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Hydroxyethyl starch (HES)

Assessment of evidence since the 2013 referral

Table of Contents

1. General information 2

2. Background 3

3. Methodology 3

4. Summary of newest evidence 4

4.1. Meta-analysis and systematic reviews 4
4.2. Individual studies-general surgery indication (abdominal, urology, orthopaedic) 4
4.3. Individual studies-Cardiovascular medicine 5
4.4. Trauma patients 5
4.5. Pediatrics 6
4.6. Other uses 6
4.7. Ongoing trials that might provide useful information 6
4.8. Drug utilisation studies 7

5. Conclusion 7

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1. General information

Title	Hydroxyethyl starch-Assessment of evidence since the 2013 referral
Date of last version	24 November 2017
Active substance	Hydroxyethylstarch (Blood substitutes and plasma protein fractions)
Product reference:	
Procedure number:	EMEA/H/A-107i/1457
Initiator	Surveillance and Epidemiology Unit, EMA
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2. Background

Hydroxyethyl starch (HES) solutions are a volume replacement therapy, used together with another class, crystalloids for volume expansion during surgeries and in shock situations. In the past, there were concerns with regards to renal toxicity and increased mortality rate in critically ill patients and those with sepsis and kidney injury, treated with HES. These concerns led to a safety referral being triggered, concluded in in 2013, with the following risk minimisation activities: restriction of indication to "treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient" and circulation of a DHPC.

To assess the effectiveness of the risk minimisation measures, the MAHs were asked to perform two drug utilisation studies. The results of these studies showed that the imposed restrictions in indication are not fully adhered to by responsible physicians. This raised concerns regarding the B/R balance for the product and led to a newly started referral, under an urgent union procedure in September 2017.

This report is aimed to support the decision making during the referral, in addition to information provided by MAHs and other stakeholders.

3. Methodology

A systematic review of literature was performed. Only the new evidence occurred since the last referral (when all available evidence was thoroughly reviewed) was considered.

Searches in PubMed and Embase were conducted, for English language articles, studies conducted in humans, published between 01/08/2013 and 22/11/2017.

The following exclusion criteria were applied:

- preclinical studies

- case studies or case series

- reviews, commentaries or opinion letters

- clinical guidances, opinion papers, recommendations

Data collection in individual studies was required to go beyond 2013 and for meta-analysis - to include studies finalized after October 2013.

The studies were reviewed only at abstract level. The full search strategy can be found in the Annex. The selection of studies is presented in Figure 1.

