Avrupa İlaç Ajansı (EMA) kararından sonra HES'in kalp cerrahisinde kullanımı

Prof.Dr.Fevzi Toraman

Acıbadem Üniversitesi

GKDA 2015 Kapadokya

Konu başlıkları

1. EMA, FDA ve sağlık bakanlığımızın kararları
2. EMA'nın kararını gözden geçirmesi
3. Revize karardan sonra (2012) kalp cerrahisinde yapılan çalışmalar;

   HES'in

   a) Kanama-pıhtılaşma sistemi üzerine etkisi
   b) Priming solüsyon olarak kullanımı
   c) Sıvı dengesi ve sonuç parametreleri üzerine etkisi
   d) İmmun sistem üzerine etkisi
4. Non-kardiyak uygulamada güncel durum

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydroxyethyl Starch 130/0.42 versus Ringer's Acetate in Severe Sepsis

Anders Perner, M.D., Ph.D., Nicolai Haase, M.D., Anne B. Guttormsen, M.D., Ph.D., Jyrki Tenhunen, M.D., Ph.D., Gudmundur Klemenzson, M.D., Anders Åneman, M.D., Ph.D., Kristian R. Madsen, M.D., Morten H. Møller, M.D., Ph.D., Jeanie M. Elkjær, M.D., Lone M. Poulsen, M.D., Asger Bendtsen, M.D., M.P.H., Robert Winding, M.D., Morten Steensen, M.D., Pawel Berezowicz, M.D., Ph.D., Peter Søe-Jensen, M.D., Morten Bestle, M.D., Ph.D., Kristian Strand, M.D., Ph.D., Jørgen Wiis, M.D., Jonathan O. White, M.D., Klaus J. Thornberg, M.D., Lars Quist, M.D., Jonas Nielsen, M.D., Ph.D., Lasse H. Andersen, M.D., Lars B. Holst, M.D., Katrin Thormar, M.D., Anne-Lene Kjældgaard, M.D., Maria L. Fabritius, M.D., Frederik Mondrup, M.D., Frank C. Pott, M.D., D.M.Sci., Thea P. Møller, M.D., Per Winkel, M.D., D.M.Sci., and Jørn Wetterslev, M.D., Ph.D., for the 6S Trial Group and the Scandinavian Critical Care Trials Group*

6 S çalışması

Sonuç	%6 HES (130/0.42)	Ringer asetat	Relatif risk – (%95 CI)	p-değeri
Renal replasman tedavisi	87 (22)	65 (16)	1.17 – (1.01-1.30)	0.03

