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Hydroxyethyl starch 130/0.42 for bolus resuscitation in severe sepsis: long-term follow-up, confidence intervals and clinically important differences in outcomes

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In this issue of *Intensive Care Medicine*, Perner et al. [1] present the results of a pre-planned analysis of long-term mortality for patients enrolled into the 6S trial [2]. What is truly impressive about this follow-up study is that vital status was available for 100 % of eligible patients. This was made possible by linking unique personal identification numbers with the Scandinavian cause of death registry [3]. The nationwide population-based Scandinavian registries are impressive and accurate resources available to all medical researchers.

The importance of longer follow-up periods for clinical trials conducted in general critically ill patients has been emphasized by recent key publications. For example, the 6,104 patient NICE-SUGAR trial demonstrated that 28-day mortality may not be sufficient to detect important mortality effects that only become significant with longer (90-day) follow-up [4]. Furthermore, landmark cohort studies have demonstrated that substantial impairments in physical function and health-related quality of life persist for 2–5 years after mechanical ventilation for acute lung

injury [5, 6]. On the basis of these studies, and others, we strongly recommend longer follow-up for all critically ill patients enrolled in clinical trials. For this to occur, funding agencies must recognise the importance of long-term follow-up and fund it. So, what additional information does long-term follow-up add to the primary results of the 6S trial?

The authors report that differences in mortality between groups were not statistically significant at 6 months, 1 year, or longer. However even in the context of these non-significant findings, the interpretation of the 95 % confidence intervals (95 % CI) around the estimates of treatment effect on long-term mortality can inform practice [7, 8].

At the end of the “Conclusion” of the “Abstract”, the authors highlight the 95 % CI around the estimate of mortality at 1 year; however, this treatment effect is reported using the relative risk metric. Relative risk is difficult to interpret clinically, with objective studies demonstrating that the accuracy of decisions is improved when absolute risk differences are presented [9, 10]. To aid interpretation, we have therefore recalculated the treatment effects as risk differences with exact 95 % CIs using SAS version 9.2 (SAS Institute, Cary, NC, USA).

At 6-month follow-up, the difference in mortality between patients receiving hydroxyethyl starch 130/0.42 (HES 130/0.42) compared to patients receiving Ringer’s acetate was 5.8 % (53.3 – 47.5 %) with exact 95 % CI – 1.3 to 12.8 %. The difference at 1 year was 4.5 % (56.0 – 51.5 %) with exact 95 % CI – 2.5 to 11.5 %. The lower 95 % CI at 6 months rules out any benefit greater than 1.3 % reduced mortality in favour of HES 130/0.42 whilst the lower 95 % CI at 1 year rules out any benefit greater than 2.5 % in favour of HES 130/0.42. At least two previously published clinical trials conducted in critically ill patients provide us with the context for the interpretation of the magnitude of these lower 95 % CIs.

Fig. 1 Mortality and 95 % confidence intervals rule out clinically important effects. *6S trial* Scandinavian starch for severe sepsis/septic shock trial, *TRICC* transfusion requirements in critical care trial, *SAFE* saline vs albumin fluid evaluation study; negative (<0) risk difference favours HES 130/0.42 in the 6S trial, liberal transfusion in the TRICC trial, or albumin in the SAFE study; positive (>0) risk difference favours Ringer's acetate in the 6S trial, restrictive transfusion in the TRICC trial or saline in the SAFE study; Blue stippled zone no clinically important mortality effect. Defined using the SAFE study equivalency sample size estimate: 90 % power to detect a 3 % absolute risk difference

First, let us consider the transfusion requirements in critical care (TRICC) trial, which recruited 838 critically ill patients and compared standard care liberal red blood cell transfusion thresholds with a novel more restrictive transfusion threshold [11]. Although the effect of a liberal vs. restrictive transfusion threshold did not have a statistically significant effect on mortality, the results of the TRICC trial led to significant practice change around the world towards adopting a restrictive transfusion threshold policy. The TRICC trial reported differences in mortality rates at various follow-up times: at 30 days, there was a

4.7 % mortality difference (95 % CI -0.84 to 10.2 %) and at 60 days, there was a 3.7 % mortality difference (95 % CI -2.1 to 9.5 %) between groups. The lower 95 % CI at 30 days ruled out a mortality benefit greater than 0.84 % attributable to liberal transfusion whilst the lower 95 % CI at 60 days ruled out any mortality benefit greater than 2.1 % attributable to liberal transfusion.

