Sources of Heterogeneity in Trials Reporting Hydroxyethyl Starch 130/0.4 or 0.42 Associated Excess Mortality in Septic Patients: A Systematic Review and Meta-regression

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Abstract

Background: This meta-analysis was to determine the association of the cumulative dose of 130/0.4 or 0.42 (hydroxyethyl starch [HES] 130/0.4*) or delta daily fluid balance (i.e., daily fluid balance in HES group over or below control group) with the heterogeneity of risk ratio (*RR*) for mortality in randomized control trials (RCTs).

Methods: Three databases (PubMed, EMBASE, Cochrane) were searched to identify prospective RCTs reporting mortality in adult patients with sepsis to compare HES130/0.4* with crystalloids or albumin. Meta-analysis was performed using random effects. Sensitivity and meta-regression analyses were used to examine the heterogeneity sources of *RR* for mortality.

Results: A total number of 4408 patients from 11 RCTs were included. The pooled *RR* showed no significant difference for overall mortality in patients with administration of HES130/0.4* compared with treatment of control fluids (*RR*: 1.02, 95% confidence interval: 0.90–1.17; $P = 0.73$). Heterogeneity was moderate across recruited trials ($I^2 = 34\%$, $P = 0.13$). But, a significant variation was demonstrated in subgroup with crystalloids as control fluids ($I^2 = 42\%$, $P < 0.1$). Sensitivity analysis revealed that trials with high risk of bias did not significantly impact the pooled estimates for mortality. Meta-regression analysis also did not determine a dose-effect relationship of HES130/0.4* with mortality ($P = 0.298$), but suggested daily delta fluid balance being likely associated with mortality in septic patients receiving HES130/130/0.4* ($P = 0.079$).

Conclusions: Inappropriate daily positive fluid balance was likely an important source of heterogeneity in these trials reporting HES130/0.4* associated with excess mortality in septic patients.

Key words: Hydroxyethyl Starch 130/0.4 or 0.42; Heterogeneity; Mortality; Sepsis

Introduction

Characterized with more rapid restoration of hemodynamic stability,[1,2] improvement of microcirculation,[3] and attenuation of oxidative stress or inflammatory response[4-6] as well, hydroxyethyl starch (HES) was commonly used for fluid therapy in patients with sepsis worldwide.[7] However, increasing experimental data suggested that HES, even the newest generation of HES130/0.4 or 0.42 (HES130/0.4*), had toxicity potential to induce interstitial proliferation, macrophage infiltration, and tubular damage, which consequently contributed to impairment of renal function.[8,9] Furthermore, several trials have currently demonstrated that compared with treatment of crystalloids, administration of HES130/0.4* for volume therapy was associated with an increased 90-day mortality, in addition to an extra need for renal replacement therapy (RRT), in patients with severe sepsis

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or septic shock.[1,10-12] Accordingly, a significant concern on the safety of HES solutions for volume therapy has been seriously raised in patients with sepsis now.[13-15]

However, heterogeneity was found in these randomized control trials (RCTs) reporting HES-associated excess mortality over control fluids. Inconsistent with Perner's trial[10] for example, the Myburgh *et al*.'s[11] and a recently published RCT[16] did not demonstrate a significant increase of mortality in septic patients receiving HES130/0.4* compared with control fluids. Importantly, this heterogeneity might impact the pooled estimation of the adverse effect of HES130/0.4* on outcome in these trials. Sources for these diverging results remained unclear, but likely attributable to both study design including different disease's severity of study population, randomization as well as blinding, and protocol for fluid therapy such as highly varied indication, timing, quantity, etc.[17-19] However, each of these factors has not been successfully linked with this heterogeneity by a sound data in any RCT or meta-analyses up to now.[20-23] Interestedly, the administrated doses of HES as study fluid were not identical, or even incomparable in these RCTs according to the originally published data. In addition, a variety of fluid balance was followed by different study protocols for volume therapy in these trials. We, therefore, conducted a systematic review and meta-regression to determine whether the administrated dose of HES130/0.4* or delta daily fluid balance (i.e., daily fluid balance in HES group over or below control group) were proportional to the heterogeneity of HES-associated excess mortality over treatment with control fluids for volume therapy in septic patients in these RCTs.

Methods

This systematic review was performed according to Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[24] No Institutional Review Board approval or consents were needed for this systematic review because the data were extracted from the previously published studies.

Eligibility criteria

Eligible studies were included if all criteria were met: (1) RCTs comparing 6% HES, with a molecular weight of 130 kDa and molar substitution ratio of 0.4 or 0.42 in any carrier or of any origin, with any type of fluid (crystalloids or colloids); (2) Patients aged 18 years or older; (3) Patients who were diagnosed with sepsis presented at randomization; (4) Study fluids for volume therapy was defined as fluid required to increase or maintain intravascular volume; and (5) Mortality was reported.

Search strategy

A literature search on three databases (PubMed, EMBASE, Cochrane Central Register of Controlled Trials) was last updated on October 10, 2014. We also hand-searched the reference lists of included trials and other systematic reviews for additional studies that met inclusion criteria. No restriction on language or publication status was applied. The search terms for HES solutions included hydroxyethyl starch, hetastarch, HES, or 130/0.4 or 0.42. The search terms for sepsis were sepsis, severe sepsis, and septic shock, while the search terms for RCT included randomized controlled trial, control clinical trial, randomized, randomly, or RCT.

