National Essential Medicine List Adult Hospital Level
Medication Review Process
Component: Emergencies and Trauma:

Medication: Hydroxyethyl Starch (HES) Solutions

Date of Review: September 2015

Indication: Acute hypovolaemia due to blood loss (trauma, intraoperative haemorrhage).

Executive summary:
Fluid resuscitation for hypovolaemia is an important consideration in critically ill patients. Although colloids such as HES solutions are widely used in critically ill patients, there are concerns regarding their relative effectiveness and safety when compared with crystalloids.

This review of the evidence comparing colloids with crystalloids indicates that colloids offer no benefit over crystalloids in resuscitation of critically ill patients. Furthermore, the use HES solutions has been associated with an increased risk of mortality.

Introduction:

HES solutions are used for the treatment of hypovolemia (low blood volume) when plasma volume expansion is desired for example in the case of blood loss due to trauma and intraoperative haemorrhage**.** However, in view of the recent safety concerns regarding HES solutions, their use remains controversial.

The two main types of medicines used for volume replacement are (European Medicines Agency, 2013):

- Crystalloids; containing smaller molecules for example saline (salt) solutions or Ringer's acetate
- Colloids; containing large molecules example starch. HES solutions belong to the class known as colloids. (European Medicines Agency, 2013)

"The first HES product, i.e., Hespan® (DuPont Pharmaceuticals, Wilmington, DE), was made available in the United States in the 1970s. Since then, further generations of HES have been developed, differing in their mean molecular weight (MW), molar substitution (MS), and C2/C6 ratio. Hydroxyethyl starches are identified by three numbers, e.g., 10% HES 200/0.5 or 6% HES 130/0.4 The first number indicates the concentration of the solution, the second represents the mean molecurlar weight (MW) expressed in kiloDalton (kDa), and the third and most significant one is molar subsitituon (MS). These parameters are highly relevant to the pharmacokinetics of HES. There are differences in pharmacokinetic properties in HES, mainly resulting from differences in molecular structure. These differences in molecular structure result in different safety profiles and effects on the coagulation system and renal function." Therefore HES solutions "should not be regarded as one homogenous group, and data for one product should not be extrapolated to another" (Westphal *et a, 2009*)

"HES solutions act as volume expanders but are not localized to the circulatory system and are known to deposit in the skin, liver, muscle, spleen, endothelial cells, and kidneys of patients. Toxic effects on renal function have been documented in experimental and clinical studies. ***Zarychanski et al (2013)*** report that some researchers have argued that adverse effects depend on the volume of HES used, MW, and patient population." As each new HES product is marketed, improved safety is

emphasised by manufacturers. However, evidence from randomized trials do not support these claims. Additionally, one should keep in mind, that risk of bias in RCTs and the HES research field is further complicated in that there is a possibility of inaccurate or fraudulent data that exists in publications from one researcher (Boldt et al). (Zarychanski et al., 2013)

In 2013, the US Food and Drug Administration (FDA) "issued a boxed warning on increased mortality and severe renal injury, and an additional risk of bleeding, for use of HES solutions in certain patient populations". The FDA outlined the following (FDA., 2013):

- ***HES not be used in critically ill adult patients***, including those with sepsis,
- HES be avoided in patients with pre-existing renal dysfunction,
- Discontinuation of HES treatment at the first sign of renal injury,
- Monitor renal function for at least 90 days in all hospitalised patients,
- Monitor the coagulation status of patients undergoing open heart surgery in association with cardiopulmonary bypass as excess bleeding has been reported with HES solutions in this population.
- HES be discontinued at first sign of coagulopathy.
- HES products not be used in patients with severe liver disease.
- Monitor liver function in patients receiving HES products.

In parallel the European Medicines Agency outlined the following statement on HES solutions: " HES may continue to be used in patients to treat hypovolaemia (low blood volume) caused by acute (sudden) blood loss, where treatment with alternative infusions solutions known as 'crystalloids' alone are not considered to be sufficient. In order to minimise potential risks in these patients, HES solutions should not be used for more than 24 hours and patients' kidney function should be monitored after HES administration." (European Medicines Agency, 2013)

The European Medicines Agency, also advised that ***further studies should be carried out on the use of these medicines in elective surgery and trauma patients***. Regarding the lack of robust long term safety data ***in patients undergoing surgical procedures, and in patients with trauma the expected benefit of treatment should be carefully weighed against the uncertainties with regard to long-term safety, and other available treatment options should be considered***. (European Medicines Agency, 2013)

Contraindications on the Medicine Control Council (MCC) approved "Voluven" package information (PI) leaflet in South Africa indicate that the following contraindications to treatment should be noted:

- ***Critically ill patients*** with or without sepsis
- Severe burns
- Moderate to severe renal impairment
- Severe hepatic impairment
- Moderate to severe dehydration
- Over-hydration with or without the pulmonary oedema
- Congestive cardiac failure
- Starch Allergy
- Renal failure with oliguria or anuria
- Intracranial bleeding
- Severe hypernatremia or sever hyperchloremia
- Patients receiving dialysis treatment

The MCC approved PI leaflet also indicates that HES should be used with caution in patients with hypernatremia and hyperchloraemia. (MCC Approved PI)

Empirical therapy
The main treatment for intravascular volume depletion is fluid resuscitation with either crystalloid or colloids. Hydroxyethyl starches (HES) are a group of synthetic colloids that have been commonly used for fluid resuscitation. **(Mutter et al., 2013)**

Objective

The aim of this review is to evaluate the effectiveness and safety of HES in the treatment of blood loss (trauma, intraoperative haemorrhage). This review will assist in deciding how HES should be recommended for use in adult patients treated at secondary level facilities in the South African public health facility.

Search strategy

Keyword searches were conducted on both titles and abstracts to identify relevant publications using combinations of the keywords “Hydroxyethyl starch solutions”, registered trade names of the Hydroxyethyl starch solutions, “Hespan” “Voluven” or” Volulyte”, “Tetrahes” or “Hestar” and abbreviations “HES” or “HAES”.

Selection of studies

Population: The primary population of interest is adults with indication for HES in treatment of acute hypovolaemia due to blood loss (trauma, intraoperative haemorrhage). Main focus is on safety concerns and recommendations for use in adults with acute hypovolaemia due to blood loss. (trauma, intraoperative haemorrhage).

