Fludrocortisone dose–response relationship in septic shock: a randomised phase II trial

James Walsham et al. ICM (2024)

RESEARCH AIM

To investigate whether adding **different dosages of fludrocortisone to hydrocortisone** therapy in septic shock results in a **faster resolution of shock** compared to hydrocortisone alone.

BACKGROUND

- Sepsis and septic shock are major causes of morbidity and mortality globally.
- **Previous trials** studied the effects of adjunctive corticosteroid therapy in septic shock but yielded **differing results** on mortality[1-4].
- Data on the efficacy, pharmacokinetics, and safety of different fludrocortisone doses in patients with septic shock are limited.

METHODS

Design: Multi-centre, open-label randomized phase II clinical trial.

Population:

- ICU patients ≥18 years of age
- Documented or strongly suspected infection
- SIRS criteria ≥ 2/4
- Mechanical ventilation
- Requiring vasopressors
- Receiving hydrocortisone 200 mg/d

METHODS

Intervention:

- Hydrocortisone alone or
- Hydrocortisone with fludrocortisone 50 µg, 100 µg or 200 µg daily for up to 7 days with peroral/enteral application.

Primary outcome:

- Time to resolution of shock, defined as the time from randomization to attaining a clinician-prescribed mean arterial pressure target for more than 24 hours without vasopressors/inotropes.

Secondary outcomes:

- Recurrent shock, ventilator-free days, maximum SOFA score, change in SOFA score, length of ICU and hospital stay, ICU and hospital mortality up to 28 days.
- Pharmacokinetic - Fludrocortisone plasma concentrations 3h after dosing
- Safety – Serious adverse events, electrolyte abnormalities, fluid balance or new infection

Statistical Analysis:

- Cox proportional hazard model without and with adjustment for sex and APACHE II at baseline.
- Fisher's exact test for binary outcomes
- T test for duration outcomes
- Linear models for continuous outcome variables

RESULTS

Enrollment:

- **153 patients** from 9 study sites in Australia

Primary outcome:

	Fludrocortisone			
	0 µg	50 µg	100 µg	200 µg
Median days to shock resolution (IQR)	3 (2-5)	3 (2-4)	3 (2-6)	3 (2-6)
Hazar ratio (95% CI)	Ref.	0.93 (0.59-1.49)	0.97 (0.61-1.57)	1.01 (0.63-1.62)

- **No significant difference in time to shock resolution** between the hydrocortisone alone group and the fludrocortisone group.

Secondary outcomes:

- No significant differences in patients alive with resolution of shock at day 28, shock recurrence, ventilator-free days, ICU/hospital stay, or maximum/change in SOFA .
- No significant difference in 28-day mortality with a rate of 23.7%, 16.7%, 11.1% and 10.8% with Fludrocortisone of 0 µg, 50 µg, 100 µg and 200 µg, respectively.
- Pharmacokinetics: Plasma fludrocortisone was detectable in 97% of patients, with no significant differences in concentrations between dosage groups.
- Safety: No serious adverse events or significant differences in electrolyte abnormalities, fluid balance or new infections between groups.

SIS COMMENTS

The debate over the use of corticosteroids in septic shock, including the optimal compounds and dosing, has been ongoing in the intensive care community for decades. Since Djillali Annane's landmark study, which demonstrated a survival benefit at 28 days with adjunctive hydrocortisone and fludrocortisone therapy in 300 septic shock patients, subsequent research has produced conflicting results[1-4]. For instance, the 2018 APROCCHSS trial demonstrated a survival benefit at 90 days, though not at 28 days, with combined treatment of hydrocortisone and fludrocortisone. In contrast, the ADRENAL trial, which administered hydrocortisone alone via continuous infusion, failed to show a 90-day survival benefit but did demonstrate a faster resolution of shock with hydrocortisone[3,4].

Notably, among major trials, a survival benefit has been observed predominantly in those that included combined hydrocortisone and fludrocortisone therapy, whereas trials that used hydrocortisone alone have failed to show a significant survival advantage[1-4]. This suggests a potential additive benefit of fludrocortisone when used alongside hydrocortisone, though definitive proof remains lacking.

From a pathophysiological perspective, hydrocortisone primarily acts through the glucocorticoid receptor, supporting adrenal insufficiency and potentially reducing inflammation during sepsis. The addition of fludrocortisone, a mineralocorticoid, is expected to enhance blood pressure stabilization by increasing vascular tone and sodium retention.

In this most recent study, Walsham and colleagues provide valuable insights into the effects of adjunctive fludrocortisone therapy on shock resolution in sepsis, shedding light on pharmacokinetic and safety aspects of the drug[5]. The authors demonstrated that oral or enteral administration of fludrocortisone achieved relevant plasma concentrations, though variable plasma levels suggest significant interindividual differences in absorption. The study further highlights the safety profile of different fludrocortisone dosages, indicating that enteral administration is a safe and viable route for bioavailability.

Regarding the potential therapeutic benefit of fludrocortisone in addition to hydrocortisone, the study did not show a significant advantage in shock resolution or survival. However, given the limited sample size, which was primarily powered to assess shock resolution, a potential benefit on survival outcomes cannot be excluded. Furthermore, the relatively low overall mortality rate in this study cohort compared to previous trials may have additionally impacted the statistical significance of treatment efficacy outcomes[1-4]. Interestingly, the data show a dose-dependent numerical trend in 28-day mortality, with a reduction from 23.7% in patients treated with hydrocortisone alone to 10.8% in those receiving the highest dose of fludrocortisone (200 µg), although this trend did not reach statistical significance.

In summary, this study represents a significant step forward in understanding the pharmacokinetics of fludrocortisone in septic shock and provides a potential foundation for larger survival-centered trials in the future.

1. Annane et al. JAMA, 2002.
2. Sprung et al. NEJM, 2008.
3. Annane et al. NEJM, 2018.
4. Venkatesh et al. NEJM, 2018.
5. Walsham et al. ICM, 2024.



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