Furosemide and Albumin for Diuresis of Edema (FADE): a parallel-group, blinded, randomized controlled pilot trial

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1. Background

Fluid overload is associated with morbidity and mortality in critically ill patients. Adding hyperoncotic albumin to standard treatment with diuretics may improve diuresis and facilitate liberation from mechanical ventilation.

2. Objectives

We conducted a pilot study to assess the feasibility of a definitive randomized controlled trial testing the effectiveness of hyperoncotic albumin as an adjunct to diuretics in critically ill adults.

3. Materials & Methods

At two medical/neurotrauma ICUs in Canada, we randomized hemodynamically stable, hypoalbuminemic adults, judged to require diuresis, to receive either 25% albumin or 0.9% saline placebo, 100 mL twice daily for up to six doses, within 2 hours of prescribed furosemide. Patients, bedside staff, and research staff were blinded.

We specified five criteria for study feasibility: enrolment of 50% of eligible patients; enrolment of >1 patient/week; administration of the first dose of study treatment within 2 hours of diuretics in 85% of patients; completion of study regimen in 80% of patients; and avoidance of open label 25% albumin in 85% of patients.

4. Results

From September 2014 to October 2016 we randomized 85% of eligible patients (24 albumin, 21 placebo). Due to slow recruitment (0.42 patients/week), we stopped the trial short of our target 50 patients. 84% (95%CI 0.73, 0.96) of patients received study treatment within 2 hours of the first furosemide dose, 69% (95%CI 0.54, 0.80) received the complete study regimen, and 20% received open-label albumin (95%CI 0.11, 0.34).

The albumin group had a greater increase in serum albumin (MD 5.94 g/L, 95%CI [1.44, 6.89], $p=0.0047$) and colloid osmotic pressure (MD 3.13 mmHg, 95%CI [1.96, 4.31], $p<0.001$). The groups had similar changes in urine output (MD -422 mL, 95%CI [-1062, 218], $p=0.20$) and fluid balance (MD 147 mL 95% CI [-767, 1061], $p=0.75$).

We successfully collected all clinical outcome data for the albumin and placebo groups, including:

- ventilator free days (median [Q1, Q3]): 4.0 days [0.0, 23.5] v. 13.0 days [0.0, 21.0])
- length of ICU stay (median [Q1, Q3]): 18.25 days [11.3, 38.0] v. 16.6 days [11.2, 26.2])
- 30-day mortality (6/24 v. 2/21)

No significant harms were identified by the clinical or research teams. Interruption of study treatment occurred in 8/24 patients receiving albumin, compared to 4/21 patients receiving placebo.

5. Conclusions

The current study design was infeasible with respect to rate of recruitment, timely and complete administration of study treatment, and avoidance of open-label 25% albumin. With modifications to address these challenges, this pilot study can inform the protocol for a successful definitive trial.

Trial Registration:

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