Intensive Care Med (2013) 39:782–783
DOI 10.1007/s00134-013-2854-7

EDITORIAL

Anders Perner
Konrad Reinhart

Evidence-based fluid therapy

Received: 22 January 2013
Accepted: 23 January 2013
Published online: 14 February 2013

This editorial refers to the article available at: doi:10.1007/s00134-013-2840-0.

A. Perner (✉)
Department of Intensive Care 4131,
Copenhagen University Hospital, Rigshospitalet,
Blegdamsvej 9, 2100 Copenhagen, Denmark
e-mail: anders.perner@rh.regionh.dk
Tel.: +45-3545-8333

K. Reinhart
Department for Anaesthesiology and Intensive Care Medicine,
Jena University Hospital, Friedrich-Schiller University,
Jena, Germany

Fluid therapy is one of the most frequent interventions given to hospitalised patients, and one-third of all patients in intensive care units (ICUs) worldwide receive fluid for resuscitation each day [1]. As these patients have considerable mortality rates, any differences in outcome between different types of fluids will have a marked effect on the overall mortality of critically ill patients. Appropriate fluid therapy is therefore likely to improve global health.

For decades this has been one side of a difficult dilemma faced by clinicians, guideline committee members and regulatory authorities. The other grim side was the lack of high-quality data to support the choice of fluid therapy for resuscitation. In the recent ESICM task force guideline on colloid therapy, seven out of the nine recommendations were based on low quality of evidence and none were based on high quality of evidence [2]. Now this is changing through the publication in 2012 of several randomised trials on fluid therapy [3–5]. Following the well-established track of evidence-based medicine, these trial data are now being added to the cumulated evidence in updated meta-analyses on fluid therapy.

In the current issue of *Intensive Care Medicine*, David Gattas and colleagues present the results of their systematic review and meta-analysis on behalf of the CHEST trial management committee [6]. They have aggregated the data of 35 trials assessing the effect of 6 % hydroxyethyl starch (HES) with molecular weight of 130 and substitution ratio of approximately 0.4 for resuscitation in more than 10,000 acutely ill adults. This is highly relevant, because HES was the most frequently used colloid solution in the latest assessment of fluid resuscitation in ICUs worldwide [1] and 6 % HES130 has for years been the preferred HES solution [7]. The results of the meta-analysis are convincing, as the heterogeneity of the included trial data was low, high numbers of events were analysed for the main outcomes and the trials contributing with most events had crystalloid as comparator and low risk of bias [4, 5]. Therefore, the results should, together with those from the recent large trials on 6 % HES130 [4, 5], inform clinicians, guideline committees and regulatory authorities.

So what did Gattas and colleagues' meta-analysis on 6 % HES130 [1] show? In acutely ill surgical and intensive care patients, fluid resuscitation with 6 % HES130 increased the use of renal replacement therapy [relative risk (RR) in the 6 % HES130 group 1.25, 95 % confidence interval (CI) 1.08–1.44] and mortality (RR 1.08, 95 % CI 1.00–1.17) compared with other fluid solutions. As can be seen, the latter was borderline significant with the lower range of the 95 % CI touching the no-difference point. There are limitations to the systematic review, as the authors did not adhere to all the recommendations from the Cochrane Collaboration. Thus the protocol was not pre-published, only trials that reported specific outcomes were included, authors were not contacted to try and obtain unpublished data and not all patient-relevant outcomes were assessed (e.g. pruritus). In addition, the

mortality data may have been skewed by the inclusion of trials with short follow-up time, which may not capture delayed harm induced by HES. The trials on HES using follow-up beyond 28 days have shown either statistically significant increased mortality with HES [4] or point estimates trending towards increased mortality [3, 5, 8–11]. The reporting in the included trials of data on transfusion and bleeding differed so much that meta-analyses of these data were deemed inappropriate.

Appropriately, the authors' conclusions were conservative. Clinicians, on the other hand, may not have to be as conservative, because they should give the fluid that is likely to benefit their patients. Presently there are no data from high-quality trials showing that 6 % HES130 improves any patient-important outcome, and there are clear signals of harm. In addition, the cost of 6 % HES130 is several times higher than that of crystalloid solutions. Subsequent analyses and trial data may inform us if there are subgroups of patients who may have net benefit from resuscitation with 6 % HES130. Until then, we should rely on the results of the meta-analysis by Gattas et al. [6] and those of the recent large trials [4, 5] and avoid 6 % HES130 in critically ill patients.

Conflicts of interest Anders Perner was the sponsor-investigator of the 6S-trial, which was supported by B Braun Medical, and has received speaker's fee from LFB S.A. The Department of Intensive Care, Rigshospitalet receives support for research from Fresenius Kabi and Bioporto A/S. Konrad Reinhart was the sponsor-investigator of the VISEP trial, which was supported by B Braun Medical.

References

1. Finfer S, Liu B, Taylor C, Bellomo R, Billot L, Cook D, Du B, McArthur C, Myburgh J (2010) Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. Crit Care 14:R185
2. Reinhart K, Perner A, Sprung CL, Jaeschke R, Schortgen F, Johan Groeneveld AB, Beale R, Hartog CS (2012) Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. Intensive Care Med 38:368–383
3. Guidet B, Martinet O, Boulain T, Philippart F, Poussel JF, Maizel J, Forceville X, Feissel M, Hasselmann M, Heininger A, Van Aken H (2012) Assessment of hemodynamic efficacy and safety of 6% hydroxyethyl starch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: the CRYSTMAS study. Crit Care 16:R94
4. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Aneman A, Madsen KR, Moller MH, Elkjaer JM, Poulsen LM, Bendtsen A, Winding R, Steensen M, Berezowicz P, Soe-Jensen P, Bestle M, Strand K, Wiis J, White JO, Thornberg KJ, Quist L, Nielsen J, Andersen LH, Holst LB, Thormar K, Kjaeldgaard AL, Fabritius ML, Mondrup F, Pott FC, Moller TP, Winkel P, Wetterslev J (2012) Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 367:124–134
5. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, McGuinness S, Rajbhandari D, Taylor CB, Webb SA (2012) Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 367:1901–1911
6. Gattas JD, Dan A, Myburgh J, Billot L, Lo S, Finfer S, CHEST Management Committee (2013) Fluid resuscitation with 6% hydroxyethyl starch (130/0.4 and 130/0.42) in acutely ill patients: systematic review of effects on mortality and treatment with renal replacement therapy. Intensive Care Med. doi:10.1007/s00134-013-2840-0
7. FLUIDS study investigators for the Scandinavian Critical Care Trials Group (2008) Preference for colloid use in Scandinavian intensive care units. Acta Anaesthesiol Scand 52:750–758
8. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehntopf M, Hartog C, Natanson C, Loeffler M, Reinhart K (2008) Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 358:125–139
9. James MF, Michell WL, Joubert IA, Nicol AJ, Navsaria PH, Gillespie RS (2011) Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: the FIRST trial (Fluids in Resuscitation of Severe Trauma). Br J Anaesth 107:693–702
10. James MFM, Michell WL, Joubert IA, Nicol AJ, Navsaria PH, Gillespie RS (2012) Reply from the authors. Br J Anaesth 108:160–161
11. Feldheiser A, Pavlova V, Bonomo T, Jones A, Fotopoulou C, Sehouli J, Wernecke KD, Spies C (2013) Balanced crystalloid compared with balanced colloid solution using a goal-directed haemodynamic algorithm. Br J Anaesth 110:231–240