Study selection and data extraction

Two reviewers independently screened the initially identified studies from the search. Full-text articles of potentially eligible studies were independently assessed against the eligibility criteria. When there was more than one paper derived from the same study, we only included the most potential eligible records considering the integrity and availability of data. The main reasons for exclusion of trials were described in Figure 1. The same two reviewers independently extracted the data from each study using European Research Council data collection form for intervention reviews of RCTs that was downloaded from Cochrane Collaboration.[25] The following variables pertaining to patients and setting were collected: Published year, number of participating centers,

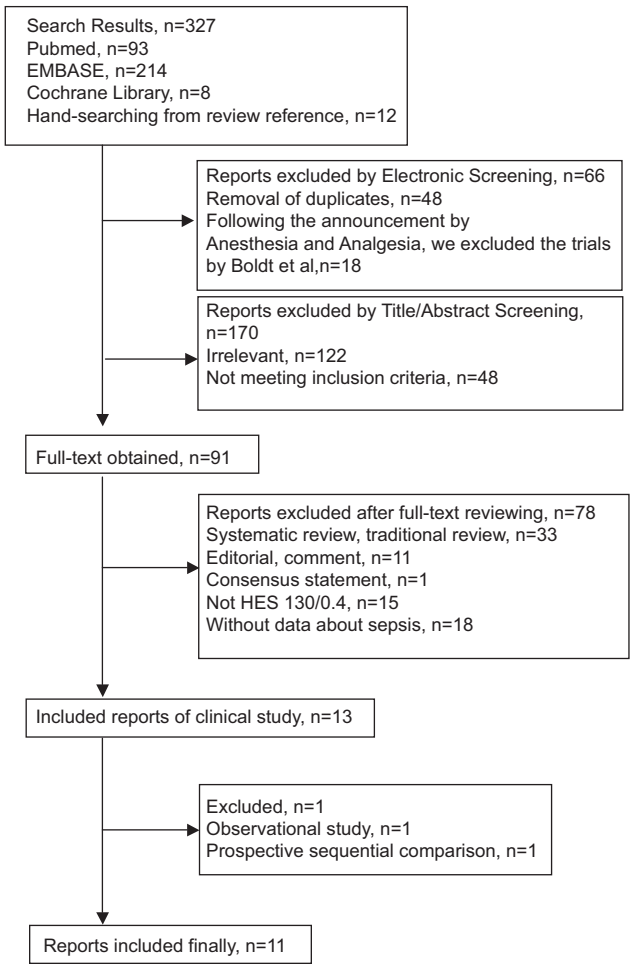

Figure 1: Flow diagram of individual studies screening. A Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram detailed the search, identification, screening, and inclusion of RCTs in the current meta-analysis. RCTs: Randomized control trial.

total number of patients, clinical setting, protocol of fluid therapy (indication, dose, treatment duration, and comparator fluid), and major outcomes. Differences were then compared and referred to the consultants (Dr. Xiao-Xia Peng and Dr. Peng-Lin Ma) for resolution.

Calculation of the dose of hydroxyethyl starch 130/0.4*

Data about the total dose of HES130/0.4* were extracted by two authors (Dr. Ma and Dr. Peng), and expressed as mean and standard deviation (SD). When the original data were expressed as median (M) and range (minimum [Min], maximum [Max]), then mean was estimated as (Max + 2M + Min)/4 and SD was estimated as (Max − Min)/4. If median and inter-quartile range (IQR) rather than median and range were provided, we only assumed that those data had a normal distribution and the mean was similar to the median, and SD was estimated by dividing the IQR by 1.35.[26]

Daily delta fluid balance

Daily delta fluid balance was defined as the mean of daily positive fluid balance in HES group minus that in control group within study period, based on the published data. Thus, a positive daily delta fluid balance indicated a large mean value of positive fluid balance in HES group over control group, while a negative daily delta fluid balance suggested mean value of positive fluid balance was less in HES group than control group.

Risk of bias assessment

To determine the validity of the enrolled studies, the same two reviewers independently assessed the risk of bias as advised by the Cochrane Collaboration,[24] including the domains of randomization sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting. Trials with all domains assessed as low were judged to have a low risk of bias. If more than one domain was assessed as high or unclear, the trial was classified as having a high risk of bias. The trials with one domain being high or unclear were judged to have an intermediate risk of bias.

Statistical analysis

We summarized data from the included studies using Review Manager (RevMan, Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The risk ratio (*RR*) with 95% confidence intervals (*CI*) of death for 6% HES130/0.4* compared to control fluids were calculated in each trial, and then pooled via a meta-analysis with the random-effects model. Subgroup assignment was performed to determine summary effect estimates of HES130/0.4* in relation to specific comparator fluids. Then, the potential impact of trial quality and risk of bias on outcome was examined through sensitivity analysis.[27] With Mantel–Haenszel test, statistical heterogeneity was assessed using the Chi-squared test (with significance being set at $P < 0.1$) and I^2 statistic to estimate the total variation across studies or between the two subgroups.[24,25] A meta-regression analysis was performed to examine the association between the overall mortality and the administrated dose of HES solutions or daily delta fluid balance (STATA 12 version).

Publication bias was assessed by plotting the effect size against standard error for each trial (funnel plot), and statistically examined by the Egger's test. Statistical significance was selected to be $P < 0.05$ for the primary analyses, as well as for meta-regression.

Results

Figure 1 outlines the PRISMA flow diagram illustrating the results of the literature search. The search yielded 327 potential studies, of which 11 trials were eligible for the systematic review. All studies reported mortality and the total dose of HES130/0.4*. But, daily fluid balance within study days was only available in 6 out of 11 RCTs.

