

# Should clinical studies guide clinical practice?

Christiane Hartog

Department for Anaesthesiology and Intensive Care Medicine Integrated Research and Treatment Centre, Centre for Sepsis Control and Care (CSCC), Jena University Hospital, Germany

Among the time-honoured standards which guide medical practice, I believe one of the most important is “first do no harm”. Every decision affecting patient management should thus be judged on the basis of the ratio of likely risks to benefits [1]. Ideally, decisions based on the best evidence should lead us to judge accordingly, in the best interest of the patient. Therefore, the randomised trial, and especially the systematic review of several randomised trials, is much more likely to inform us and much less likely to mislead us, than personal experience or expert opinion, and therefore has become the “gold standard” of clinical evidence [2].

Synthetic colloids – hydroxyethyl starch (HES), gelatin, and dextran – were developed between 1944 and 1962 [3] and have since been used to treat or prevent hypovolemia in billions of patients. However, drugs or fluids developed before the 1980’s were simply registered because government had no authority to require a manufacturer to meet meaningful efficacy standards or demonstrate that a new product had a reasonable benefit–risk relationship [4]. Legislation was changed only in the wake of the thalidomide disaster, leading to the regulatory requirement of phase 1–3 clinical trials to demonstrate efficacy and safety prior to the approval of new drugs [5].

Synthetic colloids, therefore, were never properly evaluated in large-scale clinical trials designed and powered for outcomes of interest such as long-term mortality (i.e., survival after 1 or 3 months) and morbidity (i.e., development of organ dysfunction or serious adverse effects) and compared to standard fluids, such as crystalloids. Despite decades of usage, the evidence base for these products is scarce [6–9].

Albumin is a notable exception. After a meta-analysis drawing on a multitude of small-scale clinical trials identified a 6% increase in mortality from albumin [10], the Australian and New Zealand Critical Care Trials Group ANZICS conducted a large randomised blinded pragmatic trial with 7000 intensive care patients, to compare albumin with normal saline, designed to detect a 3% mortality difference [11]. Surprisingly, there was no difference in either 28-day mortality, organ dysfunction, length of stay or any other measure of morbidity. Normal saline was equally effective and as safe as albumin to treat hypovolemia in the critically ill. Moreover, fluid ratios between the colloid and

the crystalloid groups was only 1.4 to 1 – contradicting textbook knowledge based on medical theory according to which fourfold or even higher amounts of crystalloids should be used to replace colloids [12]. The SAFE trial was notable not only because of these results, but also because it was the first ever adequate fluid resuscitation trial in the field.

In this issue, Wiedermann and Joannides [13] provide an updated meta-analysis in order to answer the open question of whether fluid therapy with HES 130/0.4, a modern HES preparation supposedly without major harm, is safe. With this analysis, they intend to account for limitations of published trials on fluid therapy which are mainly small, short-term studies not powered for clinically relevant outcomes and mostly inadequate comparators [7]. The primary outcome of their analysis was mortality. Their systematic search for clinical trials with HES 130/0.4 in comparison to other fluids identified 13 studies with 1,131 participants. The pooled relative risk for mortality showed a trend not in favour of HES 130/0.4. However, comparator fluids included not only albumin and crystalloids, but also other synthetic colloids like gelatins or HES 200/0.5 which may have reduced the observable effect.

Wiedermann and Joannides also discuss publication bias, which is pervading and widespread, seriously compromising the integrity of the current scientific database [14]. Non-publication of studies as well as selective reporting of outcomes leads to an overestimation of the efficacy of a given intervention and underestimates its harm [14, 15]. An interesting example of this is provided by two recent trials on HES 130, namely the FIRST and the CRYSTMAS trials. In the FIRST trial which compared HES 130/0.4 with normal saline for resuscitation of trauma patients, mortality data was withheld from the original publication [16]. In a letter responding to correspondence, the authors acknowledged that overall mortality was 21.4% (12/56) in the HES group versus 11.3% (6/53) in the saline group, an absolute mortality difference of 10% [17].

