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ORIGINAL

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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

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Abstract *Purpose:* To determine whether fluid resuscitation of acutely ill adults with 6 % hydroxyethyl starch (6 % HES 130) with a molecular weight of 130 kD and a molar substitution ratio of approximately 0.4 (6 % HES 130) compared with other resuscitation fluids results in a difference in the relative risk of death or treatment with renal replacement therapy (RRT). *Methods:* Systematic review and meta-analysis of randomized controlled trials comparing intravascular fluids for resuscitation of hospitalised adults that reported mortality or treatment with RRT. The risk of bias was assessed independently by two reviewers and meta-analysis was performed using random effects. *Results:* Thirty-five trials enrolling 10,391 participants were included. The three largest trials had the lowest risk of bias, were published (or completed) in 2012, and together enrolled 77 % of all participants. Death occurred in 928 of 4,691 patients (19.8 %) in the 6 % HES 130 group versus 871 of 4,720 (18.5 %) in the control fluid groups relative risk (RR) in the 6 % HES 130 group 1.08, 95 % confidence interval (CI) 1.00 to 1.17, $I^2 = 0$ %). Treatment with RRT occurred in 378 of 4,236 patients (8.9 %) in the 6 % HES 130 group versus 306 of 4,260 (7.2 %) in the control fluid group (RR in the 6 % HES 130 group 1.25, 95 % CI 1.08 to 1.44, $I^2 = 0$ %). *Conclusions:* The quality and quantity of data evaluating 6 % hydroxyethyl starch (130/0.4 and 130/0.42) as a resuscitation fluid has increased in the last 12 months. Patients randomly assigned to resuscitation with 6 %HES 130 are at significantly increased risk of being treated with RRT.

Keywords Hetastarch · Colloids · Fluid therapy · Resuscitation · Critical illness

Introduction

Administration of fluid to increase or maintain intravascular volume (resuscitation fluid) is a common intervention in the intensive care unit (ICU). A cross sectional international study reported that over one-third of patients in ICUs receive resuscitation fluid each day. In that study colloids were administered to more patients and during more resuscitation episodes than crystalloids, with hydroxyethyl starch solutions being the most frequently administered colloid solutions [1]. Previous meta-analyses have not suggested that colloids in general offer

significant advantages over crystalloids [2]. Recent guidelines from the European Society of Intensive Care Medicine taskforce on colloid volume therapy in critically ill patients recommended against the use of 6 % HES 130 in patients with severe sepsis or at risk of acute kidney injury [3]. The strength of these recommendations may be limited as previous meta-analyses have relied on the results of trials that were generally poor in quality and which reported few patient-centred outcomes [2–9].

Over the preceding 12 months, a number of randomized controlled trials report the effects of 6 % HES 130 in critically ill patients. As these additional data have the potential to substantially alter the evidence for and against the use of 6 % HES 130 in critically ill patients, we updated a systematic review and meta-analysis incorporating all the available evidence to determine whether fluid resuscitation of acutely ill adults with 6 % HES 130 compared to other resuscitation fluids resulted in a difference in patient-centred outcomes.

The aim of this updated review was to determine if there was a difference in the risk of death and treatment with renal replacement therapy (RRT) in acutely ill adult patients receiving 6 % HES 130 for fluid resuscitation compared with other resuscitation fluids.

Methods

Eligibility criteria and assessment for risk of bias [4]. The protocol for the systematic review, including the inclusion and exclusion criteria, was written before the literature search was conducted. Eligible studies were included if all criteria were met: (1) prospective, randomized controlled trials, (2) patients over 18 years, (3) a hospital or pre-hospital clinical setting, (4) patients who were acutely ill or undergoing major surgery, (5) study fluids were administered for resuscitation (defined as fluid required to increase or maintain intravascular volume), (6) at least one intervention group received 6 % hydroxyethyl starch with a molecular weight of 130 kD and a molar substitution ratio of approximately 0.4 in any carrier solution, (7) at least one intervention group received another colloid or any type of crystalloid solution for resuscitation, (8) the study reported at least one of the following five outcomes: (i) mortality, (ii) treatment with RRT, (iii) urine output, (iv) transfusion of red blood cells (RBCs), (v) estimated or measured blood loss.

Studies were excluded if any of the following characteristics were present: (1) studies enrolling only healthy volunteers or blood donors, (2) administration of fluid solely for the purposes of a planned anesthetic procedure including spinal or epidural anesthesia, acute normovolemic hemodilution, hypervolemic hemodilution or priming of a cardiopulmonary bypass circuit without subsequent intra- or post-operative use, (3) administration of fluid solely for volume therapy (hemodilution) following ischemic stroke or subarachnoid hemorrhage.