Comparators: Other medical therapies.

Outcomes: Primary outcome measure: Primary outcome is clinical improvement in acute hypovolaemia and mortality. Secondary outcome is: adverse events (safety).

Timing: Randomized controlled studies. For studies with multiple follow-up periods, the longest follow-up times were preferentially considered.

Settings: Settings not pre-specified.

Electronic sources

The following databases and website were searched: PubMed, the Cochrane Database of Systematic Reviews database, and Google Scholar. Publications describing RCTs of Hydroxyethyl starch solutions for acute hypovolaemia due to blood loss (trauma, intraoperative haemorrhage) were sourced using a systematic search strategy. The search strategy was performed in accordance with the Cochrane Handbook for Systematic Reviews with slight modification. Articles restricted to English with no set period of publication.

An electronic literature survey using the following terminology performed on the PUBMED database: ("Hydroxyethyl starch solutions "[MeSH Terms] OR "l Hydroxyethyl starch solutions "[All Fields]) AND (“acute hypovolaemia due to blood loss (trauma, intraoperative haemorrhage)"[MeSH Terms] OR ("acute hypovolaemia due to blood loss (trauma, intraoperative haemorrhage)"[All Fields]) AND (Randomized Controlled Trial[ptyp] AND "humans"[MeSH Terms] AND English[lang]), both as exploded MESH headings and free text terms.

Other sources

Relevant Cochrane reviews sourced from the Cochrane database and Guidelines via google scholar reviewed to identify any additional articles not retrieved from the literature survey and appraised accordingly for inclusion in this review.

Eligibility criteria and appraisal of studies

Studies identified systematically by reviewing abstracts initially and proceeding to the full text article. RCTs included were of adults with acute hypovolaemia due to blood loss (trauma, intraoperative haemorrhage) that investigated the efficacy and safety of Hydroxyethyl starch solutions of symptoms. Blood loss specified as blood loss due to trauma, and or intraoperative haemorrhage). Assessment of the quality of the RCTs was determined by study power, randomization, allocation concealment, inclusion and exclusion criteria, reported basic demographic and clinical data, loss to follow-up of study participants and follow-up duration. The risk of bias assessment of the included RCTs was evaluated, with adaptation, in accordance with the guidance of the Cochrane Handbook for Systematic Reviews. (Higgins., 2011)

Search Results

Evidence synthesis and Efficacy Information

Three Cochrane Reviews relating to the topic were identified through a search of the Cochrane Database and literature search. A summary is provided in table 1.

Table 1: Overview of Cochrane Reviews

Study Outcomes/Comparisons	Results / Conclusion
i. 78 eligible trials; 70 of these presented mortality data Colloids versus crystalloids for fluid resuscitation in ***critically ill patients*** Primary outcome: • Mortality	• Colloids compared to crystalloids – Albumin or plasma protein fraction - 24 trials reported data on mortality, including a total of 9920 patients. The pooled risk ratio (RR) from these trials was 1.01 (95% confidence interval (CI) 0.93 to 1.10). When we excluded the trial with poor-quality allocation concealment, pooled RR was 1.00 (95% CI 0.92 to 1.09). Hydroxyethyl starch - 25 trials compared hydroxyethyl starch with crystalloids and included 9147 patients. The pooled RR was 1.10 (95% CI 1.02 to 1.19). Modified gelatin - 11 trials compared modified gelatin with crystalloid and included 506 patients. The pooled RR was 0.91 (95% CI 0.49 to 1.72). (When the trials by Boldt et al were removed from the three preceding analyses, the results were unchanged.) Dextran - nine trials compared dextran with a crystalloid and included 834 patients. The pooled RR was 1.24 (95% CI 0.94 to 1.65). • Colloids in hypertonic crystalloid compared to isotonic crystalloid – Nine trials compared dextran in hypertonic crystalloid with isotonic crystalloid, including 1985 randomised participants. Pooled RR for mortality was 0.91 (95% CI 0.71 to 1.06). • There is no evidence from randomised controlled trials that resuscitation with colloids reduces the risk of death, compared to resuscitation with crystalloids, in patients with trauma, burns or following surgery. • Furthermore, the use of hydroxyethyl starch might increase mortality. As colloids are not associated with an improvement in survival and are considerably more expensive than crystalloids, it is hard to see how their continued use in clinical practice can be justified.
ii Eighty-six trials, with a total of 5,484 participants, Primary outcomes: • Mortality • Adverse effects were also considered	• No evidence that one colloid solution is more effective or safe. • Exclusion of the Boldt study (fraudulent data reported) from the analysis did not change the Risk Ratios or Confidence Intervals

iii 42 studies (11,399 patients) including RCTs and quasi-RCTs in which HES was compared to an alternate fluid therapy for the prevention or treatment of effective intravascular volume depletion Primary outcomes: • renal replacement therapy (RRT), • author-defined kidney failure and acute kidney injury (AKI) as defined by the RIFLE criteria.	• Evidence suggests that all HES products increase the risk in AKI and RRT in all patient populations. • A safe volume of any HES solution has yet to be determined. • In most clinical situations it is likely that these risks outweigh any benefits, and alternate volume replacement therapies should be used in place of HES products.

i. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients (Review). Cochrane Database. 2013
ii. Bunn F, Trivedi D. Colloid solutions for fluid resuscitation (Review). Cochrane Database. 2012
iii. Mutter et al. Hydroxyethyl starch (HES) versus other fluid therapies. effects on kidney function (Review). Cochrane Database. 2013

Due to the safety concerns raised by the FDA in 2013, a summary of the articles reviewed by the FDA are provided (these articles do not only include HES for the indication of acute hypovolaemia due to blood loss (trauma, intraoperative haemorrhage). The summary of these articles are provided because of the overall safety concerns. There were 15 reports cited by the FDA:

- One was not an article but a notice of a FDA workshop on the HES safety issue
- Regarding Four articles, the free full text was not available
- One article was a review article on HES and is summarised in the introduction of this report
- Three articles were RCTs, summarised below
- Five articles were systematic reviews, summarised below
- One was a Cochrane review, conclusion summarised above

