

Commentary

Recently published papers: putting fluids in and taking fluids out

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Abstract

Further work on the use of albumin in the intensive care unit is discussed. The interesting pilot study by Dubois and colleagues examines the potential benefits for albumin supplementation in the hypoalbuminaemic critically ill patient. Maintaining the fluid theme, we discuss recent work on factors influencing post-intensive care unit blood transfusion as well as another study on erythropoietin. Finally, a large multicentred trial comparing continuous venovenous haemofiltration with intermittent haemodialysis is outlined, the results of which pose more questions than answers.

primary endpoint was the effect of albumin administration on the delta Sequential Organ Failure Assessment score from day 1 to day 7. Three hundred millilitres of 20% albumin was given on day 1, followed by 200 ml/day providing the serum albumin remained below 31 g/l. The control group received no albumin.

Interestingly, nearly 2,000 consecutive patients were screened before an adequate cohort was achieved, with almost 50% of patients not being hypoalbuminaemic on admission or during admission. The results, in brief, showed a greater change in Sequential Organ Failure Assessment score between the two groups: 3.1 ± 1.0 in the albumin group compared with 1.4 ± 1.1 in those patients with no albumin administration [1]. The major effects were seen in the cardiovascular, neurological and respiratory components of the Sequential Organ Failure Assessment score. Secondary end points included a similar mortality, length of stay and diuretic use. Potential benefits, however, were seen in those patients receiving albumin; for example, the mean daily caloric intake was higher and the mean daily volume intake was lower – both variables associated with improved outcome.

Men worry over the great number of diseases, while doctors worry over the scarcity of effective remedies.

Pien Chi'ao, Chinese physician ca. 500 BC

A recurring theme in treating the critically ill, and indeed in all of medicine, is the search for evidence-based practice. As we all know, however, application of such principles is somewhat curtailed by the paucity of data even when considering aspects of treatment that to the ill-informed would seem fundamental.

So where does this study lead us in the quest for an evidence base? We know albumin is 'safe' [2] but we do not know whether its usage confers an additional benefit in our critically ill patients, and in fairness the authors do not make any extravagant claims. Dubois and colleagues [1] point out that this is a pilot study and will hopefully pave the way for further work that will aid our future decision-making.

The study by Dubois and colleagues in *Critical Care Medicine* addresses a fundamental question: the use of albumin in the critically ill [1]. One may think this is yet another study adding to the confusion regarding the use of albumin when compared with other colloids as resuscitative fluids. But no, this prospective, randomised controlled study on 100 patients in a mixed intensive care unit (ICU) setting crudely examined the effect of albumin on organ function in hypoalbuminaemic patients. All adult patients with serum albumin <30 g/l were eligible provided that they had an expected length of stay >72 hours, a life expectancy >3 months, needed full active treatment and had not undergone albumin administration in the previous 24 hours. Those patients with volume overload were excluded. The

Another intravenous treatment that has sparked much debate over the past few years is that of red blood cell transfusion. Anaemia is common in the critically ill, with between 40% and 45% of our patients receiving at least one red blood cell transfusion [3,4]. A recent prospective study reported in this journal demonstrated that up to 11% of

ICU = intensive care unit; IHD = intermittent haemodialysis.

survivors from the ICU required red blood cell transfusion within 7 days of ICU discharge, in keeping with other studies [5]. Unsurprisingly, associated factors for the need for transfusion included the haemoglobin level at discharge, sepsis and unresolved organ failure.

There are potential negative outcomes associated with repeated blood transfusion in the critically ill patient, and an alternative approach is the use of erythropoietin. A recent study in *Critical Care Medicine* examined the use of recombinant erythropoietin in patients in post-ICU long-term acute care to assess the impact on the need for transfusion [6]. A total of 84 patients in two centres were randomised to treatment or to placebo in a double-blind trial for a period of 12 weeks, or until death/discharge. The transfusion threshold was a haematocrit level less than 24% together with the clinician's discretion. Patient groups were well matched, including biochemical parameters such as iron stores and serum creatinine (although the starting haemoglobin level was higher in the treatment group). The primary end point was the number of red cell units transfused. At 40 days there was a significant reduction in the number of units transfused between the groups ($P < 0.006$); at 84 days the reduction was still evident but less marked ($P < 0.05$), reflecting the increased use of red cells in the initial study period.

Beyond this it is difficult to draw too much more from the paper by Silver and colleagues. The authors themselves concede that there are several flaws in the study. The patient numbers were small with a relatively short follow-up period, and also the study was powered for the primary endpoint with 86 participants; however, there were 23 patients who were withdrawn from the study. Analysis was on an intention-to-treat basis, but there appears to be a degree of post-hoc analysis in an attempt to add strength to the conclusions provided; examining mortality/morbidity, the effect on mechanical ventilation and the length of stay in hospital revealed no significant differences between the actively treated and placebo groups. As clinicians we require robust data that we can then apply to our daily practice, and it is difficult to take a message from this study that supports any such change. As concluded by Silver and colleagues, larger studies are required to take the investigation of the use of recombinant erythropoietin forward in this patient population. Clinical studies with a more robust design are required to investigate safety, efficacy, and potential economic advantages.

One area of critical care management that continually provokes debate is the modality of choice for the treatment of acute renal failure in the setting of the ICU. The study by Vinsonneau and colleagues appears at first glance to answer this burning question; but although the title promises much, one is left a little dissatisfied [7]. This was a large, prospective, randomised multicentre study in 21 ICUs over a 3.5-year period, and the organisation involved was impressive. The primary end point was the 60-day mortality following

the randomisation of 360 patients to either continuous venovenous haemodiafiltration or intermittent haemodialysis (IHD) in centres familiar with both techniques. As with all studies on acute renal failure, the eligibility criteria suffer from a lack of consensus with regard to a definition for acute renal failure. This is exemplified by the need to change the criteria for entry into this study after 8 months due to the inclusion rate being too low.

So what conclusions can be drawn from this study? Vinsonneau and colleagues fail to demonstrate any differences in 60-day mortality between the two groups and conclude that all patients with acute renal failure as part of multiple-organ dysfunction syndrome can be treated with intermittent haemodialysis [7]. But can these conclusions really be drawn? A problem when comparing any two treatments is ensuring both adequate and comparative dosing regimens, and herein lies a major flaw in this study. The study started more than 7 years ago, during which time the practices in both continuous venovenous haemodiafiltration and IHD have changed considerably [8,9]. As conceded by Vinsonneau and colleagues, this may have led to changes in investigator practices during the study period, particularly with respect to the delivered dose of renal support. This possibility, however, is hard to ascertain given that the dialysis dose in the IHD group is not stated. Interestingly the mortality decreased in the IHD arm of the study over the time of recruitment, which reflected a change in practice towards an increase in dialysis prescription. Given the lack of control regarding the dosage in both arms of the study, definitive conclusions are hard to make regarding treatment. Furthermore, doubts exist regarding the statistical power of the study – a point raised in the excellent accompanying clinical comment, which concludes that whether IHD is as good as or even better than continuous renal replacement therapy cannot be answered by this study [10].

The debate surrounding the use of albumin in the critically ill will continue to run until a well-designed, adequately powered study to definitively answer this question is undertaken. This study would need strict adherence to the delivered dose, would need to assess the timing of initiation of treatment (perhaps employing the Risk, Injury, Failure, Loss and End-stage Kidney Classification: RIFLE criteria) and should examine more secondary endpoints. So what is the answer? Perhaps the best practice is to offer the patient the technique with which the unit is most familiar until we have a definitive answer.

Competing interests

The authors declare that they have no competing interests.

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