Characteristics of the included trials

The characteristics of the 11 enrolled trials were summarized in Table 1. A total number of 4408 patients with sepsis (ranged from 25 to 1935) were recruited in these trials. Six percent HES130/0.4 or 0.42 was used in all trials, with 0.9% normal saline ($n = 4$), Ringer's lactate ($n = 3$) or Ringer's

Table 1: Characteristics of trials enrolled in the meta-analysis

Source	Centers	Number of patients	Diagnosis	Fluids		Follow-up days	All-cause mortality in days, (*P*)
				Study	Control		
Annane *et al.*, 2013[16]	57	969	Sepsis	6% HES 130/0.4*	RA/NS	90	90-day (*P*>0.05)
Perner *et al.*, 2012[10]	26	798	Severe sepsis	6% HES 130/0.42	RA	90	90-day (*P*<0.05)
Myburgh *et al.*, 2012[11]	32	1937	Sepsis	6% HES 130/0.4	NS	90	90-day (*P*>0.05)
Guidet *et al.*, 2012[1]	24	196	Severe sepsis	6% HES 130/0.4	NS	90	90-day (*P*>0.05)
Siegemund, 2012[28]	1	241	Sepsis	6% HES 130/0.4	NS	90	90-day (*P*>0.05)
Lv *et al.*, 2012[30]	1	42	Septic shock	6% HES 130/0.4	RL	NA	LT28-day (*P*>0.05)
Zhu *et al.*, 2011[32]	1	90	Severe sepsis	6% HES 130/0.4	RL	NA	LT28-day (*P*>0.05)
Dubin *et al.*, 2010[3]	2	25	Severe sepsis	6% HES 130/0.4	NS	NA	LT28-day (*P*>0.05)
Gondos *et al.*, 2010[33]	11	46	Severe sepsis	6% HES 130/0.4	RL	10	LT28-day (*P*>0.05)
Dolecek *et al.*, 2009[29]	1	56	Severe sepsis	6% HES 130/0.4	20% albumin	28	28-day (*P*>0.05)
Palumbo *et al.*, 2006[31]	1	20	Severe sepsis	6% HES 130/0.4	20% albumin	28	28-day (*P*>0.05)

HES: Hydroxyethyl starch; 6% HES130/0.4*; 6% HES 130/0.4 or 0.42; NS: Normal saline; RA: Ringer's acetate; RL: Ringer's lactate; NA: Not applied; LT28-day: Less than 28 days.

acetate (n = 1), both 0.9% normal saline and Ringer's fluids (n = 1), and human albumin (n = 2) as control fluids.

Risk of bias assessment

The quality of included trials was detailed in Table 2. Only 5 out of 11 trials were judged to have a low risk of bias in all domains,[1,10,11,28,29] while 3 of the left 6 trials (trial from China,[30] Argentina,[3] and Italy,[31] respectively) had a high risk of bias due to nonblind and insufficient allocation concealment. Other 3 trials had an intermediate risk of bias.[16,32,33]

Risk ratio for mortality and heterogeneity

Data were obtained from all trials including 4408 patients. The pooled *RR* showed no significant difference for overall mortality in patients with administration of HES130/0.4* compared with treatment of control fluids (*RR*: 1.02, 95% *CI*: 0.90–1.17; P = 0.73; I^2 = 34%; Figure 2). Similarly, significant pooled *RR* of HES130/0.4* for mortality was demonstrated neither in comparing with crystalloids (*RR*: 1.01, 95% *CI*: 0.88–1.16; P = 0.90; I^2 = 42%) nor with albumin (*RR*: 1.64, 95% *CI*: 0.72–3.73; P = 0.65; I^2 = 0) in subgroup analysis.

Based on original data, 6 of 11 recruited trials reported an excess mortality in patients receiving HES130/0.4* in comparison with administration of control fluids (crystalloids in 4 trials and albumin in 2 trials). But, statistical significance was only emerged in Perner's trial.[10]

Table 2: Assessment of risk of bias advised by 2011 Cochrane Collaboration's Handbook

Source	Randomization	Allocation concealment	Blinding	ITT-analysis	No loss to follow-up	Risk of bias
Annane *et al.*, 2013[16]	Low	Low	High	Low	Low	Intermediate
Perner *et al.*, 2012[10]	Low	Low	Low	Low	Low	Low
Myburgh *et al.*, 2012[11]	Low	Low	Low	Low	Low	Low
Guidet *et al.*, 2012[1]	Low	Low	Low	Low	Low	Low
Siegemund, 2012[28]	Low	Low	Low	Low	Low	Low
Lv *et al.*, 2012[30]	Low	High	Unclear	Unclear	Low	High
Zhu *et al.*, 2011[32]	Low	Low	High	Low	Low	Intermediate
Dubin *et al.*, 2010[3]	Low	Low	High	High	High	High
Gondos *et al.*, 2010[33]	Low	Low	High	Low	Low	Intermediate
Dolecek *et al.*, 2009[29]	Low	Low	Low	Low	Low	Low
Palumbo *et al.*, 2006[31]	Low	High	High	Low	Low	High

ITT-analysis: Intention-to-treat analysis.