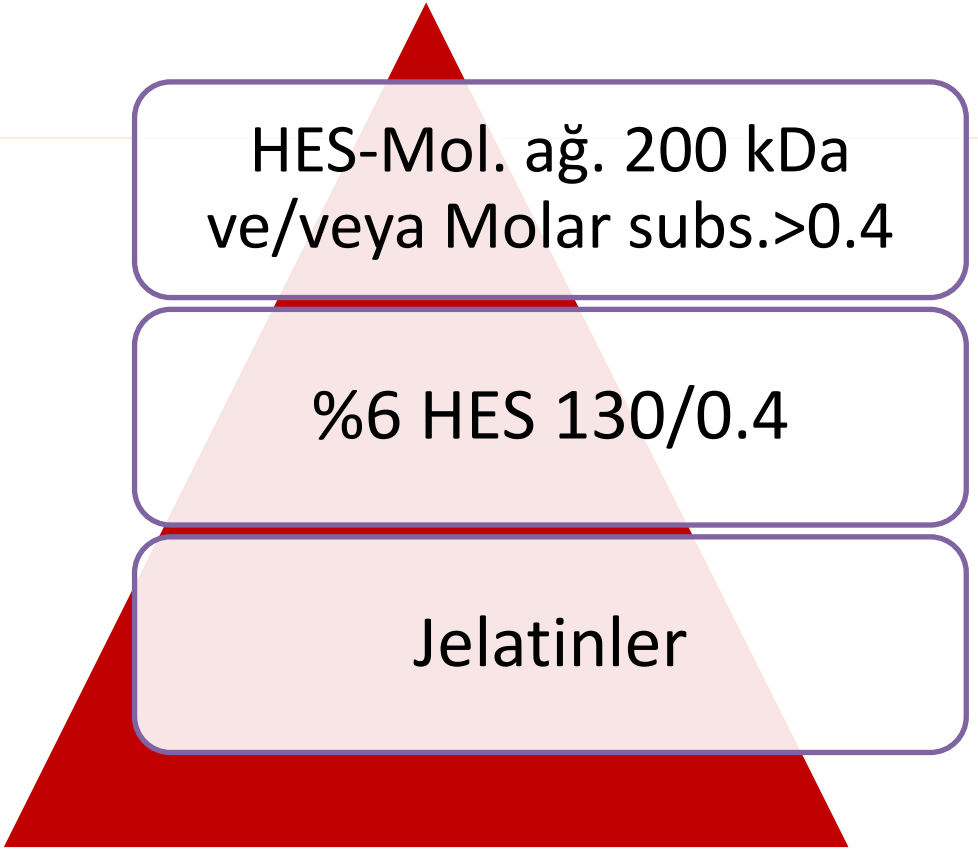
N Engl J Med 2012;367:124-34

Intensive Care Med (2012) 38:368–383
DOI 10.1007/s00134-012-2472-9

SPECIAL ARTICLE

Konrad Reinhart
Anders Perner
Charles L. Sprung
Roman Jaeschke
Frederique Schortgen
A. B. Johan Groeneveld
Richard Beale
Christiane S. Hartog

Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients



WARNING: MORTALITY
RENAL REPLACEMENT THERAPY

- **In critically ill adult patients, including patients with sepsis, use of hydroxyethyl starch (HES) products, including Voluven®, increases risk of**
  - **o Mortality**
  - **o Renal replacement therapy**
- **Do not use HES products, including Voluven®, in critically ill adult patients, including patients with sepsis.**

FDA, 2013

HİDROKSİETİL NİŞASTA (HES) İÇEREN PARENTERAL SOLÜSYONLAR HAKKINDA ÖNEMLİ GÜVENLİLİK BİLGİSİ

Sayın Doktor,

Bu mektubun amacı hidroksietil nişasta (HES) içeren ürünlerin sepsisli kritik hastalarda kullanımına bağlı olarak gelişen ölüm ve böbrek yetmezliği risklerinin artması hakkında sizleri bilgilendirmektir.

Özet

Son çalışmalarda sepsisli kritik hastalarda, HES ve diğer kan hacim artırıcılar karşılaştırılmıştır. Bu çalışmalar, HES ile tedavi edilen hastalarda ölüm ve böbrek yetmezliği risklerinin daha fazla olduğunu göstermiştir. Sepsisli kritik hastalığı olan ve yoğun bakım ünitesine giriş yapmış kritik hastalığı olan yetişkinlerde HES kullanılmamalıdır.

Hekimlere yönelik tavsiyeler

- Sepsis, ağır sepsis ve septik şok tanısı konulmuş kritik hastalığı olan ve yoğun bakım ünitesine yatışı veya devri yapılan kritik hastalığı olan yetişkinlerde HES kullanılmamalıdır.
- Akut ağır karaciğer yetersizliği olan kişilerde HES kullanılmamalıdır. Kronik karaciğer hastalığı olan hastalarda fayda-zarar değerlendirilmesi yapılarak kullanılmalı, bu hastalar gözlem altında tutulmalıdırlar.
- Böbrek fonksiyon bozukluğu öyküsü olan hastalarda kullanımından kaçınılmalıdır
- Böbrek hasarına işaret eden ilk bulgu tespit edildiğinde HES kullanımı sonlandırılmalıdır.
- HES uygulamasını takiben 90 gün içerisinde renal replasman tedavisi rapor edilmiştir. Bu nedenle tüm hastaların, en az 90 günlük süreç boyunca renal fonksiyonlarının takibine devam edilmelidir.
- Açık kalp ameliyatı yapılan hastalarda, kardiyopulmoner bypass sırasında aşırı kanama riskinden dolayı priming solüsyonunda HES kullanımından kaçınılmalıdır.
- Koagülopatiye işaret eden ilk bulgu tespit edildiğinde HES kullanımı kesilmelidir.

Guidet et al. Critical Care 2012, 16:R94
http://ccforum.com/content/16/3/R94

CRITICAL CARE

RESEARCH Open Access

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

Bertrand Guidet[1,2,3*], Olivier Martinet[4], Thierry Boulain[5], Francois Philippart[6,7], Jean François Poussel[8], Julien Maizel[9], Xavier Forceville[10], Marc Feissel[11], Michel Hasselmann[4], Alexandra Heininger[12] and Hugo Van Aken[13]

- YB'de yatış süresinde fark yok
- AKI ve RRT oranında fark yok
- Mortalitede fark yok

Research

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effects of Fluid Resuscitation With Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting With Hypovolemic Shock

The CRISTAL Randomized Trial

Djillali Annane, MD, PhD; Shidasp Siami, MD; Samir Jaber, MD, PhD; Claude Martin, MD, PhD; Souheil Elatrous, MD; Adrien Descorps Declère, MD; Jean Charles Preiser, MD; Hervé Outin, MD; Gilles Troché, MD; Claire Charpentier, MD; Jean Louis Trouillet, MD; Antoine Kimmoun, MD; Xavier Forceville, MD, PhD; Michael Darmon, MD; Olivier Lesur, MD, PhD; Jean Reignier, MD; Fékri Abroug, MD; Philippe Berger, MD; Christophe Clec'h, MD, PhD; Joël Cousson, MD; Laure Thibault, MD; Sylvie Chevret, MD, PhD; for the CRISTAL Investigators