Summary of RCTs Used in FDA Review

Mayburgh et al. 2012 conducted a multicenter, prospective, blinded, parallel-group, randomized, controlled trial in 32 hospitals in Australia and New Zealand comparing 6% HES with a molecular weight of 130 kD and a molar substitution ratio of 0.4 (130/0.4, Voluven) in 0.9% sodium chloride to 0.9% sodium chloride (saline). Primary outcome was all-cause mortality (90 days after randomization). A total of 597 of 3315 patients (18.0%) in the HES group and 566 of 3336 (17.0%) in the saline group died. There was no significant difference in mortality in six predefined subgroups (i.e. RIFLE (risk, injury or failure) criteria for acute kidney injury, sepsis, trauma, traumatic brain injury, APACHE (Acute Physiology and Chronic Health Evaluation) II score ≥25, receipt of HES before randomization). Relative Risk for death in the HES group, 1.06; 95% [CI], 0.96 to 1.18; P = 0.26.
Secondary outcomes included incidence of acute kidney injury, as defined with the use of a five-category scoring system to evaluate risk, injury, failure, loss, and end-stage kidney injury (RIFLE); the use of renal-replacement therapy; new organ failures for cardiovascular, respiratory, coagulation, and liver systems that were not present at baseline; duration of mechanical ventilation and renal-replacement therapy; and cause-specific mortality." Renal-replacement therapy was used in 235 of 3352 patients (7.0%) in the HES group and 196 of 3375 (5.8%) in the saline group (relative risk, 1.21; 95% CI, 1.00 to 1.45; P = 0.04). In the HES and saline groups, renal injury occurred in 34.6% and 38.0% of patients, respectively (P = 0.005), and renal failure occurred in 10.4% and 9.2% of patients, respectively (P = 0.12). HES was associate with significantly more adverse events (5.3% vs. 2.8%, P<0.001). HES was associate with significantly more adverse events (5.3% vs. 2.8%, P<0.001). Fresenius Kabi, the manufacturer of Voluven was a funding agency but had no input into the design, conduct, data collection, statistical analysis, or writing of the manuscript. Fresenius Kabi supplied the study fluids and distributed them to participating sites. The study included centralized randomization, allocation concealment, and blinding of study group assignments. Researchers published statistical analysis plan including predefined subgroups, before the unbinding of study-group assignments. ***No significant difference in mortality between HES and saline. However, those who received resuscitation with HES were more likely to receive renal-replacement therapy.***

Perner et al., 2012 conducted a parallel-group, blinded trial on patients with severe sepsis. Patients were given fluid resuscitation in the ICU with either 6% HES 130/0.42 (Tetraspan) or Ringer's acetate. The outcomes under investigation were death or end-stage kidney failure (dependence on dialysis). 201 of 398 patients (51%) assigned to HES 130/0.42 had died vs 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); 1 patient in each group had end-stage kidney failure. It should also be noted that patients with acute renal injury were randomised into the study although in both groups. There was a degree of bias in the study because protocol violations occurred example - 77 patients were given open label synthetic colloids during the trial period. There was comparable attrition between the two groups, 124 discontinued in the HES group vs 92 in the other group. ***Poorer outcomes with HES were concluded.***

Guidet et al., 2012 conducted a prospective, multicenter, active-controlled, double-blind, randomized study in intensive care units. Patients requiring hemodynamic stabilization (HDS) with severe sepsis were randomised to 6% HES 130/0.4 and NaCl 0.9%. 174 out of 196 patients reached HDS (88 and 86 patients for HES and NaCl, respectively). Significantly less HES was used to reach HDS vs. NaCl (1,379 ±886 ml in the HES group and 1,709 ±1,164 ml in the NaCl group (mean difference = -331± 1,033, 95% CI -640 to -21, P = 0.0185). Time to reach HDS was 11.8 ±10.1 hours vs. 14.3 ±11.1 hours for HES and NaCl, respectively. Acute renal failure occurred in 24 (24.5%) and 19 (20%) patients for HES and NaCl, respectively (P = 0.454). There was no difference between AKIN and RIFLE criteria among groups and no difference in mortality, coagulation, or pruritus up to 90 days after treatment initiation. ***Significantly less volume was required to achieve HDS for HES vs. NaCl in the initial phase of fluid resuscitation in severe sepsis patients without any difference for adverse events in both groups***

See table 2 for summary on the 3 RCTs discussed above.

Study (year)	Study design	Participants (studies) Follow up	Study comparators	Summary of findings					Quality of study	Risk of bias
				Study event rates (%)		Absolute risk (AR) reduction (95% CI)	NNT/NNH:	Relative risk (RR): (95% CI)		
				Intervention	Comparator					
ii Maybu rgh et al. 2012	Multicent er, prospectiv e, blinded, parallel-group, randomize d,controll ed trial	32 hospitals in Australia and New Zealand.	6% HES with a molecular weight of 130 kD and a molar substitution ratio of 0.4 (130/0.4, Voluven) in 0.9% sodium chloride or 0.9% sodium chloride (saline)	***Primary outcome:*** All-cause mortality (90 days after randomization) A total of 597 of 3315 patients (18.0%) in the HES group and 566 of 3336 (17.0%) in the saline group died. There was no significant difference in mortality in six predefined subgroups (i.e. RIFLE (risk, injury or failure) criteria for acute kidney injury, sepsis, trauma, traumatic brain injury, APACHE (Acute Physiology and Chronic Health Evaluation) II score ≥25, receipt of HES before randomization).				RR in the HES group, 1.06; 95% [CI], 0.96 to 1.18; P = 0.26).	Fresenius Kabi, the manufacturer of Voluven was a funding agency but had no input into the design, conduct, data collection, statistical analysis, or writing of the manuscript. Fresenius Kabi supplied the study fluids and distributed them to participating site. Centralized randomization, allocation concealment, and blinding of study group assignments. Published statistical analysis plan including predefined subgroups, before the unbinding of study-group assignments	Selection(randomization): Selection (allocation):
				Secondary outcome(s): "Incidence of acute kidney injury, as defined with the use of a five-category scoring system to evaluate risk, injury, failure, loss, and end-stage kidney injury (RIFLE); the use of renal-replacement therapy; new organ failures for cardiovascular, respiratory, coagulation, and liver systems that were not present at baseline; duration of mechanical ventilation and renal-replacement therapy; and cause-specific mortality." Renal-replacement therapy was used in 235 of 3352 patients (7.0%) in the HES group and 196 of 3375 (5.8%) in the saline group (relative risk, 1.21; 95% CI, 1.00 to 1.45; P = 0.04). In the HES and saline groups, renal injury occurred in 34.6% and 38.0% of patients, respectively (P = 0.005), and renal failure occurred in 10.4% and 9.2% of patients, respectively (P = 0.12).						
								See secondary outcome note		Performance:
				Adverse effects: HES was associate with significantly more adverse events (5.3% vs. 2.8%, P<0.001).						Detection:
										Attrition:
				Adverse effects:						
Perner et al.,	Parallel-group,	Patients with	Fluid resuscitation in	***Primary outcome:*** Death at 5 days (dependent on analysis)					Protocol violations e.g. 77 patients were given	Selection(randomization): Patients with acute kidney