Internal validity was evaluated using a tool based on 'yes/no' responses to the following five domains of trial quality: randomization, allocation concealment, blinding, intention-to-treat analysis, and minimal (<10 %) loss to follow-up [10]. Low risk of bias was defined as scoring 'yes' to all five domains. Intermediate risk of bias was defined as scoring 'yes' to four out of five domains. High risk of bias was defined as scoring 'yes' to three or less out of five domains. For randomization, use of term 'randomization' in any form without a clear description of sequence generation was deemed pseudo-randomization and judged 'no' to randomization. Allocation concealment was considered to have been 'yes' if any method for doing so was described. Blinding was assessed in three areas (patient, clinicians, and outcome assessors) and all three elements had to be blinded in order for the trial to be considered blinded overall. Blinding of the fluid alone without any further description was considered to be 'no' to blinding. Intention-to-treat analysis was interpreted strictly, with any patients removed from analysis after randomization and receipt of intervention considered to be 'no' for that trial. Loss to follow-up of <10 % for the primary outcome was considered acceptable.

Search strategy. Five electronic databases were searched on 28 July 2012: Ovid MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), the metaRegister of Controlled Trials (controlled-trials.com), and clinicaltrials.gov. In addition, the reference lists from other published systematic reviews were hand searched for any additional studies that met inclusion criteria. No language restriction was placed on the search. Contact was made with experts in the field for any unpublished trials. The search terms used in MEDLINE, EMBASE and CENTRAL are contained in the "appendix".

Study selection and data extraction. Two reviewers (DG, AD) screened the results of the search independently. Full-text manuscripts of potentially eligible articles were obtained and assessed independently against inclusion and exclusion criteria. The same two authors independently extracted the data and appraised the internal validity of each study. Differences were then compared and resolved by agreement or referral to a third reviewer (JM). The variables pertaining to patients and setting were: total number of patients, number of participating centres, clinical setting and diagnostic group. We collected details regarding mean daily volume of 6 % HES 130.

For the clinical setting, we categorized the data into three groups: peri-operative (defined as fluid used intra-operatively and post-operatively), operative (fluid used intra-operatively only), and ICU (patients admitted to an