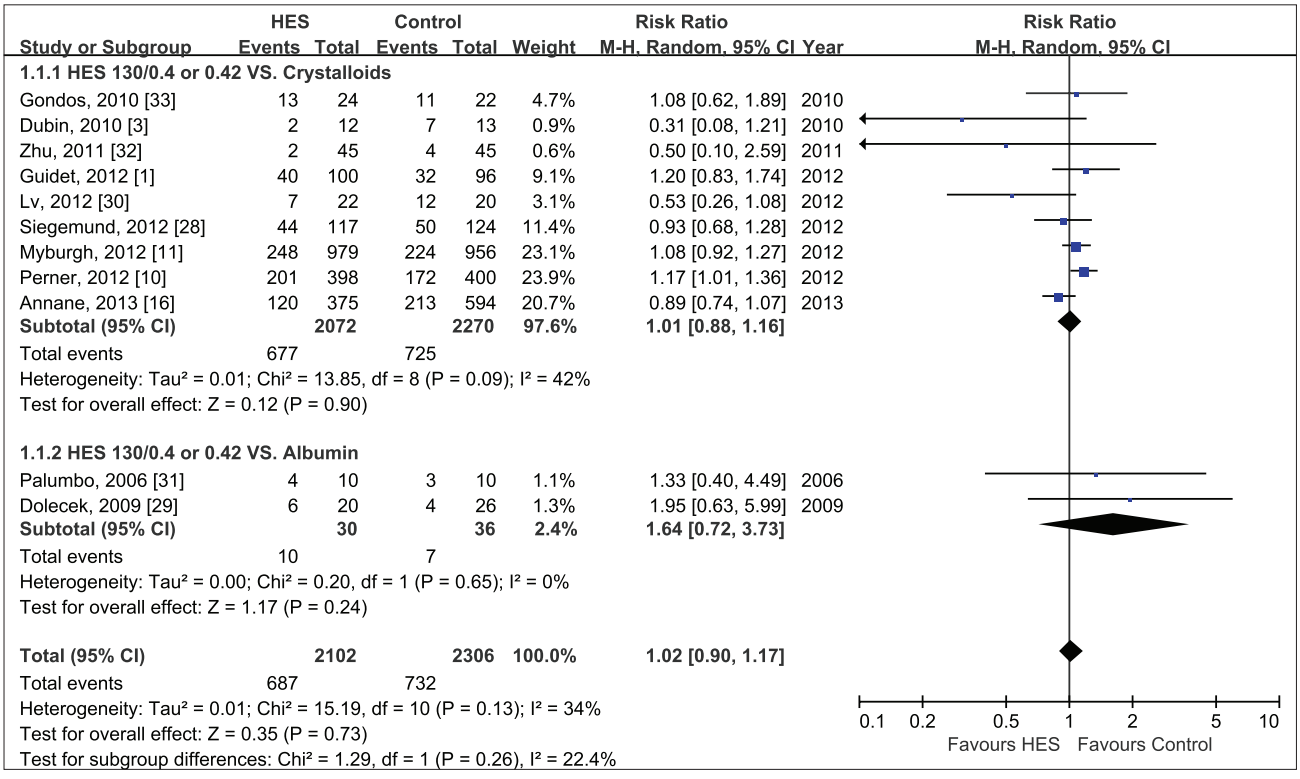

Figure 2: Forest plot of overall mortality. Twelve trials including 4408 patients were analyzed for the pooled overall mortality (i.e., the worst all-cause mortality reported in original paper). HES: Hydroxyethyl starch 130/0.4 or 0.42.

The other 5 trials reported a lower mortality in HES group than in control group (crystalloids in all 5 trials), but all without statistical significance. A moderate heterogeneity across recruited trials was found as assessing overall mortality (I^2 = 34%, P = 0.13, Figure 2). In subgroup with crystalloids as control fluids, a significant variation was demonstrated with I^2 = 42% (P < 0.1). However, the test for subgroup difference was not significant (χ^2 = 1.29, P = 0.26, I^2 = 22.4%).

Sensitivity and meta-regression analysis

Excluding the 3 trials with high risk of bias, sensitivity analysis revealed that the pooled *RR* of exposure of HES130/0.4* for mortality was still not significant in comparing with control fluids (*RR*: 1.06, 95% *CI*: 0.95–1.17; P = 0.29), although variation across studies (I^2) was lowed from 34% to 16% [Figure 3].

The cumulative total doses of HES130/0.4* administrated as study fluid within study days (ranged from 1 to 7 days) were reported in all 11 trials as shown on Table 3. The dosages were ranged from 500 ± 0 in Zhu's trial (within 1-day)[32] to 4017 ± 462 ml in Perner's trial (within 3-day).[10] Daily delta fluid balance (predefined in methods) within the study days was extracted from the published data of 6 trials. We sent an E-mail to each of corresponding author for the other 5 articles to inquire about the fluid balance data, but failed. Daily delta fluid balance was positive from 86 to 667 ml (i.e., more positive daily fluid balance in HES130/0.4* group than in control group, mean value in the study days) in 3 trials, and negative from − 61 to − 3749 ml in other 3 trials (i.e., less positive daily fluid balance in HES130/0.4* group than in control group, mean value in the study days). Meta-regression analysis did not find a significant association between the *RR* for mortality and total administrated dose of HES130/0.4* (log*RR* = −0.124,10 + 0.000,06 × total dose of HES, P = 0.298, Figure 4). However, it demonstrated a trend of dose-effect relationship between daily delta fluid balance and *RR* for mortality in patients receiving HES130/0.4* for volume therapy in these trials (log*RR* = 0.111,77 + 0.000,39 × delta daily fluid balance, P = 0.079, Figure 5).