JAMA 2013;310:1809-17

mortalitede fark yok

Figure 3. Assessment of Treatment × Diagnosis Interaction and Death Within First 28 Days

Reason for ICU Admission	Colloids Group (n = 1414) No. of Patients	Colloids Group (n = 1414) No. of Deaths	Crystalloids Group (n = 1443) No. of Patients	Crystalloids Group (n = 1443) No. of Deaths	HR (95% CI)
Other causes of hypovolemic shock	555	131	572	152	0.87 (0.69-1.10)
Sepsis	774	215	779	226	0.95 (0.78-1.10)
Trauma	85	13	92	12	1.19 (0.54-2.60)
All patients	1414	359	1443	390	0.93 (0.80-1.10)

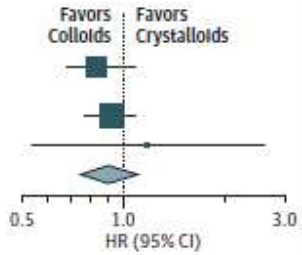
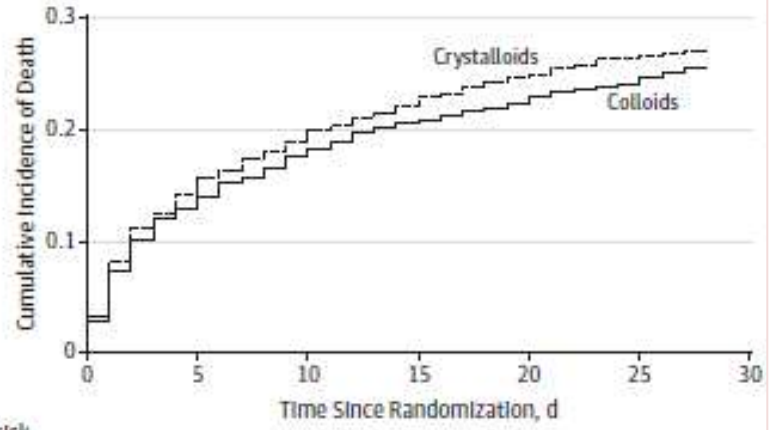


Figure 2. Cumulative Incidence of Death Within First 28 Days After Randomization



No. at risk

Colloids	1414	1233	1167	1124	1099	1076
Crystalloids	1443	1239	1172	1124	1089	1064

Akut kan kaybına bağlı hipovolemide kullanılabilir

HES, 24 saatten fazla kullanılmamalı

Renal fonksiyonlar 90 gün izlenmeli

2012 SONRASI

- Kalp cerrahisinde sorunlar ne idi,
- 2012 sonrası Sorunlar ile ilgili hangi yazılar çıktı ?

Thrombosis Research xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Regular Article

Impact of 6 % hydroxyethyl starch (HES) 130/0.4 on the correlation between standard laboratory tests and thromboelastography (TEG®) after cardiopulmonary bypass

Gregory A. Hans [a,*], Gary Hartstein [a], Laurence Roediger [a], Bernard Hubert [a], Pierre Peters [b], Marc Senard [a]

[a] Department of Anesthesia and Intensive Care Medicine, CHU of Liege, Domaine Universitaire du Sart Tilman, Avenue de l'hopital Bat, B35, 4000 Liege, Belgium
[b] Department of Thrombosis and Hemostasis, CHU of Liege, Domaine Universitaire du Sart Tilman, Avenue de l'hopital Bat. B35, 4000 Liege, Belgium

Results: The type of fluid used significantly affected the MA ($P < 0.001$), the K time ($P < 0.001$) and the alpha angle ($P < 0.001$) regardless of the results of the standard clotting tests. According to standardized ß regression coefficients the platelet count and the type of fluid used were stronger predictors of the MA, the alpha angle and the K time than the fibrinogen level. MA better predicted platelets < 80.000 μl^{-1} than K time and alpha angle ($P = 0.023$). The best cutoff value of MA identifying patients with platelets < 80.000 μl^{-1} was 62 mm in the crystalloid group and 53 mm in the HES group. MA, K time and alpha angle were poor predictors of the postoperative fibrinogen level.

Conclusion: HES significantly changes the cutoff value of TEG® MA best identifying patients < 80.000 μl^{-1} after on-pump cardiac surgery.

Table 2
Laboratory Results and TEG Values after Protamine.

	Crystalloid (n = 56)	HES (n = 40)
Hemoglobin (gr/dL)	9.7 [7.1-13.5]	8.25 [6.9-11.7]
Platelet ($\times 10^3/\mu L$)	113 [38-245]	94 [49-260]
Fibrinogen (g/L)	1.5 [0.74-5.72]	2.12 [1.09-4.78]
aPTT(s)	35 [22.2-59.2]	40.9 [30-180]
INR	1.4[1.17-1.97]	1.4[1.23-2.48]
R time (min)	5.8[1.8-19.4]	6.4[3.8-16]
K time (min)	1.6 [1-3.4]	2.4[1.2-9.2]
MA (mm)	64 ± 7	57 ± 8

Data are mean ± sd or median [range]. aPTT = activated partial thromboplastin time. INR = International Normalized Ratio. MA = Maximal Amplitude.