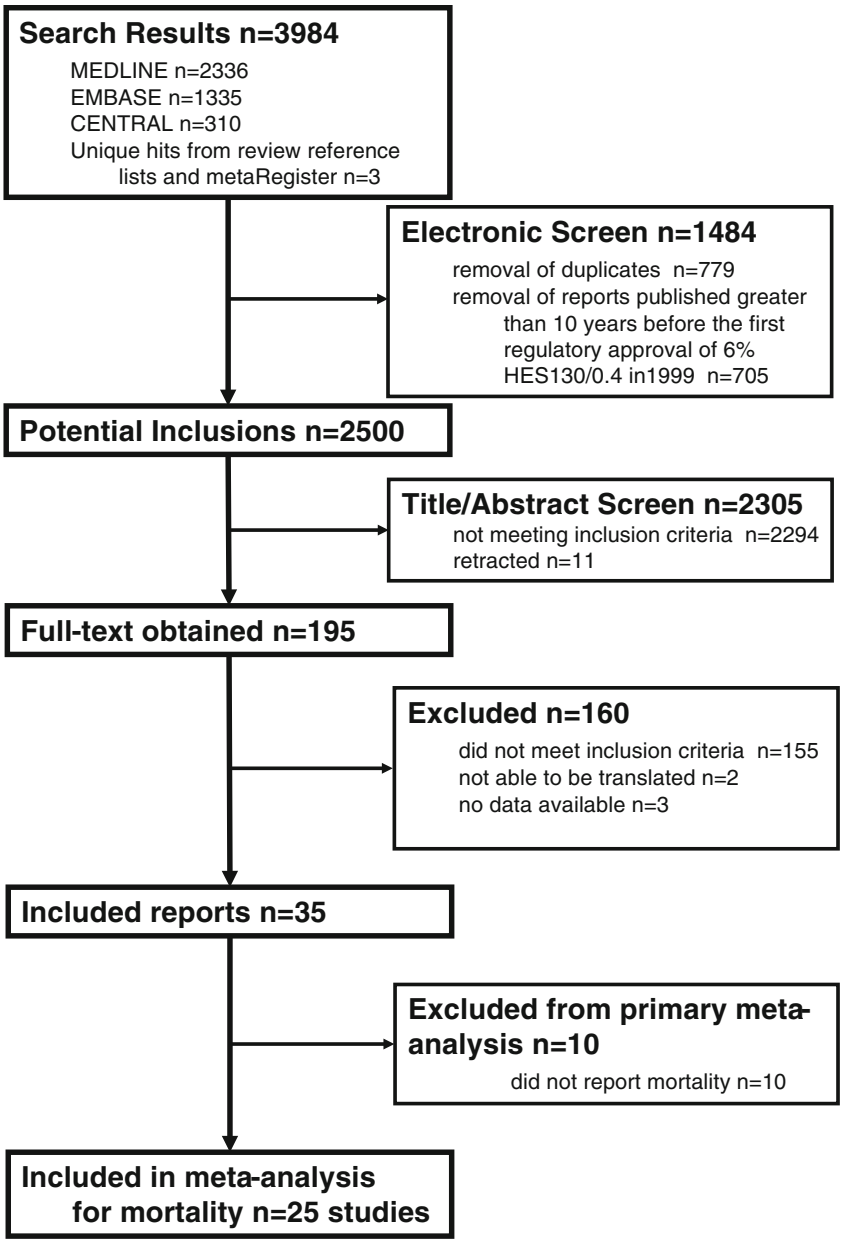

Fig. 1 Study flow diagram

ICU at the time of enrolment for a reason that was not associated with routine post-operative care). For volume of fluid administered, we categorized the data into three groups according to the mean daily volume of exposure to 6 % HES 130 throughout the study period: <1 l, 1–3 l, or >3 l. These groupings were chosen to approximate low (<15 ml/kg), medium (15–40 ml/kg), and higher (>40 ml/kg) dose exposure to 6 % HES 130 for a typical 70 kg individual. All-cause mortality was collected preferentially if reported. When mortality was reported at more than one time point, we used the longest complete follow up time after exposure to study fluids.

Data analysis. The relative risk (RR) and 95 % confidence intervals (CI) of death and treatment with RRT for 6 % HES 130 compared to control group fluid were calculated for each study and then pooled via a meta-analysis with random effects using the metan routine in Stata version 11. I^2 was calculated as a measure of consistency. Trials with no deaths were excluded from the pooled estimate of relative risk. Studies with zero deaths in one group were added to the pooled estimate by adding 0.5 to each cell of the 2-by-2 table [11]. For studies with more than one control group, a single control comparison was selected with preference given to a crystalloid control group, then another class of colloid, and finally another hydroxyethyl starch with a molecular weight >130 kD as comparator. If there was more than one crystalloid control group, these were

Table 1 Characteristics of included studies

Author	Year	N	Number of centres	Population	Diagnostic group	Daily mean 6 % HES 130 (range, litres)	Number of control groups	Control fluid class	Control fluid(s)	Reports mortality	Reports treatment with RRT	Reports urine output	Reports transfusion	Reports bleeding
Compares 6 % HES (130/0.4 or 130/0.42) to at least 1 crystalloid control group														
Myburgh	2012	7,000	32	ICU	General ICU population	<1	1	Crystalloid	Normal saline	Yes	Yes	Yes	Yes	No
Perner	2012	804	26	ICU	Severe sepsis	1–3	1	Crystalloid	Ringer's acetate	Yes	Yes	Yes	Yes	Yes
Siegemund	2012	241	1	ICU	Sepsis	ns	1	Crystalloid	Normal saline	Yes	Yes	ns	ns	No
Gondos	2010	200	11	ICU	Postoperative, hypovolemia	ns	3	2 colloids, crystalloid	4 % gelatin,5 % albumin, Ringer's lactate	Yes	No	No	No	Yes
Guidet	2012	196	24	ICU	Severe sepsis	1–3	1	Crystalloid	Normal saline	Yes	Yes	Yes	Yes	Yes
Zhu	2011	135	1	ICU	Severe sepsis	<1	2	Crystalloid, colloid	7.5 % saline, Ringer's lactate	Yes	No	Yes	No	No
James	2011	115	1	ICU	Trauma	>3	1	Crystalloid	Normal saline	Yes	Yes	Yes	Yes	No
Yang	2011	90	1	Perioperative	Liver surgery	1–3	2	Colloid, crystalloid	20 % albumin, Ringer's lactate	Yes	No	Yes	Yes	Yes
Nagpal	2012	70	1	Operative	Cardiac surgery	1–3	1	Crystalloid	Normal saline	Yes	Yes	Yes	Yes	Yes
Mittermayr	2007	66	1	Perioperative	Orthopaedic surgery	1–3	2	Colloid, crystalloid	4 % gelatin, Ringer's lactate	No	No	No	Yes	Yes
Schramko	2010	45	1	Perioperative	Cardiac surgery	ns	2	Colloid, crystalloid	4 % gelatin, Ringer's acetate	No	No	Yes	Yes	Yes
Lu	2012	42	1	ICU	Sepsis	1–3	1	Crystalloid	Ringer's lactate	Yes	No	Yes	No	No
Volta	2007	36	1	Operative	Abdominal surgery	1–3	2	Colloid, crystalloid	3.4 % polygeline, Ringer's lactate	No	No	Yes	Yes	No
Dubin	2010	25	2	ICU	Septic shock	1–3	1	Crystalloid	Normal saline	Yes	No	Yes	Yes	No
Compares 6 % HES (130/0.4 or 130/0.42) to at least 1 other class of colloid														
Van der Linden	2005	132	1	Perioperative	Cardiac surgery	ns	1	Colloid	3 % gelatin	Yes	No	No	Yes	Yes
Ooi	2009	90	1	Perioperative	Cardiac surgery	1–3	1	Colloid	4 % gelatin	Yes	Yes	No	Yes	Yes
Zdolsek	2011	84	1	Operative	Orthopaedic surgery	1–3	3	HES, colloid	130/0.42/6:1, 200/0.5, Dextran 70	No	No	No	Yes	Yes
Wu	2010	80	1	Operative	Kidney transplant	1–3	1	Colloid	4 % gelatin	No	No	Yes	No	No
Godet	2008	65	7	Perioperative	Vascular surgery, renal impairment	1–3	1	Colloid	3 % gelatin	Yes	Yes	Yes	Yes	No
Mahmood	2007	62	1	Perioperative	Vascular surgery	>3	2	HES, colloid	200/0.62, 4 % gelatin	Yes	Yes	Yes	Yes	Yes
Dolecek	2009	56	1	ICU	Severe sepsis	1–3	1	Colloid	20 % albumin	Yes	No	No	No	No
Schramko	2009	45	1	Perioperative	Cardiac surgery	1–3	2	HES, colloid	200/0.5, 4 % albumin	No	No	Yes	Yes	Yes
Mukhtar	2009	40	1	Perioperative	Liver transplant surgery	>3	1	Colloid	5 % albumin	Yes	Yes	Yes	Yes	Yes
Inal	2010	30	1	ICU	Hypovolemia	<1	1	Colloid	3.5 % gelatin	Yes	No	No	No	No
Palumbo	2006	20	1	ICU	Sepsis	ns	1	Colloid	20 % albumin	No	No	Yes	Yes	No
Compares 6 % HES (130/0.4 or 130/0.42) to other hydroxyethyl starch														
Kasper	2003	120	1	Perioperative	Cardiac surgery	>3	1	HES	200/0.5	Yes	Yes	No	Yes	Yes
Gandhi	2007	100	6	Operative	Orthopaedic surgery	1–3	1	HES	670/0.75	Yes	No	No	Yes	Yes