2012	blinded trial	severe sepsis	the ICU with either 6% HES 130/0.42 (Tetraspan) or Ringer's acetate	201 of 398 patients (51%) assigned to HES 130/0.42 had died vs 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); 1 patient in each group had end-stage kidney failure.	open label synthetic colloids during the trial period	injury were randomized although equally between both groups Selection (allocation):
				See note above		
				Secondary outcome(s):		
						Performance:
				Adverse effects:		Detection:
						Attrition: 124 discontinued in the HES group vs 92 in the other group
				Adverse effects:		
Iii Guidet et al., 2012	Prospective, multicenter, active-controlled, double-blind, randomized in intensive care units	Patients requiring hemodynamic stabilization with severe sepsis	6% HES 130/0.4 and NaCl 0.9%	***Primary outcome:***, Hemodynamic Stabilization 174 out of 196 patients reached HDS (88 and 86 patients for HES and NaCl, respectively). Significantly lessHES was used to reach HDS vs. NaCl (1,379 ±886 ml in the HES group and 1,709 ±1,164 ml in the NaCl group (mean difference = -331± 1,033, 95% CI -640 to -21, P = 0.0185). Time to reach HDS was 11.8 10.1 hours vs. 14.3±11.1 hours for HES and NaCl, respectively. There was no difference between AKINand RIFLE criteria among groups and no difference in mortality, coagulation, or pruritus up to 90 days after treatment initiation	Poor Power	Selection(randomization) Selection (allocation):
				Secondary outcome(s):		
						Performance:
				Adverse effects		Detection:
						Attrition:

i. Myburgh J, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, McGuinness S, Rajbhandari D, Taylor CB, and Webb SAR. Hydroxyethyl Starch or Saline for FluidResuscitation in Intensive Care. N Engl J Med. 2012 367;20.

ii. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.4 versus Ringer's acetate in severe sepsis. N Engl J Med 2012;367:124-34.

iii. Guidet B, Martine O, Boulain T, Philippart F, Poussel JF, Maizel J, Forceville X, Feissel M, Hasselmann M, Heininger A and Van Aken H. 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. Critical Care 2012, 16:R94

Summary of Systematic Reviews Used in FDA Review

Five Systematic Reviews were also identified through the FDA summary (see table below for summaries).

Zarychanskit et al .,2013 conducted a systematic review and meta-analysis on 38 RCTs comparing HES to crystalloids, albumin, or gelatin. The primary outcome was mortality or acute kidney injury. This review included results from 7 trials performed by an investigator whose subsequent research had been retracted because of scientific misconduct. When these 7 trials (n=590) were excluded, HES was found to be associated with increased risk of mortality among 10 290 patients (RR, 1.09; 95% CI, 1.02 to 1.17; I2, 0%; AR, 1.51%; 95% CI, 0.02% to 3.00%), increased risk of renal failure among 8725 patients (RR, 1.27; 95% CI, 1.09 to 1.47; I2, 26%; AR, 5.45%; 95% CI, 0.44% to 10.47%), and increased use of renal replacement therapy among 9258 patients (RR, 1.32; 95% CI, 1.15 to 1.50; I2, 0%; AR, 3.12%; 95% CI, 0.47% to 5.78%). Absolute risk of death among patients randomized to receive HES was 1.20%; 95% CI, −0.26% to 2.66%. Relative Risk for death among patients randomized to receive HES was 1.07 (95% CI, 1.00 to 1.14). "Secondary outcomes included reduction in urine output, glomerular filtration rates, incidence of renal recovery, or the incidence of anuria, intensive care unit length of stay, overall hospital length of stay an average duration of ventilation. HES administration was associated with a reduction in urine output (standardized mean difference, −0.15; 95% CI, −0.19 to −0.10). Included trials did not report changes in the glomerular filtration rates, incidence of renal recovery, or the incidence of anuria among patients. No differences in intensive care unit length of stay or overall hospital length of stay were reported. There was no reported difference in the average duration of ventilation. The reports on the incidence of hemorrhage and use of blood transfusions were conflicting with most trials providing no extractable data. None of the included trials reported the average volume of blood loss among patients; however, 1 trial 53 involving 800 patients reported no significant difference in the incidence of severe hemorrhage. Pooled results from 5 trials involving 1482 patients showed a significantly higher incidence of red blood cell transfusions in patients randomized to receive HES (RR, 1.42; 95% CI, 1.15 to 1.75; I2, 0%); however, the transfusion volume was not reported to be different between groups in 3 trials, involving 162 patients. Most trials did not systematically screen for, or report the incidence of allergic reactions to resuscitation fluids. When reported, allergies rarely (<1%) occurred among 984 patients involved in 3 trials." The majority of trials were categorized as having an unclear risk or high risk of bias. ***Conclusion stated by the authors was that "Clinical use of hydroxyethyl starch for acute volume resuscitation is not warranted due to serious safety concern."***