Conclusion: HES significantly changes the cutoff value of TEG® MA best identifying patients < 80.000 μl^{-1} after on-pump cardiac surgery.

Espinosa et al. BMC Anesthesiology 2014, 14:80
http://www.biomedcentral.com/1471-2253/14/80

BMC Anesthesiology

RESEARCH ARTICLE Open Access

Comparison of three point-of-care testing devices to detect hemostatic changes in adult elective cardiac surgery: a prospective observational study

Aurora Espinosa[1*], Roar Stenseth[2,3], Vibeke Videm[1,4] and Hilde Pleym[3,5]

Abstract

Background: Bleeding complications in cardiac surgery may lead to increased morbidity and mortality. Traditional blood coagulation tests are not always suitable to detect rapid changes in the patient's coagulation status. Point-of-care instruments such as the TEG (thromboelastograph) and RoTEM (thromboelastometer) have been shown to be useful as a guide for the clinician in the choice of blood products and they may lead to a reduction in the need for blood transfusion, contributing to better patient blood management.

Methods: The purpose of this study was to evaluate the ability of the TEG, RoTEM and Sonoclot instruments to detect changes in hemostasis in elective cardiac surgery with cardiopulmonary bypass and to investigate possible correlations between variables from these three instruments and routine hematological coagulation tests. Blood samples from thirty-five adult patients were drawn before and after surgery and analyzed in TEG, RoTEM, Sonoclot and routine coagulation tests. Data were compared using repeated measures analysis of variance and Pearson's test for linear correlation.

Results: We found significant changes for all TEG variables after surgery, for three of the RoTEM variables, and for one variable from the Sonoclot. There were significant correlations postoperatively between plasma fibrinogen levels and variables from the three instruments.

Conclusions: TEG and RoTEM may be used to detect changes in hemostasis following cardiac surgery with CPB. Sonoclot seems to be less suitable to detect such changes. Variables from the three instruments correlated with plasma fibrinogen and could be used to monitor treatment with fibrinogen concentrate.

Table 1 Nomenclature, variable definitions and reference ranges of the TEG, RoTEM and Sonoclot instruments

	TEG	RoTEM	Sonoclot
Clot time	R (Reaction time)	CT (Clotting time)	-
Time to 2 mm amplitude	(4–8 min.)	-EXTEM CT (42–74 sec)*	
		-INTEM CT (137–246 sec)	
Clot kinetics	K (kinetics)	CFT (Clot formation time)	-
Time from 2 to 20 mm clot firmness	(1–4 min.)	-EXTEM CFT (46–148 sec)	
		-INTEM CFT (40–100 sec)	
Clot kinetics	Alpha angle	Alpha angle	-
Alpha angle	(53–67 deg)	-EXTEM angle (63–81 deg)	
		-INTEM angle (71–82 deg)	
Clot strength	MA (Maximum amplitude)	MCF (Maximum Clot Firmness)	-
		-EXTEM MCF (49–71 mm)	
	(55–73 mm)	-INTEM MCF (52–72 mm)	
		-FIBTEM MCF (9–25 mm).	
Clot elasticity	G (4.6-10.9 dynes/cm^2)	-	-
Time until the beginning of fibrin formation	-	-	Son Act (85–145 sec)
Rate of fibrin formation	-	-	Clot Rate R1 (15–45 clot signal units/min)
Completion of fibrin formation	-	-	Peak (mm)
Index of fibrinogen conversion to fibrin	-	-	Time to Peak (540–600 sec)
Platelet-induced clot retraction	-	-	R3 (>2 mm/min)

*EXTEM reagent contains tissue factor, INTEM reagent contains ellagic acid, FIBTEM reagent contains platelet inhibitor.

Table 2
Laboratory Results and TEG Values after Protamine.

	Crystalloid (n = 56)	HES (n = 40)
Hemoglobin (gr/dL)	9.7 [7.1-13.5]	8.25 [6.9-11.7]
Platelet ($\times 10^3/\mu L$)	113 [38-245]	94 [49-260]
Fibrinogen (g/L)	1.5 [0.74-5.72]	2.12 [1.09-4.78]
aPTT(s)	35 [22.2-59.2]	40.9 [30-180]
INR	1.4[1.17-1.97]	1.4[1.23-2.48]
R time (min)	5.8[1.8-19.4]	6.4[3.8-16]
K time (min)	1.6 [1-3.4]	2.4[1.2-9.2]
MA (mm)	64 ± 7	57 ± 8

Data are mean ± sd or median [range]. aPTT = activated partial thromboplastin time. INR = International Normalized Ratio. MA = Maximal Amplitude.