Table 1 continued

Author	Year	N	Number of centres	Population	Diagnostic group	Daily mean 6 % HES 130 (range, litres)	Number of control groups	Control fluid class	Control fluid(s)	Reports mortality	Reports treatment with RRT	Reports urine output	Reports transfusion	Reports bleeding
Langeron	2001	100	4	Perioperative	Orthopaedic surgery	1–3	1	HES	200/0.5	Yes	No	No	Yes	Yes
Sander	2003	60	1	Perioperative	Gynaecological surgery	1–3	1	HES	200/0.5	Yes	No	No	Yes	Yes
Gallandat Huet	2000	59	2	Perioperative	Cardiac surgery	1–3	1	HES	200/0.5	Yes	No	Yes	Yes	Yes
Jungheinrich	2004	52	1	Perioperative	Orthopaedic surgery	1–3	1	HES	200/0.5	No	No	Yes	Yes	Yes
Mehta	2007	40	1	Perioperative	Cardiac surgery	ns	1	HES	200/0.5	No	No	No	No	Yes
Ellger	2006	40	1	Perioperative	Urological surgery	ns	1	HES	200/0.5	No	No	No	Yes	Yes
Neff	2003	31	1	ICU	Traumatic brain injury	>3	1	HES	200/0.5	Yes	No	Yes	Yes	Yes
Boldt	2000	20	1	Operative	Cardiac surgery	<1	1	HES	200/0.5	Yes	No	Yes	Yes	Yes
		35		Number of included trials					Number of trials reporting	25	11	21	27	23
			9	Number of multicentre trials					Number of events reported	1799	684			
		10,391		Total number of participants in 36 Included trials					Number of cases reported	9411	8496			
									Crude rate	19.1 %	8.1 %			

6 % HES 130 = 6 % hydroxyethyl starch with a molecular weight of 130 kD and a molar substitution ratio of approximately 0.4. Daily Mean 6 % HES 130 is the mean daily dose, categorised into litre ranges

Other (higher molecular weight) forms of hydroxyethyl starch given as control fluids, are defined by xxx/y.y, describing the molecular weight xxx (kDa) and molar substitution y.y. Transfusion = transfusion of red blood cells reported using any measure. Bleeding = estimated or measured blood loss reported using any measure