Van de Linden et al., 2012 conducted a systematic review addressing mortality; coagulation, coagulation, trauma renal aspects and renal replacement therapy (RRT), creatinine: and urine output. See table below for summary as reported in the article on each of the outcomes. Of particular interest to this review was coagulation trauma. "Two studies reported data on blood loss or transfusion requirements in trauma patients. The first study was a single-center randomized single-blind trial that evaluated the effects of repetitive doses of up to 70 mL/kg of HES 130/0.4 compared with pentastarch plus albumin in intensive care unit patients with severe head injury. Blood drainage and estimated other blood loss were not different between the 2 groups of patients. Intracranial bleeding complications were not different between groups (5/16 in the tetrastarch group and 5/15 in the pentastarch + albumin group) and were not accompanied by coagulation disorders. The second study was a single-center randomized double-blind trial conducted in South Africa comparing HES 130/0.4 with isotonic saline in severely injured patients requiring more than 3 L of fluid resuscitation in which blunt and penetrating trauma were analyzed separately. In the penetrating trauma patients, the volume of erythrocytes transfused was not different between groups (HES 130/0.4, 1553 ± 1562 mL; NaCl 0.9%: 1796 ± 1361 mL). In the blunt trauma patients, the volume of erythrocytes transfused was significantly higher in the tetrastarch group than that in the

saline group (HES 130/0.4, 2943 ± 1628 mL; NaCl 0.9%: 1473 ± 1071 mL; P = 0.005), as was the volume of transfused fresh frozen plasma and platelet concentrates. These may have been related to a clinically and statistically significant greater severity of injury in the HES group. "Several limitations were noted included sample size concerns, blinding of participants and short follow up periods.

Hasse et al conducted a systematic review with meta-analyses comparing Hydroxyethyl starch 130/0.38-0.45 with either crystalloid or human albumin in patients with sepsis. All cause mortality, Renal replacement therapy at end of follow-up, Renal replacement therapy at anytime during follow-up, Acute kidney injury, transfusions with red blood cells, bleeding, and blood loss were the outcomes of interest. "Nine trials that randomised 3456 patients with sepsis were included. Overall, hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin did not affect the relative risk of death (1.04, 95% confidence interval 0.89 to 1.22, 3414 patients, eight trials), but in the predefined analysis of trials with low risk of bias the relative risk of death was 1.11 (1.00 to 1.23, trial sequential analysis (TSA) adjusted 95% confidence interval 0.95 to 1.29, 3016 patients, four trials). In the hydroxyethyl starch group, renal replacement therapy was used more (1.36, 1.08 to 1.72, TSA adjusted 1.03 to 1.80, 1311 patients, five trials), and the relative risk of acute kidney injury was 1.18 (0.99 to 1.40, TSA adjusted 0.90 to 1.54, 994 patients, four trials). More patients in the hydroxyethyl starch group were transfused with red blood cells (1.29, 1.13 to 1.48, TSA adjusted 1.10 to 1.51, 973 patients, three trials), and more patients had serious adverse events (1.30, 1.02 to 1.67, TSA adjusted 0.93 to 1.83, 1069 patients, four trials). The transfused volume of red blood cells did not differ between the groups (mean difference 65 mL, 95% confidence interval −20 to 149 mL, three trials)."

Gattas et al reviewed the literature for RCTs on fluid resuscitation of acutely ill adults with HES compared with other resuscitation fluids results in terms of the difference in the relative risk of death or treatment with renal replacement therapy (RRT). 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 %). Follow up was not analysed in the systematic review. ***Patients randomly assigned to resuscitation with 6 %HES 130 are at significantly increased risk of being treated with RRT***.

Patel et al., 2013 set out to "assess the impact of 6 % tetrastarch [hydroxyethyl starch (HES) 130/0.4 and 130/0.42] in severe sepsis patients. The primary outcome measure was mortality. Six RCTs were included (n = 3,033): three from 2012 (n = 2,913) had low risk of bias. No difference between groups was observed for 28-day mortality, for comparison with colloid as control, or for waxy maize-derived tetrastarch, but power was lacking. Overall mortality was associated with tetrastarch exposure (RR 1.13; 95 % CI 1.02–1.25; p = 0.02). Tetrastarch as part of initial fluid resuscitation for severe sepsis was associated with harm and, as alternatives exist, in our view should be avoided."

Table 3: Systematic Review Summaries

Study (year)	Study design	Participants (studies) Follow up	Study comparators	Summary of findings					Quality of study	Risk of bias
				Study event rates (%)		Absolute risk (AR) reduction (95% CI)	NNT/NNH:	Relative risk (RR): (95% CI)		
				Intervention	Comparator					
i. .Zarychanskit et al .,2013	Systematic Review and Meta-Analysis	38 Randomised Controlled Trials	Hydroxyethyl starch to crystalloids, albumin, or gelatin.	***Primary outcome:*** mortality and acute kidney injury.					Majority of trials were categorized as having an unclear risk or high risk of bias	Selection: (randomization): Selection (allocation):
				*This summary effect measure included results from 7 trials performed by an investigator whose subsequent research had been retracted because of scientific misconduct. When these 7 trials (n=590) were excluded, HES was found to be associated with increased mortality among 10 290 patients (RR, 1.09; 95% CI, 1.02 to 1.17; I2, 0%; AR, 1.51%; 95% CI, 0.02% to 3.00%), increased renal failure among 8725 patients (RR, 1.27; 95% CI, 1.09 to 1.47; I2, 26%; AR, 5.45%; 95% CI, 0.44% to 10.47%), and increased use of renal replacement therapy among 9258 patients (RR, 1.32; 95% CI, 1.15 to 1.50; I2, 0%; AR, 3.12%; 95% CI, 0.47% to 5.78%).		AR or death among patients randomized to receive HES was 1.20%; 95% CI, −0.26% to 2.66%.*		RR for death among patients randomized to receive HES was 1.07 (95% CI, 1.00 to 1.14)*		
				Secondary outcome (aspects reviewed in bold): "HES administration was associated with a ***reduction in urine output*** (standardized mean difference, −0.15; 95% CI, −0.19 to −0.10). Included trials did not report changes in the ***glomerular filtration rates***, **incidence of renal recovery**, or the **incidence of anuria** among patients. No differences in **intensive care unit length of stay** or **overall hospital length of stay** were reported. There was no reported difference in the **average duration of ventilation**. The reports on the **incidence of**						