Parametre	Referans değer
R time(min)	4-8
K time(min)	1-4
MA (mm)	55-73

Conclusion: HES significantly changes the cutoff value of TEG® MA best identifying patients < 80.000 μl^{-1} after on-pump cardiac surgery.

Journal of Thrombosis and Haemostasis, **7**: 1099–1105 DOI: 10.1111/j.1538-7836.2009.03460.x

ORIGINAL ARTICLE

Mechanisms of hydroxyethyl starch-induced dilutional coagulopathy

C. FENGER-ERIKSEN,*† E. TØNNESEN,* J. INGERSLEV† and B. SØRENSEN†‡

*Departments of *Anaesthesiology* and †Clinical Biochemistry, Centre for Haemophilia and Thrombosis, Aarhus University Hospital, Aarhus, Denmark; and ‡Centre for Haemostasis and Thrombosis, St Thomas' Hospital, London, UK*

To cite this article: Fenger-Eriksen C, Tønnesen E, Ingerslev J, Sørensen B. Mechanisms of hydroxyethyl starch-induced dilutional coagulopathy. *J Thromb Haemost* 2009; **7**: 1099–105.

Amaç

- HES ‘e bağlı dilüsyonel koagulopatinin biokimyasal mekanizmasını öğrenmek
- Bu amaçla %30 dilüsyon oluşturdukları **sistektomi** hastalarını izliyorlar
- Kazanılmış **fibrinojen** eksikliğinin etkilerini ve tedaviye yanıtını değerlendiriyorlar

Table 1 Laboratory characteristics before (baseline) and after 30% *in vivo* hemodilution with hydroxyethyl starch 130/0.4

	Baseline	30% Hemodilution	Absolute decrease	Relative change (%)
Hematocrit (0.28–0.47)	0.43 ± 0.03	0.29 ± 0.02*	0.14 ± 0.03	− 32 ± 5
Standard coagulation parameters				
Platelet count, 10^9 L^{-1} (150–450)	248 ± 66	181 ± 50*	61 ± 25	− 27 ± 5†
APTT, s (25–38)	32 ± 3.9	43 ± 11*	9.2 ± 5	+ 28 ± 13
Prothrombin time, relative (> 0.80)	0.93 ± 0.08	0.69 ± 0.08*	0.25 ± 0.06	− 27 ± 6†
Antithrombin, 10^3 IU L^{-1} (0.88–1.24)	0.94 ± 0.08	0.56 ± 0.07*	0.40 ± 0.06	− 42 ± 5†
D-dimer, mg L^{-1} (< 0.50)	0.54 ± 0.37	1.4 ± 2.6	0.75 ± 2.36	+ 99 ± 177†
Single coagulation factors				
Fibrinogen (μM)				
Ad modum Clauss	9.5 ± 1.9	5.1 ± 0.8*	4.04 ± 0.90	− 44 ± 4.4†
Antigen level	10.2 ± 1.9	5.9 ± 1.5*	4.3 ± 0.90	− 43 ± 6.1†
FII:C, U mL^{-1} (0.80–1.32)	1.25 ± 0.2	0.68 ± 0.1*	0.56 ± 0.16	− 44 ± 6†
FVII:C, U mL^{-1} (0.68–1.69)	1.07 ± 0.2	0.73 ± 0.2*	0.33 ± 0.11	− 31 ± 7
FVIII:C, U mL^{-1} (0.66–1.55)	1.45 ± 0.6	0.88 ± 0.4*	0.61 ± 0.48	− 39 ± 16
FX:C, U mL^{-1} (0.74–1.52)	1.19 ± 0.2	0.73 ± 0.2*	0.46 ± 0.11	− 39 ± 6†
FIX:C, U mL^{-1} (0.69–1.49)	1.22 ± 0.26	0.89 ± 0.16*	0.32 ± 0.14	− 28 ± 6.6†
FXIII:C, U mL^{-1} (0.61–1.77)	1.26 ± 0.2	0.71 ± 0.1*	0.54 ± 0.12	− 43 ± 6†
VWF ristocetin cofactor, U mL^{-1} (0.47–1.59)	1.51 ± 0.60	1.02 ± 0.38*	0.49 ± 0.38	− 30 ± 14
Endogenous thrombin potential (nM × min)	1471 ± 309	1532 ± 247	37 ± 164	+ 3.8 ± 11

Data presented as mean ± standard deviation. Values in parentheses indicate normal reference ranges. APTT, activated partial thromboplastin time; VWF, von Willebrand factor. $n = 20$. *Significantly different from baseline value. †Relative decrease significantly different from expected decrease (hemotocrit).