Next, let us look at the 7,000-patient saline vs. albumin fluid evaluation (SAFE) study [12]. Although there were no statistically significant differences in mortality, the SAFE study concluded “4 percent albumin or normal saline for intravascular volume resuscitation in a heterogeneous population of patients in the ICU resulted in equivalent rates of death from any cause during the 28-day study period.” To support this claim of equivalency, the authors reported that the difference in mortality at day 28 was -0.21 %, with 95 % CI -2.1 to 1.8 %. These 95 % CIs rule out any mortality benefit greater than 2.1 % attributable to albumin and also rule out any mortality benefit greater than 1.8 % attributable to saline.

The TRICC trial and the SAFE study did not support clinical decisions because they found statistically significant differences in mortality attributable to a treatment under study. They were able to inform clinical decision-making because their estimates of treatment effects were precise enough to rule out any clinically important differences in mortality [13]. Interpreted in the context of significant excess mortality attributable to HES 130/0.42 at 90-day follow-up [2], the lower 95 % CIs around the differences in mortality at 6 months and 1 year help rule out any clinically important mortality benefits attributable to HES 130/0.42 used as a bolus resuscitation fluid in patients with severe sepsis. Furthermore, the upper 95 % CIs are consistent with a clinically important mortality benefit attributable to Ringer's acetate (Fig. 1).

In summary, the 6S trial follow-up study is well conducted, with long-term outcomes reported for 100 % of eligible patients. It provides useful information that can support clinical decision-making. The lower 95 % CIs around the absolute risk differences between groups, interpreted in the context of other major clinical trials, help to rule out any clinically important mortality benefit attributable to HES 130/0.42 in severe sepsis.

Conflicts of interest Neither author has any relevant commercial conflicts.

References

1. Perner A, Haase N, Winkel P et al (2014) Long-term outcomes in patients with severe sepsis randomised to resuscitation with hydroxyethyl starch 130/0.42 or Ringer's acetate. *Intensive Care*. doi:10.1007/s00134-014-3311-y
2. Perner A, Haase N, Guttormsen AB et al (2012) Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 367(2):124–134
3. Sokka T (2004) National databases and rheumatology research I: longitudinal databases in Scandinavia. *Rheum Dis Clin North Am* 30(4):851–867

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4. Finfer S, Chittock DR, Su SY et al (2009) Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 360(13):1283–1297
 5. Fan E, Dowdy DW, Colantuoni E et al (2014) Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. *Crit Care Med* 42(4):849–859
 6. Herridge MS, Tansey CM, Matte A et al (2011) Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 364(14):1293–1304
 7. Walters SJ (2009) Consultants' forum: should post hoc sample size calculations be done? *Pharm Stat* 8(2):163–169
 8. Montori VM, Kleinbart J, Newman TB et al (2004) Tips for learners of evidence-based medicine: 2. Measures of precision (confidence intervals). *CMAJ* 171(6):611–615
 9. Gigerenzer G, Wegwarth O, Feufel M (2010) Misleading communication of risk. *BMJ* 341:c4830
 10. Covey J (2011) The effects of absolute risks, relative risks, frequencies, and probabilities on decision quality. *J Health Commun* 16(7):788–801
 11. Hebert PC, Wells G, Blajchman MA et al (1999) A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion requirements in critical care investigators, Canadian Critical Care Trials Group. *N Engl J Med* 340(6):409–417
 12. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R (2004) A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 350(22):2247–2256
 13. Jaeschke R, Singer J, Guyatt GH (1989) Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials* 10(4):407–415