Study	Study	Participants	Study	Summary of findings	Quality of study	Risk of bias
				hemorrhage and **use of blood transfusions** were conflicting with most trials providing no extractable data. None of the included trials reported the average volume of blood loss among patients; however, 1 trial 53 involving 800 patients reported no significant difference in the **incidence of severe hemorrhage**. Pooled results from 5 trials involving 1482 patients showed a significantly higher incidence of **red blood cell transfusions** in patients randomized to receive HES (RR, 1.42; 95% CI, 1.15 to 1.75; I2, 0%); however, the **transfusion volume** was not reported to be different between groups in 3 trials, involving 162 patients. Most trials did not systematically screen for, or report the incidence of allergic reactions to resuscitation fluids. When reported, allergies rarely (<1%) occurred among 984 patients involved in 3 trials."		
						Performance:
				Adverse effects		Detection:
						Attrition: 250 (137 from HES group and 113 from Saline group) withdrew consent and 10 (5 from each arm) were lost to follow up
ii VandeLinden et al	Systematic Review Searched MEDLINE, CENTRAL (Cochrane Central Register of Controlled Trials), and EMBASE from January 1, 1997, to December 1, 2011	213 publications of which 59 were determined to meet the a priori inclusion criteria in the acute surgical environment (excluding abstracts and duplicate publications). These studies included 4529 unique patients who had been randomly allocated to be treated with a tetrastarch(n = 2139) or a comparator (n	Brand Names of Various HES Products 670/0.75: Hextend 600/0.75: Hespan 250 or 262/0.45: Pentaspan 200/0.5: Hemohes 200/0.62: Hyperhes 130/0.4:	***Primary outcome:*, Mortality:** "There were 11 deaths reported in the 956 patients given a tetrastarch (1.15% [95% CI, 0.57%–2.05%] and 22 deaths in the 982 patients given a comparator (2.24% [1.41%–3.37%]. The OR for mortality for HES administration versus all comparators was 0.51 ([0.24–1.05]; $\boldsymbol{P}$ = 0.079)" **Coagulation:** "In summary, 38 studies have evaluated the effects of tetrastarch on blood loss in patients undergoing various surgical procedures, mainly cardiac, major abdominal, or orthopedic surgery. Overall, no study demonstrated an increase in perioperative blood loss, allogeneic blood volume transfused, or exposure to allogeneic blood products in patients receiving tetrastarches compared with those receiving other colloids or crystalloids. The ratio of blood loss in the tetrastarch group to other groups varied from 0.75 to 1.01, with a mean and 95% CIs that were < 1.0 for comparison with other HES or human serum albumin, and inclusive of 1.0 for gelatin and crystalloid." **Coagulation, trauma:** "Two studies reported data on blood loss or transfusion requirements in trauma patients. The first study was a single-center randomized single-blind trial that evaluated the effects of repetitive doses of up to 70 mL/kg of HES 130/0.4 compared with pentastarch plus albumin in intensive care unit patients with severe head injury. Blood drainage and estimated other blood loss were not different between the 2 groups of patients. Intracranial bleeding complications were not different between groups (5/16 in the tetrastarch group	Included blinded and unblinded trials. One would expect more bias in an unblended study, although no differences were found between the two types of study results. Follow Up periods were short Some trials had a relatively small sample size.	Selection(randomization) Selection (allocation):

Study	Study	Participants	Study	Summary of findings	Quality of study	Risk of bias
		= 2390).	Voluven 130/0.42: Tetraspan; Venofundin	and 5/15 in the pentastarch + albumin group) and were not accompanied by coagulation disorders. The second study was a single-center randomized double-blind trial comparing HES 130/0.4 with isotonic saline in severely injured patients requiring more than 3 L of fluid resuscitation in which blunt and penetrating trauma were analyzed separately. In the penetrating trauma patients, the volume of erythrocytes transfused was not different between groups (HES 130/0.4, 1553 ± 1562 mL; NaCl 0.9%: 1796 ± 1361 mL). In the blunt trauma patients, the volume of erythrocytes transfused was significantly higher in the tetrastarch group than that in the saline group (HES 130/0.4, 2943 ± 1628 mL; NaCl 0.9%: 1473 ± 1071 mL; ***P*** = 0.005), as was the volume of transfused fresh frozen plasma and platelet concentrates. These may have been related to a clinically and statistically significant greater severity of injury in the HES group." **Renal:**, "41 publications included data regarding renal outcomes of acute renal failure, need for **Renal Replacement Therapy (**RRT), serum creatinine, creatinine clearance, blood urea nitrogen (BUN), or urine output. There was no suggestion of adverse mortality (no deaths in 16 patients in the tetrastarch group and 2 deaths in 15 patients in the pentastarch group) or adverse renal effects (renal failure: 0 with tetrastarch, 2 with pentastarch, and no differences between groups in serum creatinine or creatinine clearance)." **Renal Replacement Therapy (RRT): "**Seven studies reported the need for RRT. Seven of 388 (1.8%) patients receiving a tetrastarch had RRT compared with 12 of 402 (3.0%) receiving a comparator (OR, 0.60 [0.23–1.53]; P = 0.35; all were other colloids, except for 1 group of crystalloid in 1 trial)." **Creatinine:** "Twenty-one studies reported on serum creatinine concentrations or creatinine clearance after administration of the test fluids. Overall, there was no indication that administration of a tetrastarch resulted in creatinine clearance or plasma concentrations that differed from that of any other group. The ratio of peak serum creatinine in the tetrastarch group to other groups varied from 0.86 to 1.08, with 95% CIs inclusive of 1.0." **Urine Output:** "Thirty-five trials with 2616 patients compared urine output after random allocation to receive a tetrastarch (1264 patients) or a comparator (1352). No study reported a statistical difference between groups. In summary, 24 trials evaluated the need for RRT or creatinine clearance or concentration in 1134 patients given a tetrastarch and 1177 given a comparator. There was no		