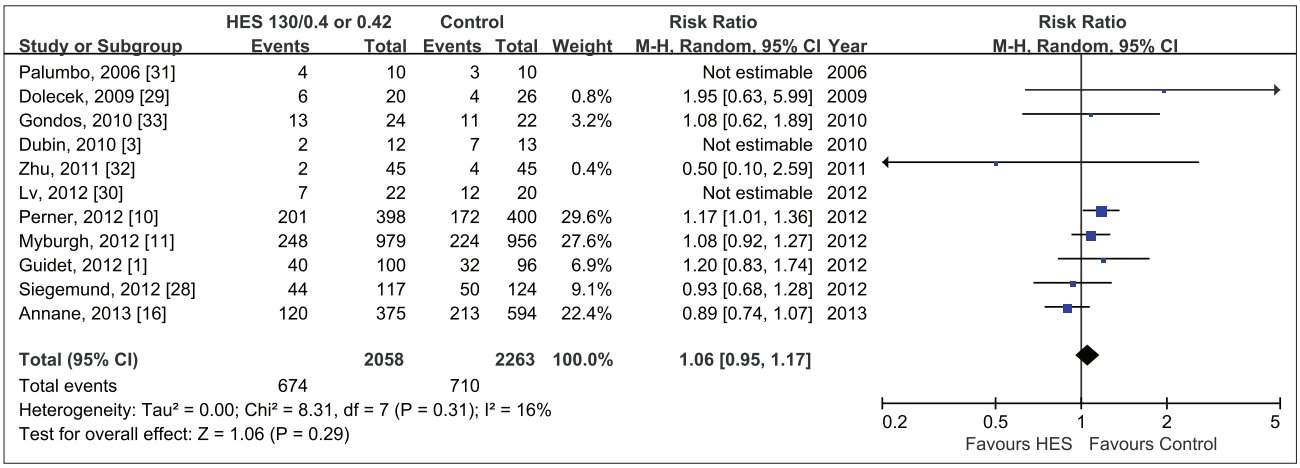

Figure 3: Sensitivity analysis for the polled of *RR* for mortality. Three trials with high risk of bias were excluded. However, the polled *RR* of HES 130/0.4 or 0.42 for mortality was still no significant in comparison with control fluids (crystalloids and albumin). HES: Hydroxyethyl starch 130/0.4 or 0.42.

Table 3: Fluid therapy after randomization

Source	Periods (day)	Total dose of fluids (ml)		*P*	Fluid balance (ml/d)		Delta fluid balance (ml/d)
		HES	Control		HES	Control	
Annane *et al.*, 2013[16]	7	1500 ± 250	2750 ± 1500	<0.01	NA	NA	NA
Perner *et al.*, 2012[10]	3	4017 ± 462	4185 ± 564	<0.01	1798 ± 483	1667 ± 460	+131
Myburgh *et al.*, 2012[11]	4	2104 ± 1700	2464 ± 1952	<0.01	921 ± 1069	982 ± 1161	−61
Guidet *et al.*, 2012[1]	4	2615 ± 1499	2788 ± 1799	>0.05	4278*	4192*	+86*
Siegemund, 2012[28]	5	3978 ± 1082	NA	NA	NA	NA	NA
Lv *et al.*, 2012[30]	1	2770 ± 590	3460 ± 730	<0.01	NA	NA	NA
Zhu *et al.*, 2011[32]	1	500 ± 0	500 ± 0	>0.05	4135 ± 186	5439 ± 167	−1304
Dubin *et al.*, 2010[3]	1	2610 ± 885	8368 ± 2405	<0.01	2857 ± 1596	6606 ± 2669	−3749
Gondos *et al.*, 2010[33]	1	771 ± 179*	852 ± 176*	<0.05	NA	NA	NA
Dolecek *et al.*, 2009[29]	3	3000 ± 0	600 ± 0	<0.05	534 ± 1300	−133 ± 1300	+667
Palumbo *et al.*, 2006[31]	5	2500 ± 0	500 ± 0	<0.05	NA	NA	NA

*Data were calculated with the BMI = Weight (kg)/height^2 (m^2). BMI was provided by the original publication, and the average height was estimated as 1.7 m. If BMI is not available, average body weight was estimated as 65 kg. HES: Hydroxyethyl starch; NA: Not applied; BMI: Body mass index.

Publication bias

The funnel plot constructed with overall mortality and the result of Egger's test without significance (P = 0.31) suggested an absence of potential publication bias [Figure 6].

Discussion

Different from previous meta-analyses,[21,23] our results revealed that exposure of HES130/0.4* did not significantly increase the pooled *RR* for mortality in comparison with treatment of control fluids (crystalloids or albumin) in septic patients. We found a moderate heterogeneity in all recruited trials (I^2 = 34%, P = 0.73) and a significant variation across trials with crystalloids as control fluids (I^2 = 42%, P < 0.1). Moreover, meta-regression analysis did not determine that the total administrated dose of HES130/0.4* was the source for this heterogeneity [Figure 4]. Interestedly, daily delta fluid balance was suggested to be likely associated with mortality in patients receiving HES130/0.4* in these trials (P = 0.079, Figure 5).

As well-known, HES solutions have been identified to be renal toxicity potential in previously basic researches[8,9] and clinical trials,[10-12] which most likely contributes to morbidity and mortality in critically ill patients.[34,35] Several previous trials have questioned the safety of HES solutions including HES130/0.4* too. However, only Perner's trial reported a significant long-term (90-day) mortality in septic patients with administration of HES130/0.4* compared with control fluids so far [Table 1]. Their data weighted the highest in both Haase's (31.3%,[21]) and Patel's (47.3%,[23]) meta-analyses, which was closely tied with a border significance in increasing *RR* of HES130/0.4* administration for all-cause mortality in subgroup of trials with low risk of bias and only for 90-day mortality, respectively. In our meta-analysis, sample size was largely expanded (n = 4408, 11 RCTs) over Haase's (n = 3414, 9 RCTs) and Patel's recruits (n = 3033, 6 RCTs) by adding updated data. However, our results did not convince Haase's and Patel's findings, but suggested that insufficient data proved HES130/0.4* administration being a significant risk factor for overall mortality in septic patients.

Trial's quality was commonly examined to determine the source of heterogeneity, which could counterbalance the effect of intervention in conventional meta-analysis. Successfully lowering the variation across studies (I^2) from 34% to 16%, however, sensitivity analysis indicated that trials with high risk of bias unlikely confounded the pooled estimates for mortality in our work [Figure 3], in spite of being a significant impact on Haase's results.[21] In addition, under predefined dose limitation (the highest dosage of 33 ml·kg^{-1}·d^{-1} was used by most of study protocols), a dose-effect of cumulative HES130/0.4* administration on mortality was not demonstrated by meta-regression analysis [Figure 4]. These results indicated that certain events, rather than domains with high risk of bias in evaluating the quality of trials and the dosage of HES130/0.4* as well, were more probably associated with the divergent outcomes in these RCTs.

