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New insights into fluid resuscitation

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Abstract Recent high-quality randomised-controlled trials comparing the effects of hydroxyethyl starch (HES) preparations and crystalloids for fluid resuscitation in critically ill patients have demonstrated an increased risk of death and use of renal replacement therapy (RRT). Consequently, a number of systematic reviews incorporating these new results have been published that have consistently demonstrated an increased risk of death and use of RRT associated with HES solutions, regardless of type of HES and dose administered, both in general intensive care patients and in those with severe sepsis. These effects become apparent in the post-resuscitation period and may relate to increased tissue accumulation associated with HES. These results question the clinical role of semi-synthetic colloids for fluid resuscitation and mandate a reappraisal about how these fluids are administered to critically ill patients, specifically considering the potential for toxicity.

Keywords Fluid resuscitation · Semi-synthetic colloids · Hydroxyethyl starch · Nephrotoxicity · Sepsis · Septic shock

Over the last 12 months, a number of high-quality randomized controlled trials (RCTs) addressing the safety and efficacy of currently used hydroxyethyl starch (HES) fluids—6 % HES (130/0.4–0.42) or tetrastarches—for resuscitation of critically ill patients have been published [1–3]. These RCTs include the Crystalloid vs. Hydroxyethyl Starch Trial (CHEST) [1] and the Scandinavian Starch for Severe Sepsis/Septic Shock study (6S) [2] that demonstrated that resuscitation with 6 % HES preparations was associated with increased 90-day mortality and use of renal replacement therapy (RRT) when compared with crystalloids.

These patient-centred outcomes are highly relevant to clinicians given the uncertainty about the safety of older, high-molecular-weight, highly substituted HES preparations that were associated with increased mortality and acute kidney injury (AKI), particularly in patients with sepsis. In addition, the retraction of a number of publications related to the safety of tetrastarch preparations raised further concerns amongst clinicians.

On the basis of the results of these RCTs, the Surviving Sepsis Campaign guidelines recommended against use of HES for fluid resuscitation of severe sepsis and septic shock for the first time in the latest iteration of guidelines.

A number of systematic reviews have been conducted following the publication of RCTs in 2012. In this issue of *Intensive Care Medicine*, Patel and colleagues [4] report the effects of resuscitation with tetrastarch preparations (both potato or waxy maize derivatives) compared with non-HES fluids in patients with severe sepsis. The primary outcome was 90-day mortality, and requirement for RRT was a tertiary outcome. From 6 studies that included 3,033 patients, tetrastarches were associated with a

Table 1 Summary table of systematic reviews and meta-analyses published in 2013 comparing hydroxyethyl starch preparations (HES) versus other resuscitation fluids in randomized controlled trials that reported mortality and use of renal replacement therapy (RRT) as outcome measures

Systematic review	HES preparation	Comparator	Patient population	Mortality RR (95 % CI)	RRT RR (95 % CI)
Gattas [6]	6 % HES (130/0.4–0.42)	Isotonic saline Hypertonic saline Lactated Ringer's Acetated Ringer's Albumin 4 %, 5 %, 20 % Gelatin 4 % Polygeline 3.4 % Dextran 70 HES (200/0.5) HES (670/0.75)	Acutely ill patients in intensive care, perioperative and operative setting	1.08 (1.00–1.17)	1.25 (1.08–1.44)
Haase [7]	6 % HES (130/0.4–0.42)	Isotonic saline Lactated Ringer's Acetated Ringer's Albumin 20 %	Sepsis/septic shock	1.04 (0.89–1.22)	1.36 (1.08–1.72)
Zarychanski [5]	6–10 % HES (130/0.4–0.42) 6–10 % HES (200/0.43–0.66)	Isotonic saline Hypertonic saline Lactated Ringer's Acetated Ringer's Albumin 4 %, 5 %, 20 % Gelatin 3 %, 4 % Plasma	Critically ill patients in emergency or intensive care setting	1.06 (1.00–1.13)	1.32 (1.15–1.50)
Patel [4]	6 % HES (130/0.4–0.42)	Isotonic saline Acetated Ringer's Albumin 20 %	Severe sepsis	1.13 (1.02–1.25)	1.42 (1.09–1.85)

RR relative risk, *95 % CI* 95 % confidence interval

significant, 13 % relative increase in the risk of death at 90 days and 41 % relative increase in requirement for RRT compared with crystalloids. Three trials published in 2012 were adjudicated to be at low risk of bias and contributed 96 % of the patients [1–3]. A sensitivity analysis limited to the results of these trials produced similar results.

These results are consistent with recent systematic reviews published in 2013 comparing the effects of HES, both low- and high-molecular-weight preparations [5], on patient-centred outcomes versus a range of resuscitation fluids in acutely ill patients [6] and patients with sepsis [7] (Table 1).

From these reviews, it appears that resuscitation with HES is associated with an increased relative risk of death and use of RRT regardless of the type of HES or the patient population.

Before the publication of the above papers, HES was the most commonly prescribed colloid globally, particularly in Europe [8]. It would be expected that the use of HES will decrease, not least in patients with sepsis or at risk of AKI, to accord with the publication of recent high-quality evidence.

Does this new evidence about the use of HES apply to other colloids? Whilst recent trials have demonstrated short-term haemodynamic differences with colloids, the relative volume-sparing effect compared with crystalloids is low [1–3, 9].