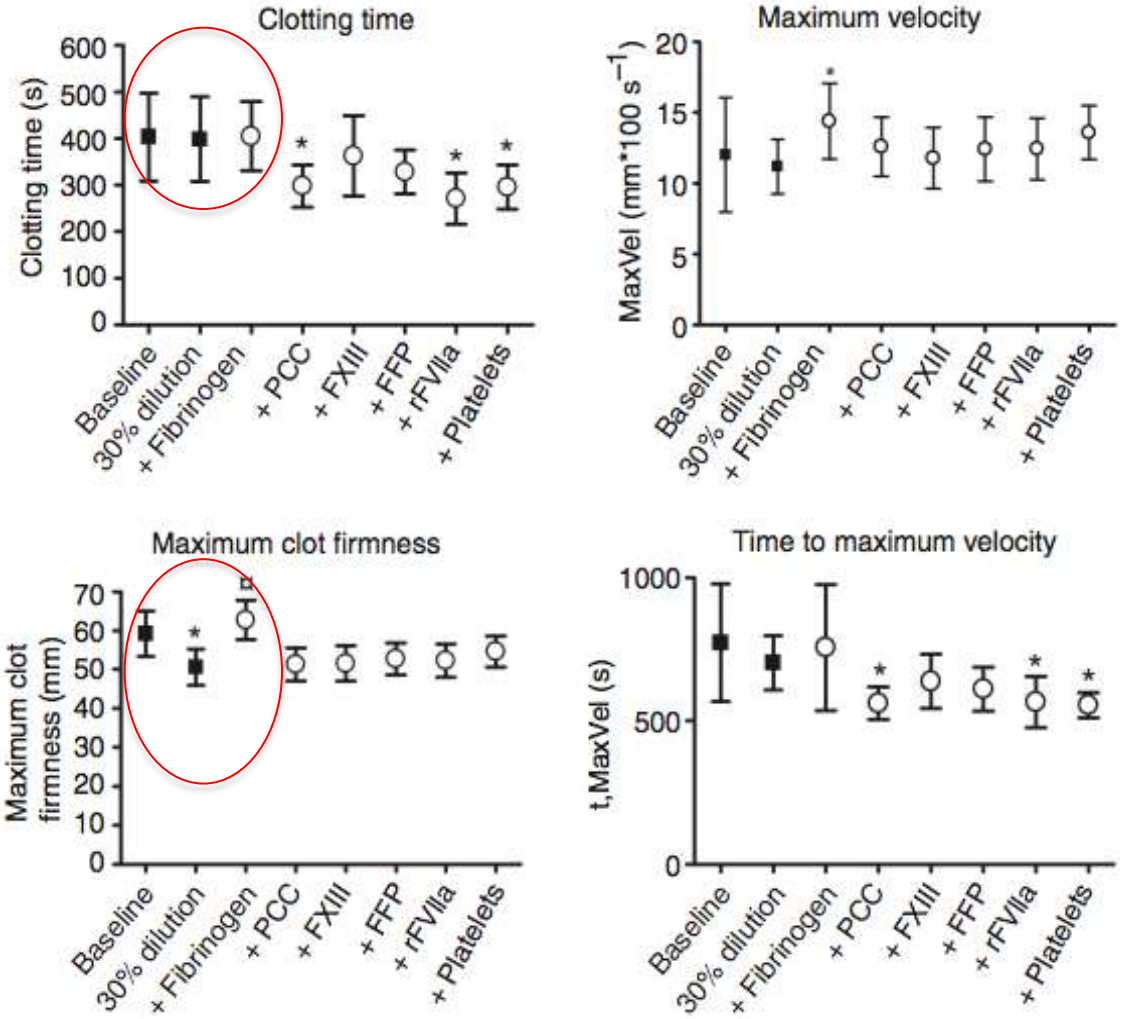


Fig. 1. Parameters of thromboelastometric whole blood clot formation before (baseline) and after 30% *in vivo* hemodilution (squares) with hydroxyethyl starch 130/0.4 and after *ex vivo* (open circles) addition of fibrinogen, prothrombin complex concentrate (PCC), factor VIII (FVIII), fresh frozen plasma (FFP), activated recombinant FVII (rFVIIa), and platelets. $n = 20$. *Significantly different from baseline value. ¤Significantly different from 30% dilution. MaxVel, maximum velocity.

Sonuç

- Kazanılmış fibrinojen eksikliği (dilüsyonel) koagülopatinin nedeni ise
- Fibrinojen replasmanı ile koagülopati tamamen düzelmektedir

British Journal of Anaesthesia **112** (2): 255–64 (2014)
Advance Access publication 29 October 2013 · doi:10.1093/bja/aet348

BJA

CARDIOVASCULAR

Comparison of the effects of albumin 5%, hydroxyethyl starch 130/0.4 6%, and Ringer's lactate on blood loss and coagulation after cardiac surgery