In the CRYSTMAS trial by Guidet et al., HES 130/0.4 or saline was used for fluid therapy of patients with severe sepsis [18]. Results showed a doubling of the number of patients undergoing RRT in the HES 130/0.4 arm and more than doubling of the mean duration of RRT (9.1 days vs. 4.3 days) [19]; the Kaplan-Meier curves for time to RRT

showed a trend against HES ( $p = 0.06$ , fig.1 [19]). Serious adverse events (SAEs) and SAEs leading to death numbered 53 versus 44 and 38 versus 32, respectively (HES vs. saline [19]). These outcomes were not published in the journal article.

Both study publications draw positive conclusions about the efficacy or safety of HES 130/0.4. Both studies were funded by a HES manufacturer. Research funded by drug companies is less likely to be published than research funded by other sources, and studies sponsored by pharmaceutical companies are more likely to have outcomes which are favourable for the sponsor's drug [20].

Therefore, critical appraisals by independent groups such as the meta-analysis by Wiedermann [13] are necessary. The concern that this analysis raised – namely a trend towards higher mortality after HES – is fully supported by the findings of the first HES 130/0.4 trial powered for survival in 800 sepsis patients which became public after the submission of the Wiedermann manuscript. The Scandinavian Critical Care Trials Group performed a multicenter blinded randomised trial to compare the effect of HES 130/0.4 with Ringer's Acetate on outcome. They found that at 90 days after randomisation, 201 of 398 patients (51%) assigned to HES 130/0.4 had died, compared with 172 of 400 patients (43%) assigned to Ringer's acetate (relative risk, 1.17; 95% confidence interval [CI], 1.01 to 1.36;  $p = 0.03$ ); one patient in each group had end-stage kidney failure. In the 90-day period, 87 patients (22%) assigned to HES 130/0.4 were treated with renal-replacement therapy versus 65 patients (16%) assigned to Ringer's acetate (relative risk, 1.35; 95% CI, 1.01 to 1.80;  $p = 0.04$ ), and 38 patients (10%) and 25 patients (6%), respectively, had severe bleeding (relative risk, 1.52; 95% CI, 0.94 to 2.48;  $p = 0.09$ ) [21]. The ANZICS group is currently conducting another large-scale randomised blinded fluid trial, where HES 130/0.4 is compared with normal saline in 7,000 intensive care patients [22] and results are expected to become public later this year.

Given the lack of benefit and the safety risks, how did HES 130/0.4 become one of the preferred plasma expanders worldwide [23–26]? A partial explanation may be that clinicians like to read reviews, but may not be aware that reviews can be part of marketing efforts. A systematic review on HES reviews found that positive HES reviews far outnumbered critical reviews and were mostly written by a select group of authors with potential conflicts of interest with HES manufacturers [27].

What can we learn from the HES story? Many of the clinical therapies we are accustomed to have not yet been put to the test, and neither the inclination nor the funding will be generally available to revisit accepted dogma [1]. The lesson from the HES story is that more adequately designed clinical studies are needed with full disclosure of their outcomes.

**Funding / potential competing interests:** The CSCC is supported by the Federal Ministry of Education and Research (BMBF), Germany, FKZ: 01EO1002. No other potential conflict of interest relevant to this article was reported.

**Correspondence:** Christiane Hartog, MD, Department for Anesthesiology and Intensive Care Medicine Integrated Research and Treatment Center, Center for Sepsis Control and Care (CSCC), Jena University Hospital, DE-07747 Jena, Germany, [christiane.hartog\[at\]med.uni-jena.de](mailto:christiane.hartog[at]med.uni-jena.de)