ICU intensive care unit, *ns* not stated, *RRT* renal replacement therapy

Table 2 Assessment of quality and risk of bias

Author	Year	Randomisation	Allocation concealment	Blinding	Intention to treat analysis	No loss to follow-up
Low risk of bias						
Myburgh	2012	Yes	Yes	Yes	Yes	Yes
Perner	2012	Yes	Yes	Yes	Yes	Yes
Siegemund	2012	Yes	Yes	Yes	Yes	Yes
Intermediate risk of bias						
Guidet	2012	Yes	Yes	Yes	Yes	No
Nagpal	2012	Yes	Yes	Yes	Yes	No
James	2011	Yes	Yes	Yes	No	Yes
Gondos	2010	Yes	Yes	No	Yes	Yes
Schramko	2010	Yes	Yes	No	Yes	Yes
Mukhtar	2009	Yes	Yes	No	Yes	Yes
Schramko	2009	Yes	Yes	No	Yes	Yes
Gandhi	2007	Yes	Yes	No	Yes	Yes
Mahmood	2007	Yes	Yes	No	Yes	Yes
Neff	2003	Yes	Yes	No	Yes	Yes
Boldt	2000	Yes	Yes	No	Yes	Yes
High risk of bias						
Lu	2012	Yes	No	No	Yes	Yes
Zdolsek	2011	Yes	Yes	No	No	Yes
Wu	2010	Yes	Yes	No	No	Yes
Dolecek	2009	Yes	No	No	Yes	Yes
Godet	2008	Yes	Yes	No	No	Yes
Volta	2007	Yes	No	No	Yes	Yes
Ellger	2006	Yes	Yes	No	Yes	No
Van der Linden	2005	Yes	No	No	Yes	Yes
Kasper	2003	Yes	Yes	No	No	Yes
Zhu	2011	No	No	No	Yes	Yes
Dubin	2010	Yes	Yes	No	No	No
Inal	2010	No	No	No	Yes	Yes
Ooi	2009	No	No	No	Yes	Yes
Mittermayr	2007	Yes	Yes	No	No	No
Palumbo	2006	Yes	No	No	No	Yes
Jungheinrich	2004	Yes	Yes	No	No	No
Sander	2003	Yes	No	No	No	Yes
Langeron	2001	No	No	No	Yes	Yes
Gallandat Huet	2000	No	No	No	Yes	Yes
Yang	2011	Yes	No	No	No	No
Mehta	2007	Yes	No	No	No	No

Trials were scored 'yes' or 'no' by two reviewers in five domains of quality: randomization, allocation concealment, blinding, intention-to-treat analysis, and minimal loss to follow-up. Low risk of bias was defined as scoring 'yes' to all five domains. Intermediate risk of bias was defined as scoring 'yes' to four out of five domains. High risk of bias was defined as scoring 'yes' to three or less out of five domains

pooled in order to make a single comparison between 6 % HES 130 and crystalloid. The remaining control groups were not included in the pooled mortality or RRT analyses.

Ethical approval was not required.

Results

The process for screening and assessing reports is shown in Fig. 1. The search yielded 3,984 potential reports of which 35 trials that recruited a total of 10,391 participants were eligible for the systematic review; 25 of the 35 studies reported mortality and 11 of 35 reported treatment with RRT. The characteristics of the 35 studies are summarised in Table 1.

List of included studies. Myburgh 2012 [12], Perner 2012 [13], Siegemund 2012 [14], Gondos 2010 [15], Guidet 2012 [16], Zhu 2011 [17], James 2011 [18], Yang 2011 [19], Nagpal 2012 [20], Mittermayr 2007 [21], Schramko 2010 [22], Lu 2012 [23], Volta 2007 [24], Dubin 2010 [25], Van der Linden 2005 [26], Ooi 2009 [27], Zdolsek 2011 [28], Wu 2010 [29], Godet 2008 [30], Mahmood 2007 [31], Dolecek 2009 [32], Schramko 2009 [33], Mukhtar 2009 [34], Inal 2010 [35], Palumbo 2006 [36], Kasper 2003 [37], Gandhi 2003 [38], Langeron 2001 [39], Sander 2003 [40], Gallandat Huet 2000 [41], Jungheinrich 2004 [42], Mehta 2007 [43], Ellger 2006 [44], Neff 2003 [45], Boldt 2000 [46].

The quality of included reports is detailed in Table 2. Only three studies met the predefined criteria for having a low risk of bias, all of these studies have been published or completed in the preceding 12 months