Study	Study	Participants	Study	Summary of findings					Quality of study	Risk of bias
				evidence that tetrastarch administration induced renal impairment as judged by these variables, including in subpopulations of patients at high risk for postoperative degradation of renal function."						
				Secondary outcome(s):						
										Performance:
				Adverse effects						Detection:
										Attrition:
Study (year)	**Study design**	**Participants (studies)** **Follow up**	**Study comparators**	**Summary of findings**					**Quality of study**	**Risk of bias**
				Study event rates (%)		**Absolute risk (AR) reduction** (95% CI)	**NNT/NNH:**	**Relative risk (RR):** (95% CI)		
				Intervention	**Comparator**					
iii Hasse et al., 2013	Systematic review with meta-analyses and trial sequential analyses of RCTs	Cochrane Library, Medline, Embase, Biosis Previews, Science Citation Index Expanded, CINAHL, Current Controlled Trials, Clinicaltrials.gov, and Centerwatch to September 2012; hand search of reference lists and other systematic reviews; contact with authors and relevant pharmaceutical companies	Hydroxyethyl starch 130/0.38-0.45 with either crystalloid or human albumin in patients with sepsis. Published and unpublished trials were included irrespective of language and predefined outcomes.	***Primary outcome:*** All cause mortality, Renal replacement therapy at end of follow-up, Renal replacement therapy at anytime during follow-up, Acute kidney injury, transfusions with red blood cells, bleeding, and blood loss "Nine trials that randomised 3456 patients with sepsis were included. Overall, hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin did not affect the relative risk of death (1.04, 95% confidence interval 0.89 to 1.22, 3414 patients, eight trials), but in the predefined analysis of trials with low risk of bias the relative risk of death was 1.11 (1.00 to 1.23, trial sequential analysis (TSA) adjusted 95% confidence interval 0.95 to 1.29, 3016 patients, four trials). In the hydroxyethyl starch group, renal replacement therapy was used more (1.36, 1.08 to 1.72, TSA adjusted 1.03 to 1.80, 1311 patients, five trials), and the relative risk of acute kidney injury was 1.18 (0.99 to 1.40, TSA adjusted 0.90 to 1.54, 994 patients, four trials). More patients in the hydroxyethyl starch group were transfused with red blood cells (1.29, 1.13 to 1.48, TSA adjusted 1.10 to 1.51, 973 patients, three trials), and more patients had serious adverse events (1.30, 1.02 to 1.67, TSA adjusted 0.93 to 1.83, 1069 patients, four trials). The transfused volume of red blood cells did not differ between the groups (mean difference 65 mL, 95% confidence interval −20 to 149 mL, three trials)."					Inadequate follow-up, and trials not reporting all the outcome measures	Selection: (randomization): Selection (allocation):
				Secondary outcome						
										Performance:
				Adverse effects						Detection:
										Attrition:
				Secondary outcome(s):						
										Performance:
				Adverse effects						Detection:
										Attrition: 1
				Study event rates (%)		**Absolute risk (AR)**	**NNT/NNH:**	**Relative risk (RR):**		
				Intervention	**Comparator**					

Study	Study	Participants	Study	Summary of findings					Quality of study	Risk of bias
						reduction (95% CI)		(95% CI)		
iv. .Gattas et al	Systematic Review	Thirty-five trials 10,391 participants.	Hydroxyethyl starch compared with other resuscitation fluids	***Primary outcome:*** Mortality or treatment with RRT. Patients assigned to resuscitation with 6 % HES 130 are at significantly increased risk of being treated with RRT.						Selection: (randomization): Selection (allocation):
				Secondary outcome						
										Performance:
				Adverse effects						Detection:
										Attrition:
Patel et a., 2013	Systematic Review	Six RCTs were included (n = 3,033)	6 % tetrastarch [hydroxyethyl starch (HES) 130/0.4 and 130/0.42]	***Primary outcome:***, Mortality Overall mortality was associated with tetrastarch exposure (RR 1.13; 95 % CI 1.02–1.25; p = 0.02).						Selection(randomization) Selection (allocation):
								See note above		
				Secondary outcome(s):						
										Performance:
				Adverse effects						Detection:
										Attrition:

i. Zarychanski R, Abou-Setta A, Turgeon AF, Houston BL, McIntyre L, Marshall JC, Fergusson DA. 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(7):678-688.

ii. Van Der Linden P, James M, Michael Mythen M, and Weiskop RB. Safety of Modern Starches Used During Surgery. Anaesthesia and Analgesia. 2013; 116 (1): 35-48.

iii. Haase N, Perner A, Hennings LI, Siegemund M, Lauridsen B, Wetterslev M, Wetterslev J. 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.

iv. Gattas DJ, Dan A, Myburgh J, et al. Fluid resuscitation with 6% hydroxyethyl starch (130/0.4 and 130/0.42) in acutely ill patients: systemic review of effects on mortality and treatment with renal replacement therapy. Intensive Care Med 2013; doi 10.1007/s00134-013-2840-0

v. 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; DOI 10.1007/s00134-013-2863-6

Refining the search, a review of PubMed and Google Scholar Databases highlighted potentially 38 and 28 articles respectively in addition to the articles already identified in the FDA review. However, studies were excluded as they:

- Were not RCTs,
- Were Experimental laboratory studies
- Were not available in the English language (articles were in Serbian, Spanish or Chinese)
- Were duplicates of studies already identified
- Reviews already highlighted through the Cochrane database
- Were not full articles
- Were guidelines only (Not studies)
- Did not mention HES
- Were written by Boldt, a researcher who was identified as publishing fraudulent results
- Included in the systematic reviews already summarised

1 Article identified through google scholar (published in 2014; after the FDA review) was not a RCT, but a systematic review of HES in trauma patients. Jabaley & Roman Dudaryk, 2014 ***concluded "that despite the theoretical benefits to resuscitation with colloids, the clinical evidence available does not support their role for resuscitation in trauma or otherwise critically ill patients."*** The authors agreed with the conclusions reached in the Perel et al Cochrane review, that cost of colloids is high and therefore because they do not show clinical superiority over crystalloids their use cannot be justified. Overall, HES is associated with mortality and renal failure. Three of the 5 studies included in this review were also included in previous systematic reviews. The remaining two studies were varied and not necessarily related to HES. Interestingly one of the papers included (James et al) was a study conducted in a South African population.