Specific patient populations are at increased risk of death when resuscitated with colloids—namely patients with traumatic brain injury and albumin [10]. Whether albumin confers a benefit in sepsis, as suggested in a substudy of the Saline vs. Albumin Evaluation (SAFE) study, remains undetermined [11].

There is no substantive evidence to support the use of other semi-synthetic colloids, such as gelatin, as alternatives to albumin or HES. Recent observational data suggest that gelatin may be associated with development of nephrotoxicity similar to that observed with HES [12].

Whether the impact of these publications will change practice in critically ill patients remains to be seen. Further cross-sectional translational studies, such as that done following the publication of the SAFE study are required [8].

Tetrastarches continue to be widely used in surgical patients undergoing general anaesthesia. In the light of data in critically ill patients, there is an imperative to evaluate their safety and efficacy in large RCTs powered for patient-centred outcomes relevant to perioperative patients.

So, what does this mean for clinicians in 2013? That increased caution about use of colloids, particularly with HES, in critically ill patients is evident. However,

crystalloids as alternative resuscitation fluids do not automatically confer increased safety to our patients.

Resuscitation with normal saline is associated with chloride excess that has been associated with adverse metabolic effects and potential nephrotoxicity [13].

To date, no high-quality RCT has been conducted comparing the effects of saline, the most commonly used crystalloid globally, versus "balanced" salt solutions. This is a further fundamental research question that needs to be addressed.

As the optimal type of resuscitation fluid remains uncertain, more attention needs to be given to the dose and volumes administered.

Fluids accumulate over time. This is associated with development of interstitial oedema and applies to both colloids and crystalloids. There is an increasing body of observational evidence suggesting that excess use of intravenous fluids is associated with adverse outcomes [14]. Accumulation of HES within the reticulo-endothelial system is implicated in adverse events and toxicity.

The role of bolus fluid resuscitation has been questioned following the Fluid Expansion as Supportive Therapy (FEAST) study that demonstrated increased mortality associated with bolus resuscitation with albumin and saline [15]. Whilst the generalizability of these results remains unclear, the principle of questioning the efficacy of bolus resuscitation, in terms of both volume and timing, needs to be carefully considered in all critically ill patients.

Clearly, the time has come to regard resuscitation fluid with the same degree of critical thought as that when administering a potentially toxic drug. The prescription of fluid needs to consider the specific indication: shock versus physiological measurements such as low urine output or central venous pressure; severity, type and source of insult: sepsis versus trauma; the time context in which fluid is administered: fluid resuscitation requirements change markedly over time; the constituents of the fluid: potential impact on metabolic and organ function; the potential for toxicity related to fluid excess and organ dysfunction that develops in the post-resuscitation period.

These considerations will also need to be considered by regulators when new formulations of semi-synthetic or non-physiological fluids are developed, so that efficacy and safety are determined in relevant pre-clinical models followed by high-quality investigator-initiated trials before registration and introduction into the market.

It is likely that this fundamental area of intensive care medicine will remain open to further intense debate and research that will ultimately change clinical practice in the future.

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References

1. 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
2. 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
3. Guidet B, Martinet O, Boulain T, Philippart F, Poussel JF, Maizel J, Forceville X, Feissel M, Hasselmann M, Heininger A, Van AH (2012) Assessment of hemodynamic efficacy and safety of 6 % hydroxyethylstarch 130/0.4 vs. 0.9 % NaCl fluid replacement in patients with severe sepsis: the CRYSTMAS study. Crit Care 16:R94
4. Patel A, Waheed U, Brett S (2013) Randomised trials of 6 % tetrastarch (hydroxyethyl starch 130/0.4 or 0.42) for severe sepsis reporting mortality: systematic review and meta-analysis. Intensive Care Med. doi: 10.1007/s00134-013-2863-6
5. Zarychanski R, AbouSetta AM, Turgeon AF, Houston BL, McIntyre L, Marshall JC, Fergusson DA (2013) Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. JAMA 309:678–688
6. Gattas DJ, Dan A, Myburgh J, Billot L, Lo S, Finfer S (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. Haase N, Perner A, Hennings LI, Siegemund M, Lauridsen B, Wetterslev M, Wetterslev J (2013) Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. BMJ 346:f839
8. 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

9. SAFE Study Investigators (2004) A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 350:2247–2256
10. SAFE Study Investigators (2007) Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med 357:874–884
11. Finfer S, McEvoy S, Bellomo R, McArthur C, Myburgh J, Norton R (2011) Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. Intensive Care Med 37:86–96
12. Bayer O, Reinhart K, Sakr Y, Kabisch B, Kohl M, Riedemann NC, Bauer M, Settmacher U, Hekmat K, Hartog CS (2011) Renal effects of synthetic colloids and crystalloids in patients with severe sepsis: a prospective sequential comparison. Crit Care Med 39:1335–1342
13. Shaw AD, Bagshaw SM, Goldstein SL, Scherer LA, Duan M, Schermer CR, Kellum JA (2012) Major complications, mortality, and resource utilization after open abdominal surgery: 0.9 % saline compared to Plasma-Lyte. Ann Surg 255:821–829
14. Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA (2011) Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. Crit Care Med 39:259–265
15. Maitland K, Kiguli S, Opoka R, Engoru C, Olupot–Olupot P, Akech S, Nyeko R, Mtove G, Reyburn H, Lang T, Brent B, Evans J, Tibenderana J, Crawley H, Russell E, Levin M, Babiker A, Gibb D (2011) Mortality after fluid bolus in African children with shock. N Engl J Med 364:2483–2495