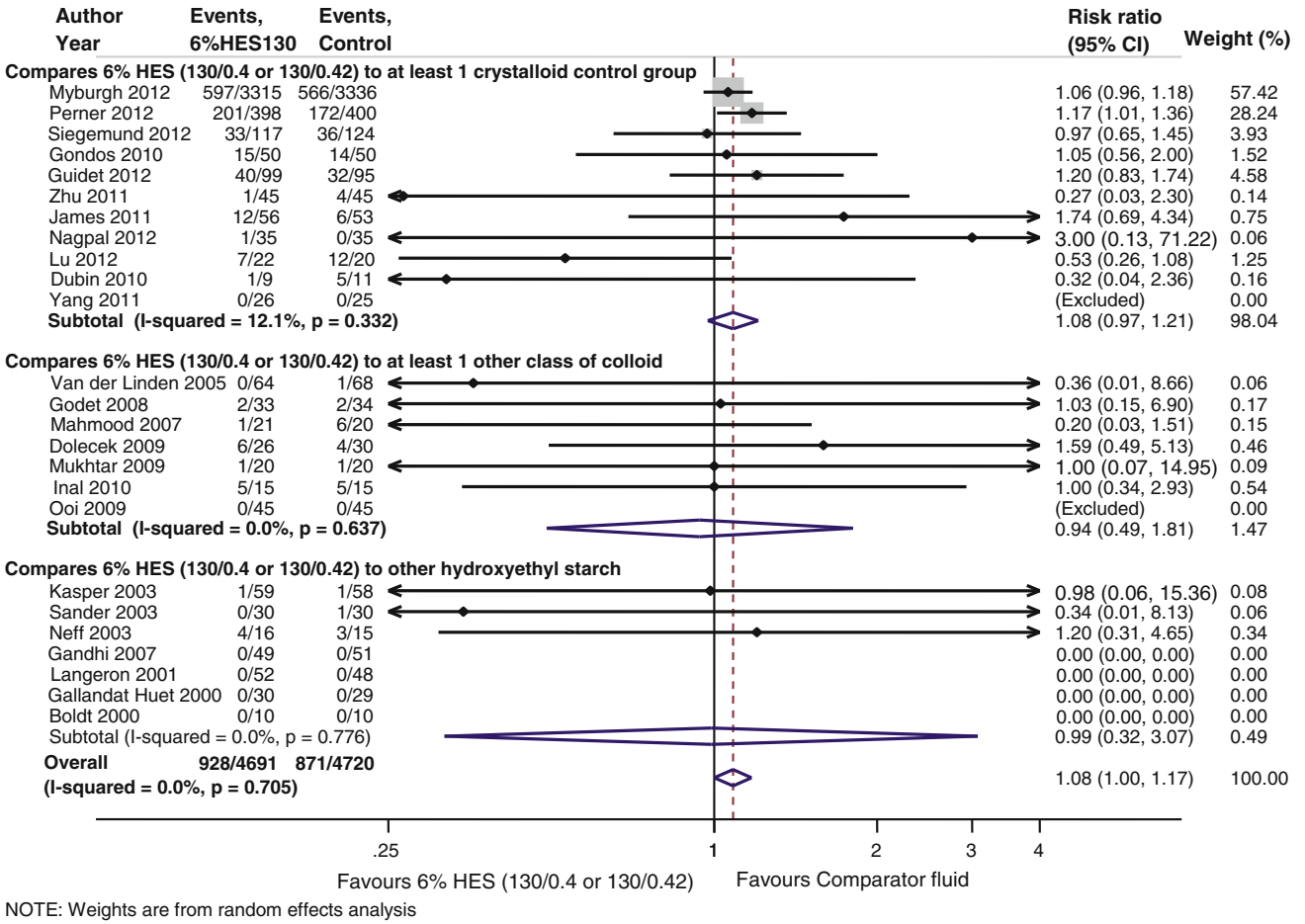

Fig. 2 Forest plot of pooled estimates for mortality. 6 % HES 130 = 6 % hydroxyethyl starch with a molecular weight of 130 kD and a molar substitution ratio of approximately 0.4. CI = confidence interval. Studies reporting at least one event in each group are arranged in ascending year of publication. Weights are from random effects analysis

[12–14]. 21 of 35 studies were judged to have a high risk of bias, including seven of 10 studies comparing 6 % HES 130 to a preparation of hydroxyethyl starch with a molecular weight >130 kD. Studies comparing 6 % HES 130 to at least one crystalloid control group were generally of higher quality (eight of 14 scored low or intermediate risk of bias).

The event rates of the 25 studies that reported mortality and the results of the meta-analysis are shown in Fig. 2. In the random effects analysis, the Crystalloid versus Hydroxyethyl Starch Trial (CHEST) [12] and Scandinavian Starch for Severe Sepsis/Septic Shock (6S) [13] studies contribute most to the pooled estimate (combined 85.7 % weight). Studies comparing 6 %HES 130 to another class of colloid or hydroxyethyl starch with a molecular weight >130 kD contributed very little to the mortality findings (1.5 and 0.5 % weight, respectively). Of 4,691 patients, 928 randomly assigned to receive 6 % HES 130 (19.8 %) died compared with 871 of 4,720 (18.5 %) of those assigned to receive other fluids, relative risk 1.08 (95 % confidence interval 1.00–1.17). There was no significant heterogeneity ($I^2 = 0$ %, $p = 0.7$).