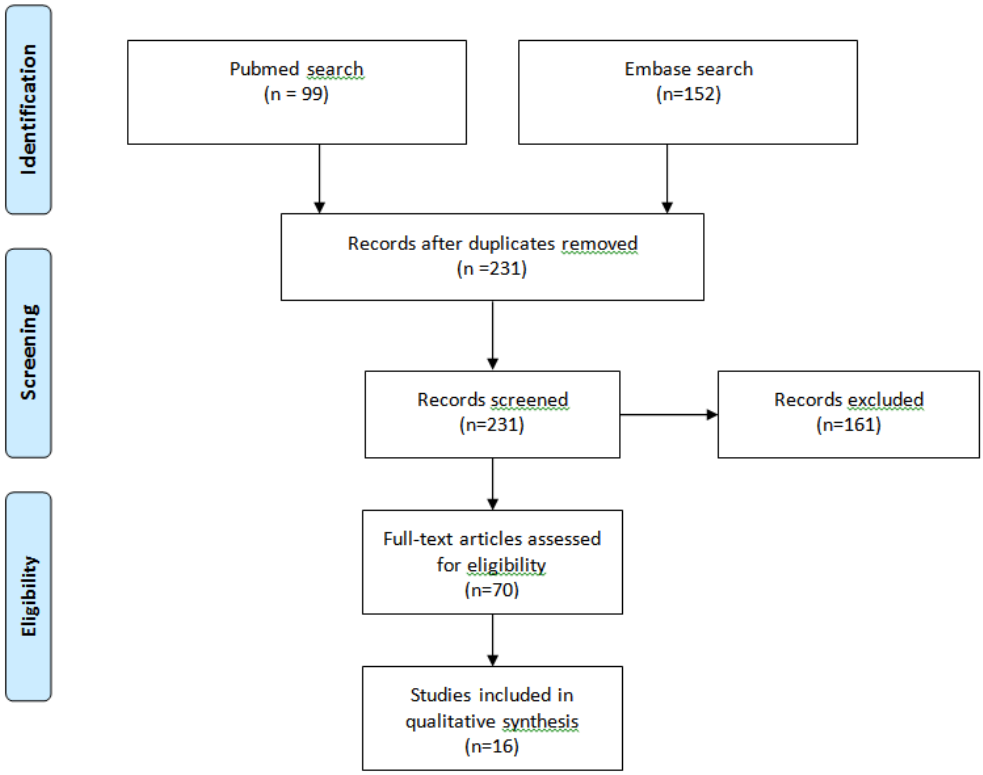

Figure 1 Selection of studies

4. Summary of new evidence

4.1. Meta-analysis and systematic reviews

The majority of meta-analysis found did not incorporate studies finalized after October 2013 therefore they were not considered in the review.

Raiman, 2016[1] is a systematic review of clinical trials which evaluated if the use of HES poses the same risk to less critically ill patients as to critically ill ones. It captured only small studies with low event rates and concluded that there are insufficient data to answer the question.

4.2. Individual studies (both RCTs and non-interventional)

4.2.1. General surgery indication (abdominal, urology, orthopaedic)

Sudfeld, 2016[2] conducted a retrospective study in radical prostatectomy patients (n=179) who were administered a median dose of 1000 mL of HES during surgery. The renal function was measured and no deterioration from baseline was found.

A retrospective study of patients undergoing thoracic surgery (n=1442 patients) aimed to find out if fluid restriction/HES administration increases the risk of acute kidney injury[3]. Out of these patients, 5% developed acute kidney injury, however HES administration was not identified as a risk factor.

A retrospective population based analysis, in 1,051,441 patients undergoing elective total hip and knee arthroplasties, in 510 hospitals across the US found an increased risk of acute renal failure associated with HES and other complications in the perioperative orthopaedic setting[4]. In contrast, two RCTs[5] including 40 and respectively 120 elderly patients undergoing hip arthroplasty found no evidence of a harmful effect of intraoperative infusion of 6% HES 130/0.4 on renal function.

A small clinical trial in patients undergoing prostatectomy (n=40) found no evidence of nephrotoxicity after infusion of 6% HES 130/0.4 in with normal preoperative renal function.[6]

4.2.2. Cardiovascular surgery

Kim et al[7] studied the incidence of postoperative acute kidney injury (AKI) and clinical outcomes in patients undergoing off-pump coronary artery bypass graft surgery (n=783).Postoperative AKI occurred in 33 patients (14.4 %) in the renal protective fluid (RPF) group compared with 210 patients (37.9 %) in the control group ($P < 0.001$). The differences between the groups where the amount of colloid solutions they were given, the control group having unlimited volume, while the RPF management had a restricted volume of HES. The incidences of severe AKI and persistent AKI were significantly lower, and the postoperative extubation time and duration of hospital stay were significantly shorter, in patients in the RPF group than in those in the control group.

Schramko et al[8] conducted a prospective, randomized, double-blinded study (n=50 patients) to compare safety of colloids and crystalloid during cardiopulmonary bypass. The study was prematurely stopped due to the safety communications with regards to HES. It was found that, after complex cardiac surgery, the use of balanced HES solution did not impair haemostasis but it increased the need for transfusions.

Minami et al[9] conducted a retrospective cohort study to investigate AKI and all-cause mortality in patients undergoing endovascular repair of abdominal aortic aneurysms. The primary outcome was all-cause mortality. The outcomes of patients with and without postoperative AKI were compared using the Kaplan–Meier method. Multivariable analysis showed AKI [hazard ratio (HR) = 1.19, 95% confidence interval (CI) 1.01–3.60, $P = 0.045$] and transfusion (HR = 1.05, 95% CI 1.01–1.09, $P = 0.011$) were predictors of mortality. In conclusion AKI and transfusion were associated with significant increases in all-cause mortality after EVAR.

Another retrospective matched study in patients undergoing elective or emergency cardiac surgery [10] found a reduced incidence of AKI in the group treated with a lower dose of HES that the group treated with high dose, supporting the reduced dosage recommendations.

A prospective multicentre cohort study sought to determine the renal safety of modern tetrastarch use in cardiac surgical patients (n=1058 patients).The intraoperative and postoperative use of modern hydroxyethyl starch 6% HES 130/0.4 was not associated with increased risks of AKI and dialysis after cardiac surgery in this multicentre cohort.