K. Skhirtladze[1], E. M. Base[1]*, A. Lassnigg[1], A. Kaider[2], S. Linke[1], M. Dworschak[1] and M. J. Hiesmayr[1]

[1] Division of Cardiothoracic and Vascular Anaesthesiology and Intensive Care Medicine, Department of Anaesthesiology, General Intensive Care and Pain Medicine, Medical University of Vienna, Vienna, Austria
[2] Centre for Medical Statistics, Informatics and Intelligent Systems, Section for Clinical Biometrics, Medical University of Vienna, Vienna, Austria
* Corresponding author. E-mail: eva.base@meduniwien.ac.at

Editor's key points

- The perioperative use of colloid solutions has potential benefits in cardiac surgical patients, but may affect coagulation.
- In this randomized study of 240 patients, the use of high volumes of colloid

Background. Infusion of 5% human albumin (HA) and 6% hydroxyethyl starch 130/0.4 (HES) during cardiac surgery expand circulating volume to a greater extent than crystalloids and would be suitable for a restrictive fluid therapy regimen. However, HA and HES may affect blood coagulation and could contribute to increased transfusion requirements.

Methods. We randomly assigned 240 patients undergoing elective cardiac surgery to receive up to 50 ml kg^{-1} day^{-1} of either HA, HES, or Ringer's lactate (RL) as the main infusion fluid perioperatively. Study solutions were supplied in identical bottles dressed in opaque covers. The primary outcome was chest tube drainage over 24 h. Blood transfusions, thromboelastometry variables, perioperative fluid balance, renal function, mortality, intensive care unit, and hospital stay were also assessed.

Randomization, fluid regimen, and blinding

Eligible patients were randomized into three groups comprising 80 patients each with the following fluid regimens:

HA group: 5% albumin up to 50 ml kg^{-1} day^{-1}, additional RL as required;
HES group: 6% HES 130/0.4 up to 50 ml kg^{-1} day^{-1}, additional RL as required;
RL group: RL up to 50 ml kg^{-1} day^{-1}, additional RL as required.

Table 2 Chest tube drainage and transfusions until the first 24 h after surgery. HA, 5% human serum albumin; HES, 6% hydroxyethyl starch 130/0.4; RL, Ringer's lactate; PRBCs, packed red blood cells; FFP, fresh frozen plasma. Chest tube drainage and PRBCs are expressed as median (25/75% percentiles). All other variables are depicted as percentages. *P*-value as determined by univariate analysis

	HA ($n=76$)	HES ($n=81$)	RL ($n=79$)	*P*-value
Chest tube drainage (ml)	835 (545/1253)	700 (540/1090)	670 (455/1015)	0.0850
PRBCs (ml)	300 (0/600)	300 (0/600)	0 (0/300)	0.0004
PRBCs (units)	1 (0/2)	1 (0/2)	0 (0/1)	0.0004
PRBCs intraoperative (ml)	0 (0/600)	0 (0/600)	0 (0/300)	0.0119
PRBCs postoperative (ml)	0 (0/275)	0 (0/250)	0 (0/0)	0.0333
FFP (%)	8	10	5	0.5152
Platelets (%)	7	14	5	0.1186
Fibrinogen (%)	12	16	4	0.0383
Factor concentrate (%)	3	6	3	0.3921
Percentage of patients receiving				
PRBCs (%)	58	61	34	0.0013
Any blood product (%)	62	64	35	0.0003

Blood transfusion was performed according to STS-SCA transfusion guidelines.[25 26] Transfusion triggers for the transfusion of PRBCs were: haemoglobin (Hb) concentrations of ≤ 7.0 g dl^{-1} during and $\leq 8.0-9.0$ g dl^{-1} after CPB.

2.-6. gün arası

- Most units of PRBC were given perioperatively during the first 24 h.
- There were no significant group differences in the number of PRBC units transfused within PODs 2 – 6
  - HA : 2.04; HES: 2.14; RL : 2.15 P= 0.544.
- No significant intergroup differences were noted for transfused FFP and platelets.
- Regarding the amount of coagulation factor concentrates, no significant differences were found between the three groups.

Safety of Modern Starches Used During Surgery

Philippe Van Der Linden, MD, PhD,* Michael James, MB ChB, PhD, FRCA, FCA(SA),‡
Michael Mythen, MD FRCA,‡§‖ and Richard B. Weiskopf, MD¶

Various hydroxyethyl starch (HES) preparations have been used for decades to augment blood volume. There has been concern recently regarding possible adverse outcomes when using HES in the intensive care setting, especially in patients with septic shock. However, the pharmacokinetic and pharmacodynamic properties of HES preparations depend on their chemical composition and source material. Thus, different clinical conditions could result in differing effectiveness and safety for these preparations. Consequently, we assessed the safety of tetrastarches when used during surgery, using a formal search, that yielded 59 primary full publications of studies that met a priori inclusion criteria and randomly allocated 4529 patients with 2139 patients treated with tetrastarch compared with 2390 patients treated with a comparator. There were no indications that the use of tetrastarches during surgery induces adverse renal effects as assessed by change or absolute concentrations of serum creatinine or need for renal replacement therapy (39 trials, 3389 patients), increased blood loss (38 trials, 3280 patients), allogeneic erythrocyte transfusion (20 trials, 2151 patients; odds ratio for HES transfusion 0.73 [95% confidence interval = 0.61–0.87], $P = 0.0005$), or increased mortality (odds ratio for HES mortality = 0.51 [0.24–1.05], $P = 0.079$). (Anesth Analg 2013;116:35–48)