Interestedly, it was calculated that delta daily fluid balance (i.e., less or more positive daily fluid balance in HES130/0.4* group than in control group) was largely varied from − 3749 to + 667 ml in 6 of 11 trials during the study days. In addition, meta-regression analysis demonstrated that daily delta fluid balance was positively correlated with the *RR* for mortality in patients receiving HES130/0.4* for volume therapy in these RCTs (log *RR* = 0.111,77 + 0.000,39 × ml of delta daily fluid balance, P = 0.079, Figure 5). Furthermore, added on data of a prospective sequential comparison,[12] the effect of delta daily fluid balance was significant (P = 0.03, not shown here). These results were alert at least for that fluid balance, an immediate consequence of fluid therapy, was more likely linked with the excess harmful effect of HES130/0.4* over control fluids on mortality. However, it was unadjusted in these RCTs.

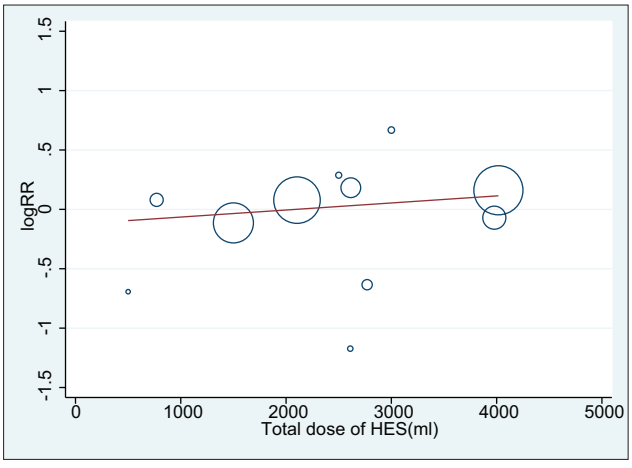

Figure 4: Meta-regression analysis for relationship of the total dose of HES with mortality. All 11 trials reported the total dose of HES. Meta-regression analysis did not determine a dose-effect relationship of HES 130/0.4 or 0.42 with mortality. HES: Hydroxyethyl starch 130/0.4 or 0.42.

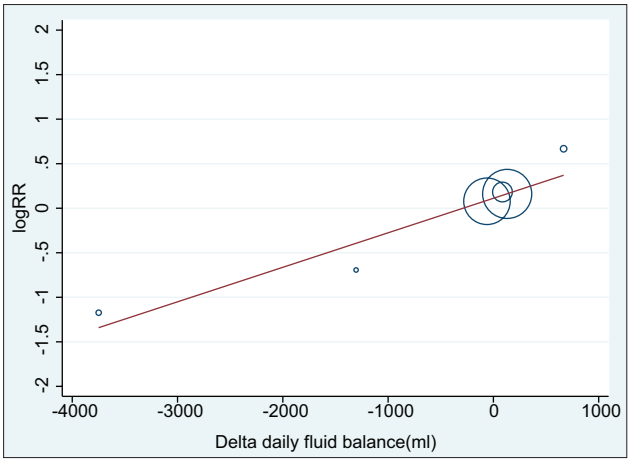

Figure 5: Meta-regression analysis for association of daily delta fluid balance with mortality. Positive daily delta fluid balance (i.e., more positive fluid balance in HES group than in control group as predefined) was calculated in three trials, while other three trials were defined with negative daily delta fluid balance. HES: Hydroxyethyl starch 130/0.4 or 0.42.

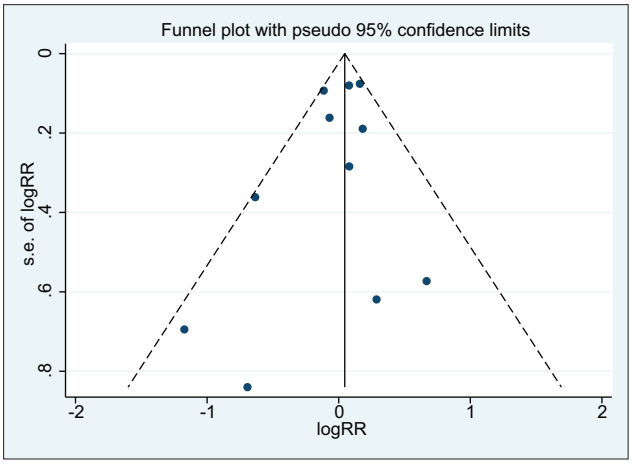

Figure 6: The funnel plot for the potential publication bias. There was no publication bias (Egger's test, $P = 0.31$).