An RCT in sixty patients undergoing elective coronary artery bypass grafting found that administration of albumin compared to HES in patients with a normal renal function results in a lower drop of GFR and platelet count, less bleeding and lower rise of serum creatinine[11]

4.2.3. Trauma patients

Kieniger et al,[12] 2017, conducted a study in critically ill patients suffering from aneurysmal subarachnoid haemorrhage, treated with HES. The study was conducted in a single centre, comprising 81 patients without pre-existing renal disorders. The application of HES did not lead to an elevated incidence of AKI in these patients.

Kunze et al[13] studied 107 patients with aneurysmal subarachnoid haemorrhage, investigating the renal safety of HES. In some patients creatinine values increased just temporarily; no patient suffered from renal failure or required renal replacement therapy. They concluded that HES was safe in SAH patients without preexisting renal insufficiency.

Kim et al,[14]investigated the effect of HES on acute kidney injury (AKI) after living donor right hepatectomy (n=1641). The colloids were compared with crystalloids therapy and no difference in risk was observed between the two groups. Another study, performed by Wang in 2015 in 174 adults with orthotopic liver transplantation, found a different result: the HES patients had an increased odds of AKI compared with patients receiving 5% albumin.

Demir et al studied the effects of fluid replacement solutions used intraoperatively on renal functions in elective living-donor liver transplantation (n=36).The comparator was gelatin infusion, which seemed to cause more renal impairment than the HES.

4.2.4. Pediatrics

Li et al[15] performed a meta-analysis of clinical trials published before January 2014. 13 RCTs involving 1,156 pediatric patients were included. They found that volume expansion with 6% HES significantly decreased the platelet count and increased the length of ICU stay and also might have an adverse effect on renal function. The authors concluded HES is not recommended in pediatric patients.

4.2.5. Other uses

Use of HES during therapeutic leukocytapheresis was shown to be beneficial and not associated with more adverse events than the non-HES group (195 patients in 6 medical centres)[16].

4.3. Ongoing trials that might provide useful information

Fluid loading in abdominal surgery - saline versus hydroxyethyl starch [17]

The FLASH trial is an multicentre, randomized, double-blinded, two-arm trial, randomizing 826 patients with moderate-to-high risk of postoperative complications to receive 6 % HES 130/0.4 or 0.9 % saline during individualized goal-directed fluid optimization. The primary outcome measure is a composite of death or major postoperative complications within 14 days following surgery. The FLASH trial may provide important data on the efficacy and safety of commonly used fluid solutions and could have a significant impact on future treatment of surgical patients.

Comparison of 6% hydroxyethyl starch and 5% albumin for volume replacement therapy in patients undergoing cystectomy (CHART) [18]

This is a single-centre, open-label, randomized, comparative trial with two parallel patient groups to compare human albumin 5% (test drug) with hydroxyethyl starch 6% 130/0.4 (comparator). The primary endpoint is cystatin C ratio, calculated as the ratio of the cystatin value at day 90 after surgery relative to the preoperative value. Secondary objectives are inter alia the evaluation of the influence of human albumin and hydroxyethyl starch on further laboratory chemical and clinical parameters, glycocalyx shedding, intensive care unit and hospital stay and acute kidney injury as defined by RIFLE criteria (risk of renal dysfunction, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage kidney disease) criteria.

4.4. Drug utilisation studies

There were no drug utilisation studies found in the period that would evaluate in which patients HES is currently used, if it is used according to the indication or dosage is adhered to.

5. Conclusion

The evidence with regards HES association with acute kidney injury and mortality in acute trauma patients, published after October 2013, still supports the causal association between HES and these events but do not change the conclusions previously reached during the 2013 referral. Most of the new evidence comes from small clinical trials and the results are sometimes contradictory. A large heterogeneity due to patient populations and study design is observed.

Since no study from the public domain evaluated the drug utilisation patterns after the restriction in indication or studies comparing the health outcomes before and after RMM, we consider there is very little evidence in the public domain to inform evaluation of effectiveness of this risk minimisation measure.

6. References

[1] Raiman M, Mitchell CG, Biccard BM, Rodseth RN. Comparison of hydroxyethyl starch colloids with crystalloids for surgical patients: A systematic review and meta-analysis. Eur J Anaesthesiol. 2016 Jan;33(1):42-8. doi: 10.1097/EJA.0000000000000328. Review. PubMed PMID: 26351826.