## References

- Singer M, Glynne P. Treating critical illness: the importance of first doing no harm. *PLoS Med.* 2005;2(6):p.e167.
- Sackett DL, et al. Evidence based medicine: what it is and what it isn't. *BMJ.* 1996;312(7023):p.71–2.
- Nitsch E. [Volume replacement with artificial colloids]. *Anesthesiol Intensivmed Notfallmed Schmerzther.* 1998;33(4):255–60.
- Avorn J. Learning about the safety of drugs—a half-century of evolution. *N Engl J Med.* 2011;365(23):2151–3.
- Maio G. [On the history of the Contergan (thalidomide) catastrophe in the light of drug legislation]. *Dtsch Med Wochenschr.* 2001;126(42):1183–6.
- Thomas-Rueddel DO, et al. Safety of gelatin for volume resuscitation—a systematic review and meta-analysis. *Intensive Care Med.* [Epub ahead of print], 2012.
- Hartog CS, Kohl M, Reinhart K. A systematic review of third-generation hydroxyethyl starch (HES 130/0.4) in resuscitation: safety not adequately addressed. *Anesth Analg.* 2011;112(3):635–45.
- Perel P, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev.* 2011.3:CD000567.
- Bunn F, Trivedi D, Ashraf S. Colloid solutions for fluid resuscitation. *Cochrane Database Syst Rev.* 2011.3:CD001319.
- Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *Cochrane Injuries Group Albumin Reviewers.* *BMJ.* 1998;317(7153):235–40.
- Finfer S, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med.* 2004;350(22):2247–56.
- Puyana JC. Resuscitation of hypovolemic shock. In: M. Fink, et al. Editors. *Textbook of critical care.* Elsevier Saunders: Philadelphia. 2005;1939–40.
- Wiedermann CJ, Joannidis M. Mortality after hydroxyethyl starch 130/0.4 infusion: an updated meta-analysis of randomized trials. *Swiss Med Wkly.* 2012;142:w13656.
- McGauran N, et al. Reporting bias in medical research – a narrative review. *Trials.* 2012;11:37.
- Jefferson T, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. *Cochrane Database Syst Rev.* 2012;(2):CD001265.
- James MF, et al. 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.* 2011;107(5):693–702.
- James MFM, et al. Re:Hydroxy ethyl starch in patients with trauma, author's reply. *Br J Anaesth.* 2011;DOI: [http://bja.oxfordjournals.org/content/107/5/693.long/reply#brjana\\_el\\_7942](http://bja.oxfordjournals.org/content/107/5/693.long/reply#brjana_el_7942).
- Guidet B, et al. Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 versus 0.9% NaCl fluid replacement in patients with severe sepsis: The CRYSTMAS study. *Critical Care.* 2012;16(3):R94.
- Package insert Voluven. Vaccines, blood & biologics 2012 [cited 2012 7th May]. Available from: <http://www.fda.gov/downloads/BiologicsBloodVaccines/>.
- Lexchin J, et al. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ.* 2003;326(7400):1167–70.
- Perner A, et al. Hydroxyethyl Starch 130/0.4 versus Ringer's acetate in severe sepsis. *N Engl J Med.* 2012;367(2):124–34.
- Myburgh J, et al. Statistical analysis plan for the Crystalloid Versus Hydroxyethyl Starch Trial (CHEST). *Critical care and resuscitation. Journal of the Australasian Academy of Critical Care Medicine.* 2012;14(1):44–52.

- 23 Schortgen F. et al. The risk associated with hyperoncotic colloids in patients with shock. *Intensive Care Med.* 2008;34(12):2157–68.
- 24 Liu FC, et al. Hydroxyethyl starch interferes with human blood ex vivo coagulation, platelet function and sedimentation. *Acta Anaesthesiol Taiwan.* 2009;47(2):71–8.
- 25 Basora M, et al. [Perioperative colloid administration: a survey of Spanish anesthesiologists' attitudes]. *Rev Esp Anestesiol Reanim.* 2007;54(3):162–8.
- 26 Preferences for colloid use in Scandinavian intensive care units. *Acta Anaesthesiol Scand.* 2008;52(6):p.750–8.
- 27 Hartog CS. et al. Systematic analysis of hydroxyethyl starch (HES) reviews: proliferation of low-quality reviews overwhelms the results of well-performed meta-analyses. *Intensive Care Med.* 2012;38(8):1258–71.