It was well-indicated that inappropriate fluid balance has been associated with worse outcomes in patients with severe sepsis and septic shock, a very complex syndrome with high risk of death.[36,37] For example, in a multicenter observational cohort including 198 Intensive Care Units (ICUs) from 24 European countries, Vincent *et al*. suggested that mean fluid balance within the first 72 h of ICU admission was an independent risk factor for death in septic patients, with odds ratio (*OR*) of 1.1 for each 1-liter increase in cumulative fluid balance.[38] In another study, to determine the association between daily fluid balance and outcomes in critically ill patients receiving RRT,[39] Bellomo *et al*. found that patients achieving a negative fluid balance had a markedly reduced risk of death at 90-day (*OR*: 0.31, 95% *CI*: 0.24–0.43; $P < 0.0001$). Despite the ongoing debates about whether this association represents causality or merely a marker of severity of illness indicating hemodynamic instability,[19,40,41] it becomes widely acknowledged that patients receiving unnecessary fluids are more likely to develop complications related to fluid overload (such as tissue edema, organ dysfunction including acute kidney injury (AKI), or even death), which was tightly associated with excess mortality.[42-45] In fact, the inappropriate fluid balance was highly suspected in these enrolled trials with positive daily delta fluid balance in HES group. First of all, study protocols for volume therapy had not specifically addressed the issue of preventing patients from unnecessary fluid input in these studies,[1,10,29] although all of their protocols were claimed to follow Surviving Sepsis Campaign guidelines delivered suggestions and recommendations.[46] In Perner's trial, for example, the baseline levels of central venous pressure, central venous oxygen saturation, and lactate in both groups suggested that most patients might not have severe intravascular volume depletion, who would be highly susceptible to fluid overload had any additional resuscitation fluids been administered.[47,48] Next, the volume of accumulative fluids was reported similar or even more pronounced in HES group than the control group in these trials.[1,10,29] In general, HES130/0.4* provided larger plasma volume expansion than crystalloids. Characterized with high incidence of,[34,35] therefore, patients with severe sepsis or septic shock were more likely placed at high risk of receiving unnecessary fluids as more volume of accumulative fluids was given in HES group. Furthermore, there was no significant relationship between the daily administrated dose of HES130/0.4* and daily delta fluid balance (calculated with the data on Table 3, not shown here). It indicated that positive daily delta fluid balance was not mainly caused by the effects of HES130/0.4* on both plasma expansion and possible renal impairment (which could lead a significant decrease of urine output), but more probably resulted from unstandardized study protocol for fluid balance control. Thus, multivariate regression analysis with involved individual data of fluid balance would provide more valid information on the association of HES130/0.4* administration with mortality of septic patients in these RCTs. As a covariate, the comparable fluid balance was essential for comparing the impact of different type of fluid on mortality in septic patients.

The important limitation of this meta-analysis was that the data of either total dose of HES130/0.4* or delta daily fluid balance in HES group in these trials was not mathematical, most of the mean values were calculated from original published data with median (range, or interquartile) or estimated with optimal body weight of 65 kg from data represented with ml/kg. In addition, lack of data in 5 of 11 trials limited our meta-regression to determine the information of fluid balance confounding the harmful effect of HES130/0.4* on mortality.

In conclusion, currently significant concern has been raised on the safety of HES solutions including HES130/0.4 or 0.42 for fluid therapy in septic patients. However, HES130/0.4 or 0.42 associated excess mortality over control fluids were not demonstrated in this meta-analysis. Heterogeneity of *RR* for mortality was existed, which was significant in trials with crystalloids as control fluids. Meta-regression analysis did not determine a dose-effect relationship of HES130/0.4 or 0.42 with mortality, but suggested daily delta fluid balance being likely associated with mortality in septic patients receiving HES130/0.4 or 0.42 in these enrolled RCTs. Our results indicated that incomparable fluid balance was likely one of the important sources for heterogeneity of *RR* for mortality in these RCTs comparing HES130/0.4 or 0.42 with control fluids for volume therapy in septic patients.

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Conflicts of interest

There are no conflicts of interest.

References

1. Guidet B, Martinet O, Boulain T, Philippart F, Poussel JF, Maizel J, *et al.* 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 2012;16:R94.