[2] Südfeld S, Leyh-Bannurah SR, Budäus L, Graefen M, Reese PC, von Breunig F, Reuter DA, Saugel B. Impact of perioperative administration of 6 % hydroxyethyl starch 130/0.4 on serum cystatin C-derived renal function after radical prostatectomy: a single-centre retrospective study. BMC Anesthesiol. 2016 Aug 30;16(1):69. doi: 10.1186/s12871-016-0236-8. PubMed PMID: 27576693; PubMed Central PMCID: PMC5006373.

[3] Ahn HJ, Kim JA, Lee AR, Yang M, Jung HJ, Heo B. The Risk of Acute Kidney Injury from Fluid Restriction and Hydroxyethyl Starch in Thoracic Surgery. Anesth Analg. 2016 Jan;122(1):186-93. doi: 10.1213/ANE.0000000000000974. PubMed PMID: 26418125.

[4] Opperer M, Poeran J, Rasul R, Mazumdar M, Memtsoudis SG. Use of perioperative hydroxyethyl starch 6% and albumin 5% in elective joint arthroplasty and association with adverse outcomes: a retrospective population based analysis. BMJ. 2015 Mar 27;350:h1567. doi: 10.1136/bmj.h1567. PubMed PMID: 25817299

[5] van der Linden P, Gazdzik TS, Jahoda D, Heylen RJ, Skowronski JC, Pellar D, Kofranek I, Górecki AZ, Fagrell B, Keipert PE, Hardiman YJ, Levy H; 6090 Study Investigators. A double-blind, randomized, multicenter study of MP4OX for treatment of perioperative hypotension in patients undergoing primary hip arthroplasty under spinal anesthesia. Anesth Analg. 2011 Apr;112(4):759-73. doi:

10.1213/ANE.0b013e31820c7b5f. Epub 2011 Feb 11. PubMed PMID: 21317165.

[6] Kancir AS, Pleckaitiene L, Hansen TB, Ekeløf NP, Pedersen EB. Lack of nephrotoxicity by 6% hydroxyethyl starch 130/0.4 during hip arthroplasty: a randomized controlled trial. Anesthesiology. 2014 Nov;121(5):948-58. doi: 10.1097/ALN.0000000000000413. PubMed PMID: 25127210.

[7] Kim JY, Joung KW, Kim KM, Kim MJ, Kim JB, Jung SH, Lee EH, Choi IC. Relationship between a perioperative intravenous fluid administration strategy and acute kidney injury following off-pump coronary artery bypass surgery: an observational study. Crit Care. 2015 Sep 28;19:350. doi: 10.1186/s13054-015-1065-8. PubMed PMID: 26415535; PubMed Central PMCID: PMC4587764.

[8] Schramko A, Suojaranta-Ylinen R, Niemi T, Pesonen E, Kuitunen A, Raivio P, Salmenperä M. The use of balanced HES 130/0.42 during complex cardiac surgery; effect on blood coagulation and fluid balance: a randomized controlled trial. Perfusion. 2015 Apr;30(3):224-32. doi: 10.1177/0267659114540022. Epub 2014 Jun 19. PubMed PMID: 24947459.

[9] Minami K, Sugiyama Y, Iida H. A retrospective observational cohort study investigating the association between acute kidney injury and all-cause mortality among patients undergoing endovascular repair of abdominal aortic aneurysms. J Anesth. 2017 Oct;31(5):686-691. doi: 10.1007/s00540-017-2380-9.

[10] Momeni M, Nkoy Ena L, Van Dyck M, Matta A, Kahn D, Thiry D, Grégoire A, Watremez C. The dose of hydroxyethyl starch 6% 130/0.4 for fluid therapy and the incidence of acute kidney injury after cardiac surgery: A retrospective matched study. PLoS One. 2017 Oct 18;12(10):e0186403. doi: 10.1371/journal.pone.0186403. eCollection 2017. PubMed PMID: 29045467;

[11] Hosseinzadeh Maleki, M., Derakhshan, P., Rahmanian Sharifabad, A., & Amouzeshi, A. (2016). Comparing the Effects of 5% Albumin and 6% Hydroxyethyl Starch 130/0.4 (Voluven) on Renal Function as Priming Solutions for Cardiopulmonary Bypass: A Randomized Double Blind Clinical Trial. Anesthesiology and Pain Medicine, 6(1), e30326. http://doi.org/10.5812/aapm.30326

