p=0.003); all favouring the use of corticosteroids. There were no differences in ventilator free-days to day 28 (p=0.07). They did not see a significant difference in death at day 28 (p=0.06), although the p-value approached 0.05. Indeed, the survival curve in Figure 1 suggests that the signal exists quite soon after onset of randomization and persists throughout the 90d period, as the data in Table 2 suggests. There were no differences in decisions to withhold or withdraw active treatments by day 90 between the two groups (p=0.69).

Validity of Results:

The results of the RCT are valid as they do collect correct data to assess the endpoints of concern. However, there are some concerns regarding the robustness of the results. This metric can be calculated using a statistical test called the fragility index. Smaller fragility indices indicate that even a small number of participants who are switched from the event group to the non-event group could make the result non-significant. This study had several outcomes, including the primary outcome, in single digit fragility scores (the primary outcome fragility score was 3). This makes it difficult to have much trust in the quoted p-value.

This can also be conceptually discerned by the way p-value hovers around the 0.05 mark for mortality at the day 28, 90 and 180 time points; sometimes over and sometimes under. It is also exemplified by the large confidence intervals around the estimate. The primary outcome had an absolute difference in mortality of 6.1% but a 95% confidence interval of 0.6-11.7%. Although this does not reach zero, it does get very close, and nonetheless it is a large margin of error around the mean.

Generalizability of Results:

This was generally a well-done study that provided adequate standard treatment for septic shock to both arms. However, it is difficult to generalize the results of this study to most patients who present with septic shock as the

patients included in this study, as evidenced by their longstanding pressor and mechanical ventilation requirements, as well as the high amounts of vasopressor support, means these patients were very sick. For example, patients in this study were on an average of 1mcg/kg/min of norepinephrine (~70 mcg/min for 70kg adult). Epinephrine was on the order of 100-140mcg/min. These are clearly very high levels of vasopressors in comparison to most presenting septic shock patients.

Taking the previous studies into context, including ADRENAL which was an international trial with a larger sample size that showed no difference, then only two large RCTs thus far have shown positive results on mortality with corticosteroids; and these are in those two RCTs published by the same group. Questions may be asked regarding whether this could affect the generalizability. One could argue that the addition of fludrocortisone is what accounts for this difference as the other studies did not include this. Additionally, one could argue that ADRENAL used continuous infusions instead of bolused stress dosing and that the patients in APROCCHSS were much sicker, which may have accounted for the difference. However, the fact remains that no other international trial has shown steroids to reduce mortality in septic shock.

The Bottom Line:

Use of steroids may be helpful if used early enough and for the sickest patients with septic shock. Its use should be reserved for those patients in refractory septic shock. No serious adverse events were reported with the use of corticosteroids.