2. Magder S, Potter BJ, Varennes BD, Doucette S, Fergusson D; Canadian Critical Care Trials Group. Fluids after cardiac surgery: A pilot study of the use of colloids versus crystalloids. Crit Care Med 2010;38:2117-24.
3. Dubin A, Pozo MO, Casabella CA, Murias G, Pálizas F Jr, Moseinco MC, *et al.* Comparison of 6% hydroxyethyl starch 130/0.4 and saline solution for resuscitation of the microcirculation during the early goal-directed therapy of septic patients. J Crit Care 2010;25:659.e1-8.
4. Marx G, Pedder S, Smith L, Swaraj S, Grime S, Stockdale H, *et al.* Resuscitation from septic shock with capillary leakage: Hydroxyethyl starch (130 kd), but not Ringer's solution maintains plasma volume and systemic oxygenation. Shock 2004;21:336-41.
5. Feng X, Hu Y, Ding J, Ge Y, Song J, Ai Q, *et al.* Early treatment with hydroxyethyl starch 130/0.4 causes greater inhibition of pulmonary capillary leakage and inflammatory response than treatment instituted later in sepsis induced by cecal ligation and puncture in rats. Ann Clin Lab Sci 2007;37:49-56.
6. Chen G, You G, Wang Y, Lu M, Cheng W, Yang J, *et al.* Effects of synthetic colloids on oxidative stress and inflammatory response in hemorrhagic shock: Comparison of hydroxyethyl starch 130/0.4, hydroxyethyl starch 200/0.5, and succinylated gelatin. Crit Care 2013;17:R141.
7. Finfer S, Liu B, Taylor C, Bellomo R, Billot L, Cook D, *et al.* Resuscitation fluid use in critically ill adults: An international cross-sectional study in 391 intensive care units. Crit Care 2010;14:R185.
8. Wittlinger M, Schläpfer M, De Conno E, Z'graggen BR, Reyes L, Booy C, *et al.* The effect of hydroxyethyl starches (HES 130/0.42 and HES 200/0.5) on activated renal tubular epithelial cells. Anesth Analg 2010;110:531-40.
9. Hüter L, Simon TP, Weinmann L, Schuerholz T, Reinhart K, Wolf G, *et al.* Hydroxyethylstarch impairs renal function and induces interstitial proliferation, macrophage infiltration and tubular damage in an isolated renal perfusion model. Crit Care 2009;13:R23.
10. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Åneman A, *et al.* Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 2012;367:124-34.
11. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, *et al.* Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 2012;367:1901-11.
12. Bayer O, Reinhart K, Sakr Y, Kabisch B, Kohl M, Riedemann NC, *et al.* Renal effects of synthetic colloids and crystalloids in patients with severe sepsis: A prospective sequential comparison. Crit Care Med 2011;39:1335-42.
13. Prowle JR, Pearse RM. Is it the end of the road for synthetic starches in critical illness? No place for hydroxyethyl starch solutions in treatment of patients with sepsis. BMJ 2013;346:f1805.
14. Estrada CA, Murugan R. Hydroxyethyl starch in severe sepsis: End of starch era? Crit Care 2013;17:310.
15. Chappell D, Jacob M. Hydroxyethyl starch – The importance of being earnest. Scand J Trauma Resusc Emerg Med 2013;21:61.
16. Annane D, Siami S, Jaber S, Martin C, Elatrous S, Declère AD, *et al.* Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: The CRISTAL randomized trial. JAMA 2013;310:1809-17.
17. Prowle JR, Bellomo R. Fluid administration and the kidney. Curr Opin Crit Care 2013;19:308-14.
18. Shaw AD, Kellum JA. The risk of AKI in patients treated with intravenous solutions containing hydroxyethyl starch. Clin J Am Soc Nephrol 2013;8:497-503.
19. Payen D, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL; Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care 2008;12:R74.
20. Gattas DJ, Dan A, Myburgh J, Billot L, Lo S, Finfer S; CHEST Management Committee. 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 2013;39:558-68.
21. Haase N, Perner A, Hennings LI, Siegemund M, Lauridsen B, Wetterslev M, *et al.* 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 2013;346:f839.
22. Zarychanski R, Abou-Setta AM, Turgeon AF, Houston BL, McIntyre L, Marshall JC, *et al.* 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 2013;309:678-88.
23. Patel A, Waheed U, Brett SJ. 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 2013;39:811-22.
24. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0. The Cochrane Collaboration 2011; 2012. Available from: http://www.cochrane-handbook.org. [Last accessed on 2014 May].
25. Cochrane Collaboration Glossary, 2010. Available from: http://www.cochrane.org/training/cochrane-handbook. [Last accessed on 2014 May].
26. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.
27. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med 2004;23:1351-75.
28. Siegemund M. NCT 00273728 BaSES Trial: Basel Starch Evaluation in Sepsis, Personal Communication 12 Sep, 2012.
29. Dolecek M, Svoboda P, Kantorová I, Scheer P, Sas I, Bíbrová J, *et al.* Therapeutic influence of 20% albumin versus 6% hydroxyethylstarch on extravascular lung water in septic patients: A randomized controlled trial. Hepatogastroenterology 2009;56:1622-8.
30. Lv J, Zhao HY, Liu F, An YZ. The influence of lactate Ringer solution versus hydroxyethyl starch on coagulation and fibrinolytic system in patients with septic shock. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 2012;24:38-41.
31. Palumbo D, Servillo G, D'Amato L, Volpe ML, Capogrosso G, De Robertis E, *et al.* The effects of hydroxyethyl starch solution in critically ill patients. Minerva Anestesiol 2006;72:655-64.
32. Zhu GC, Quan ZY, Shao YS, Zhao JG, Zhang YT. The study of hypertonic saline and hydroxyethyl starch treating severe sepsis. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 2011;23:150-3.
33. Gondos T, Marjanek Z, Ulakcsai Z, Szabó Z, Bogár L, Károlyi M, *et al.* Short-term effectiveness of different volume replacement therapies in postoperative hypovolaemic patients. Eur J Anaesthesiol 2010;27:794-800.
34. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, *et al.* Acute renal failure in critically ill patients: A multinational, multicenter study. JAMA 2005;294:813-8.
35. de Mendonça A, Vincent JL, Suter PM, Moreno R, Dearden NM, Antonelli M, *et al.* Acute renal failure in the ICU: Risk factors and outcome evaluated by the SOFA score. Intensive Care Med 2000;26:915-21.
36. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med 2013;369:2063.
37. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. Virulence 2014;5:4-11.
38. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, *et al.* Sepsis in European intensive care units: Results of the SOAP study. Crit Care Med 2006;34:344-53.
39. RENAL Replacement Therapy Study Investigators, Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, *et al.* An observational study fluid balance and patient outcomes in the randomized evaluation of normal vs. augmented level of replacement therapy trial. Crit Care Med 2012;40:1753-60.
40. Murugan R, Kellum JA. Fluid balance and outcome in acute kidney injury: Is fluid really the best medicine? Crit Care Med 2012;40:1970-2.
41. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, *et al.* Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008;358:125-39.
42. Bouchard J, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, *et al.* Fluid accumulation, survival and recovery of

kidney function in critically ill patients with acute kidney injury. Kidney Int 2009;76:422-7.
43. Van Biesen W, Yegenaga I, Vanholder R, Verbeke F, Hoste E, Colardyn F, *et al.* Relationship between fluid status and its management on acute renal failure (ARF) in intensive care unit (ICU) patients with sepsis: A prospective analysis. J Nephrol 2005;18:54-60.
44. Palevsky PM. Indications and timing of renal replacement therapy in acute kidney injury. Crit Care Med 2008;36 4 Suppl: S224-8.
45. Overberger P, Pesacreta M, Palevsky PM; VA/NIH Acute Renal Failure Trial Network. Management of renal replacement therapy in acute kidney injury: A survey of practitioner prescribing practices. Clin J Am Soc Nephrol 2007;2:623-30.
46. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, *et al.* Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36:296-327.
47. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, *et al.* Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368-77.
48. Rivers EP, Katranji M, Jaehne KA, Brown S, Abou Dagher G, Cannon C, *et al.* Early interventions in severe sepsis and septic shock: A review of the evidence one decade later. Minerva Anestesiol 2012;78:712-24.