James et al (2011) at a single center in South Africa (Cape Town) "compared resuscitation with 0.9% saline vs hydroxyethyl starch, HES 130/0.4, in severe trauma with respect to resuscitation, fluid volume, gastrointestinal recovery, renal function, and blood product requirements through a randomized, controlled, double-blind study of severely injured patients requiring.3 litres of fluid resuscitation. Blunt and penetrating trauma was randomized separately. Patients were followed up for 30 days. A total of 115 patients were randomized; of which, 109 were studied. For patients with penetrating trauma (=67), the mean (SD) fluid requirements were 5.1 (2.7) litres in the HES group and 7.4 (4.3) litres in the saline group (P<0.001). In blunt trauma (n=42), there was no difference in study fluid requirements, but the HES group required significantly more blood products [packed red blood cell volumes 2943 (1628) vs 1473 (1071) ml, P=0.005] and was more severely injured than the saline group (median injury severity score 29.5 vs 18; P=0.01). Haemodynamic data were similar, but, in the penetrating group, plasma lactate concentrations were lower over the first 4 h (P=0.029) and on day 1 with HES than with saline [2.1 (1.4) vs 3.2 (2.2) mmol litre21; P=0.017]. There was no difference between any groups in time to recovery of bowel function or mortality. In penetrating trauma, renal injury occurred more frequently in the saline group than the HES group (16% vs 0%; P¼0.018). In penetrating trauma, maximum sequential organ function scores were lower with HES than with saline (median 2.4 vs 4.5, P¼0.012). No differences were seen in safety measures in the blunt trauma patients. The authors drew the conclusion in this South African setting that in penetrating trauma, HES provided significantly better lactate clearance and less renal injury than saline. No firm conclusions could be drawn for blunt trauma." Limitations to this study included small numbers and the imbalance of the injury severity in the blunt trauma category.

Jabaley & Roman Dudaryk (2014) report that South African study is the only published randomized controlled trial to examine the effects of HES in blunt or penetrating trauma patients. Jabley et al caution that "It is inadvisable to draw concrete conclusions from the data presented above for several reasons. The study was manufacturer-sponsored and initially designed to primarily address

the volume of fluid required for resuscitation and time until return of bowel function with no intent to examine mortality, renal failure, or coagulopathy. While the authors were quick to tout the improvement in lactate clearance and markers of renal function, most adverse outcomes listed above were downplayed. In addition to the possibility of funding and reporting bias, the study was also likely underpowered to detect renal failure given the small sample size. Marked baseline differences in the blunt trauma arm of the study preclude any determination about the utility or safety of HES in that subset, and findings based on analysis non-randomized subgroups may be skewed."

Annane et al. (2013) conducted an open-label pragmatic RCT in critically ill patients in the ICU (sepsis, trauma, or hypovolemic shock without sepsis or trauma) in Europe, Canada and North Africa, where they compared the effects of colloids (n = 1414; gelatins, dextrans, hydroxyethyl starches, or 4% or 20% of albumin) with crystalloids (n = 1443; isotonic or hypertonic saline or Ringer lactate solution) for resusctitation. Randomisation was stratified according to diagnosis at admission. The primary outcome was mortality at 28-day mortality. Secondary outcomes included 90-day mortality; and days alive and not receiving renal replacement therapy (RRT), mechanical ventilation, or vasopressor therapy. There was no difference in the primary outcome between colloids and crystalloids: 359 deaths (25.4%) in colloids group vs 390 deaths (27.0%) in crystalloids group (relative risk [RR], 0.96 [95% CI, 0.88 to 1.04]; P = .26). There was a statistically significant difference in 90-day mortality favouring colloids: 434 deaths (30.7%) in colloids group vs 493 deaths (34.2%) in crystalloids group (RR, 0.92 [95% CI, 0.86 to 0.99]; P = .03). There was no difference in the requirement for RRT: 156 (11.0%) in colloids group vs 181 (12.5%) in crystalloids group (RR, 0.93 [95% CI, 0.83 to 1.03]; P = .19). The limitations of this study include its open-label design, lack of comparison of specific therapies (e.g. HES vs Normal Saline) and prolonged recruitment between February 2003 and August 2012.

Evidence Quality

Concerns and biases are summarised with each study and in the tables above. Particular caution should be applied to the results in favour of HES through the South African study. Several concerns were raised in a systematic review in 2014 (summarised above) about the South African results concerning the initial objective of the study, down playing of the side effects, industry sponsorship and small sample size.

Safety Information

In an RCT by Mayburgh *et al*. (2012) HES was associated with significantly more adverse events. Although Guidet *et al* indicated that the difference in side effects between HES and normal saline was not significantly different in a patient group requiring haemodynamic stabilisation. Again, special note should be given to the South African Study (on HES in trauma environment) published by James *et al*; where a review in 2014 pointed out that James al might have down played the side effects of HES summarising an overall positive outcome of HES use in a trauma environment.

Alternative Agents

Comparisons or alternatives to HES included crystalloids (e.g. normal saline). A cochrane review concluded that "there is no evidence from RCTs that resuscitation with colloids reduces the risk of death, compared to resuscitation with crystalloids, in patients with trauma, burns or following surgery."

Summary

Due to the safety concerns, studies reviewed by the FDA were included in this review (despite not all the studies considering acute hypovolaemia due to blood loss due to trauma or haemorrhage). Data shows that there are safety concerns with the use of HES. International regulatory bodies and the MCC approved package information leaflet clearly indicate under which conditions HES should be contraindicated and used with caution. Cochrane reviews indicate that colloids are not superior to crystalloids and that the higher cost of colloids can no therefore be justified. Additionally, HES has been associated with acute renal failure and mortality. From this review there is no clear benefit of HES compared to other resuscitation fluids.

Recommendations

Consideration should be given to:

- the black box warning released by the FDA and
- the MCC recommendations for contraindications.

A South African study is available that shows the benefit of HES compared to saline in penetrating trauma victims. However, there are several limitations to this local study and results should be interpreted with caution as pointed out in a review by Jabaley & Roman Dudaryk in 2014.

The overall safety concerns (not only shown in trauma population) should be taken into consideration before a decision is made.

Because of the safety concerns, especially in an unpredictable, non-homogenous group that might require fluid resuscitation due to blood loss (trauma and haemorrhage); if the committee decides to include HES on an essential medicines list, the recommendation should:

- include a summary of which patient groups the agent can be administered
- under what conditions the item is contraindicated
- a statement of how patients on HES should be managed and monitored
- level of care the item can be used under supervision of a clinical expert.

However, in general, from this review, the risk of use of HES seems to outweigh the benefit especially since safer alternatives are available.

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