[12] Kieninger M, Unbekannt D, Schneiker A, Sinner B, Bele S, Prasser C. Effect of Hydroxyethyl Starch Solution on Incidence of Acute Kidney Injury in Patients Suffering from Cerebral Vasospasm Following Aneurysmal Subarachnoid Hemorrhage. Neurocrit Care. 2017 Feb;26(1):34-40. doi: 10.1007/s12028-016-0265-7. PubMed PMID: 27059048

[13] Kunze E, Stetter C, Willner N, Koehler S, Kilgenstein C, Ernestus RI, Kranke P, Muellenbach RM, Westermaier T. Effects of Fluid Treatment With Hydroxyethyl Starch on Renal Function in Patients With Aneurysmal Subarachnoid Hemorrhage. J Neurosurg Anesthesiol. 2016 Jul;28(3):187-94. doi: 10.1097/ANA.0000000000000205. PubMed PMID: 26147464.

[14] Kunze E, Stetter C, Willner N, Koehler S, Kilgenstein C, Ernestus RI, Kranke P, Muellenbach RM, Westermaier T. Effects of Fluid Treatment With Hydroxyethyl Starch on Renal Function in Patients With Aneurysmal Subarachnoid Hemorrhage. J Neurosurg Anesthesiol. 2016 Jul;28(3):187-94. doi: 10.1097/ANA.0000000000000205. PubMed PMID: 26147464.

[15] Li L, Li Y, Xu X, Xu B, Ren R, Liu Y, Zhang J, He B. Safety evaluation on low-molecular-weight hydroxyethyl starch for volume expansion therapy in pediatric patients: a meta-analysis of randomized controlled trials. Crit Care. 2015 Mar 10;19:79. doi: 10.1186/s13054-015-0815-y. Review. PubMed PMID: 25887704; PubMed Central PMCID: PMC4391127.

[16] Pagano MB, Harmon C, Cooling L, Connelly-Smith L, Mann SA, Pham HP, Marques MB, Schlueter AJ, Case R, King KE, Cataife G, Wu Y, Wong EC, Winters JL. Use of hydroxyethyl starch in leukocytapheresis procedures does not increase renal toxicity. Transfusion. 2016 Nov;56(11):2848-2856. doi: 10.1111/trf.13795. Epub 2016 Sep 7. PubMed PMID: 27600855.

[17] Futier E, Biais M, Godet T, Bernard L, Rolhion C, Bourdier J, Morand D, Pereira B, Jaber S; FLASH trial management committee. Fluid loading in abdominal surgery - saline versus hydroxyethyl starch (FLASH Trial): study protocol for a randomized controlled trial. Trials. 2015 Dec 21;16:582. doi: 10.1186/s13063-015-1085-3. PubMed PMID: 26690683; PubMed Central PMCID: PMC4687283.

[18] Kammerer T, Klug F, Schwarz M, Hilferink S, Zwissler B, von Dossow V, Karl A, Müller HH, Rehm M. Comparison of 6% hydroxyethyl starch and 5% albumin for volume replacement therapy in patients undergoing cystectomy (CHART): study protocol for a randomized controlled trial. Trials. 2015 Aug 28;16:384. doi: 10.1186/s13063-015-0866-z. PubMed PMID: 26314293; PubMed Central PMCID: PMC4552376.

Annex 1. Search strategy

Pubmed

(((Hydroxyethyl Starch Derivatives/administration AND dosage OR Hydroxyethyl Starch Derivatives/adverse effects*) AND ("2013/01/01"[PDat] : "2017/12/31"[PDat]) AND Humans[Mesh])) AND ((death OR 'renal injury' OR 'renal' OR 'mortality')) AND (("2013/01/01"[PDat] : "2017/12/31"[PDat]) AND Humans[Mesh])

Embase

#4 AND (2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py) AND [humans]/lim AND [english]/limHetastarch

#4#2 AND #3Hetastarch

#3'(death*':ti,ab,kw OR 'mortalit*':ti,ab,kw OR 'fatalit*':ti,ab,kw OR 'deceas*':ti,ab,kw OR 'renal*':ti,ab,kw OR 'kidney*)':ti,ab,kwHetastarch

#2#1 AND ('adverse drug reaction'/lnk OR 'complication'/lnk OR 'drug administration'/lnk OR 'drug dose'/lnk OR 'intramuscular drug administration'/lnk OR 'intravenous drug administration'/lnk OR 'oral drug administration'/lnk OR 'side effect'/lnk)Hetastarch

#1'hetastarch'/exp OR hetastarch