The event rates of the 11 studies that reported treatment with RRT and the results of the meta-analysis are shown in Fig. 3. In the random effects analysis, the CHEST [11] and Scandinavian Starch for Severe Sepsis/Septic Shock (6S) [12] studies contribute most to the pooled estimate (combined 84.6 % weight). Studies comparing 6 % HES 130 to another class of colloid or hydroxyethyl starch with a molecular weight greater than 130 kD contributed very little to the RRT findings (0.9 and 0.7 % weight, respectively). Of 4,236 patients, 378 randomly assigned to receive 6 % HES 130 (8.9 %) were treated with RRT compared with 306 of 4,260 (7.2 %) of those assigned to receive other fluids, relative risk 1.25 (95 % confidence interval 1.08–1.44). There was no significant heterogeneity ($I^2 = 0$ %, $p = 0.8$).

Urine output data were reported in 21 of 35 studies. Time periods of collection were highly variable, or not reported with sufficient detail to enable valid data

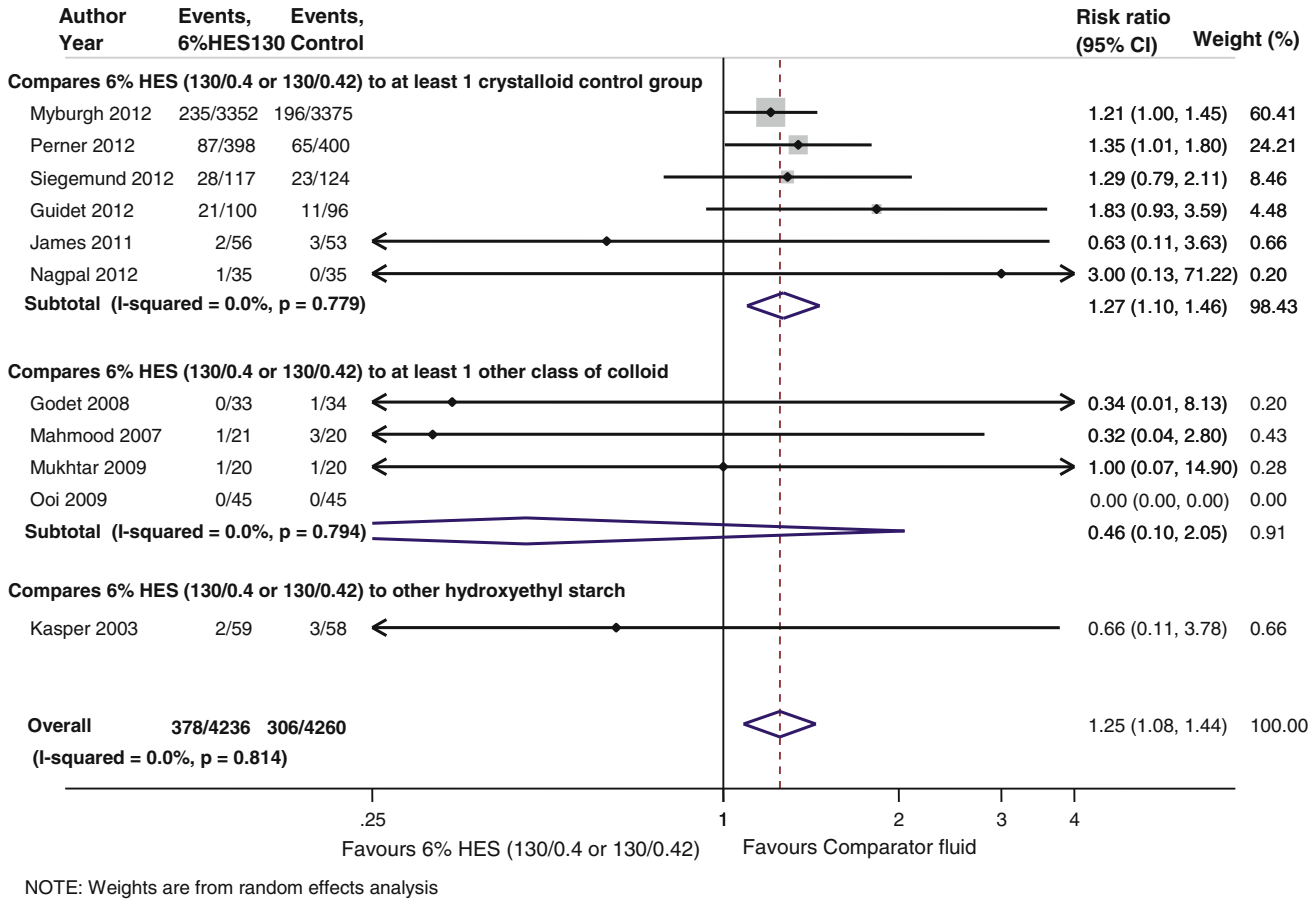

Fig. 3 Forest plot of pooled estimates for need for renal replacement therapy. 6 % HES 130 = 6 % hydroxyethyl starch with a molecular weight of 130 kD and a molar substitution ratio of approximately 0.4. CI = confidence interval. Studies reporting at least one event in each group are arranged in ascending year of publication. Weights are from random effects analysis

extraction. Meta-analysis of urine output was deemed inappropriate and not performed. Similar findings were made in trials reporting transfusion (27 of 35 studies) and bleeding (23 of 35 studies). Transfusion was reported using semi-quantitative units of measurement such as 'units transfused' in some studies. Methods used to collect and report bleeding data were usually not stated.

Discussion

The principal finding of this systematic review is that fluid resuscitation with 6 % HES 130 as compared to other fluids is associated with an 8 % increase in the relative risk of death which is of borderline statistical significance, and a significant 25 % increase in the relative risk of being treated with RRT. There was no significant heterogeneity among the included trials, and the magnitude and direction of these associations were similar across the recent trials with larger sample size and lower risk of bias.

The strength of this review is that it includes recent large-scale trials that have focused on mortality and treatment with RRT. The methods we used were the same as for a previous review [4], which resulted from the retraction of clinical trials of 6 % HES 130 [47–51] during the enrolment period of the CHEST trial [12]. The two reviews demonstrate the increase in the number of patients recently randomized into clinical trials evaluating 6 % HES 130. The limitations of this review are that we did not extract data for other outcomes, and did not contact authors to try and obtain additional unpublished data. The duration of study follow up was not analysed. The results of this review are predominated by two large-scale trials [12, 13] which may limit the applicability of these results in other patients populations and treatment settings.

Several systematic reviews that have been published concerning colloids for resuscitation [2, 5–8]. Some have focussed on 6 % HES 130 specifically [8], and others

have evaluated all hydroxyethyl starch preparations [6] or colloids in general [2, 5]. The risks associated with exposure to the newer formulations of hydroxyethyl starch are now consistent across several large-scale trials with a low risk of bias. It is unlikely that any clinical benefits of using 6 % HES 130 not studied in this review would outweigh these risks, at least in the patient populations enrolled in these trials.

Further research may identify which patient subgroups are at greater risk of harm from exposure to 6 % HES 130, in particular individual patient data meta-analysis of existing trials might identify patient characteristics conferring increased risk. We would recommend the use of other fluids until it is understood if there are any patients who are likely to receive a net benefit when they are fluid resuscitated with 6 % HES 130.

Conclusion

Fluid resuscitation of acutely ill adults with 6 % HES 130 is associated with an increase in risk of death and treatment with RRT. These associations are consistent across recent large-scale randomised controlled trials with a low risk of bias.

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Appendix

Electronic Search strategy. The intersection of: fluid resuscitation, hydroxyethyl starch, and randomized controlled trials.

MEDLINE.

1. exp Fluid Therapy.
2. ((fluid$ or volume$ or plasma$ or rehydrat$) adj3 (replace$ or therap$ or substitut$ or restor$ or resuscitat$ or rehydrat$)).ab,ti.
3. or/1-2.
4. exp Starch.
5. exp Blood Substitutes.
6. exp Colloids.
7. hetastarch$.tw.
8. hydroxyethyl starch.tw.
9. hydroxyethylstarch.tw.
10. hydroxy ethyl starch.tw.
11. pentastarch.tw.
12. voluven$.tw.
13. tetrastarch.tw.
14. or/4-13.
15. 3 and 14.
16. limit 15 to "therapy (sensitivity)" [from the MEDLINE limit 'Clinical Queries', based on Haynes et al [52].].

EMBASE.

#14. #3 AND #12 AND #13.

#13. random:ti OR 'clinical trial':de,rn,ab,ti OR 'health care quality'/exp.

#12. #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11.

#11. tetrastarch.

#10. voluven*.

#9. pentastarch.

#8. 'hydroxy ethyl starch'.

#7. hydroxyethylstarch.

#6. 'hydroxyethyl starch'.

#5. hetastarch*.

#4. 'starch'/exp OR starch.

#3. #1 OR #2.

#2. (fluid* OR volum* OR plasma* OR rehydrat*) NEAR/3 (therap* OR substitut* OR restor* OR resusc* OR replac*).

#1. 'fluid therapy'/exp OR 'fluid therapy'.

CENTRAL.

#1 starch* or *starch or voluven* in Clinical Trials.

#2 MeSH descriptor Fluid Therapy explode all trees.

#3 ((fluid* or volume* or plasma* or rehydrat*) NEAR/3 (replace* or therap* or substitut* or restor* or resuscitat* or rehydrat*)):ab,ti in Clinical Trials.

#4 (#2 OR #3).

#5 (#1 AND #4).

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