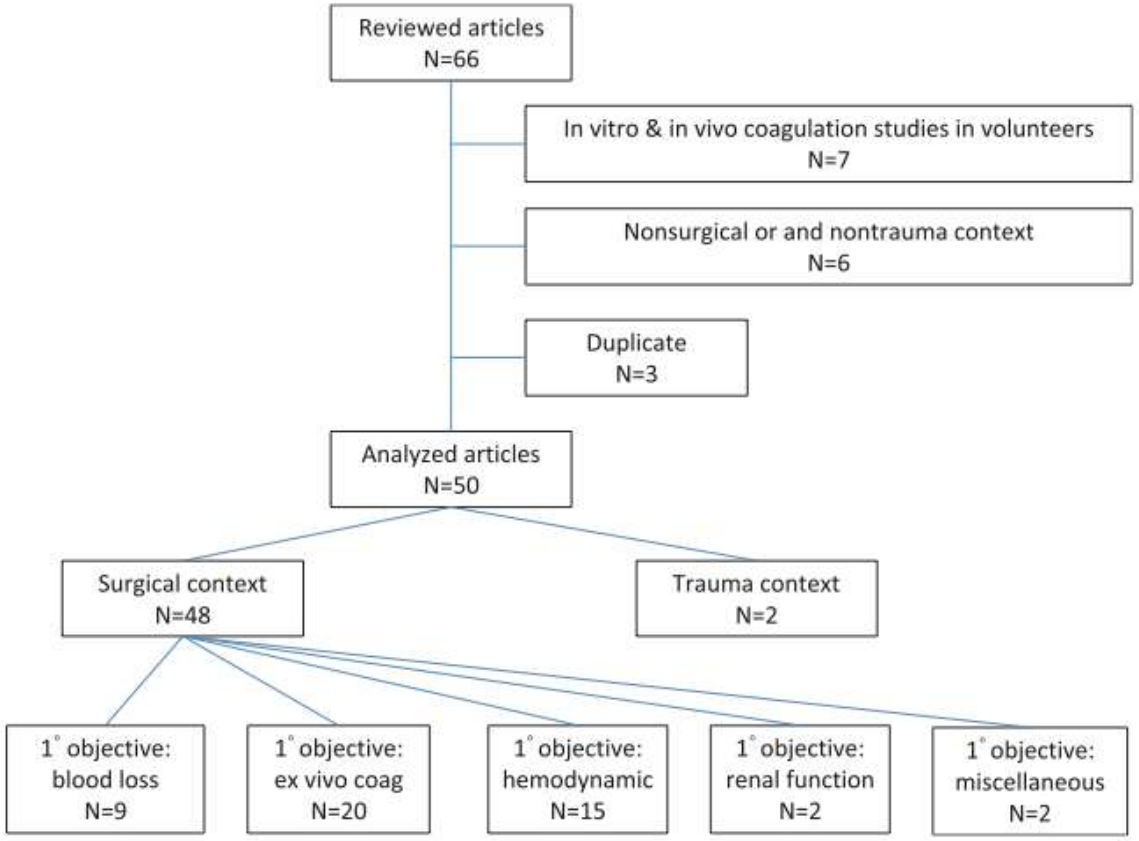


Figure 2. Flow chart of reviewed and analyzed publications related to coagulation.

Table 1. Studies Using Blood Loss as the Primary Objective

Authors	Surgery	Starch/comparator	Volume (mL)	No. patients (N)	Blood loss (mL)	Volume packed red blood cells	% Transfused
Kasper et al.[54]	Cardiac	130/0.4	3500 (2000–4500)	59	660 (380–1440)	1 (0–6) U	32%
		HES 200/0.5[a]	2500 (1850–3250)	58	705 (330–1750)	1 (0–6) U	32%
Van der Linden et al.[52]	Cardiac	130/0.4	48.9±17.2 mL/kg	64	544±305[b]	0 (0–6) U	38%
		MF gelatin	48.9±14.6 mL/kg	68	504±327[b]	0 (0–6) U	31%
Ellger et al.[65]	Major	130/0.4	50 mL/kg	20	2563 (750–5500)	1.7 (0–6) U	NR
	Abdominal	HES 200/0.5+MF gelatin	30 + 20 mL/kg	20	2430 (1000–4000)	1.3 (0–4) U	NR
Chong Sung et al.[66]	Cardiac	130/0.4	10 mL/kg	21	9.9±4.8 mL/kg	7.5±6.0 mL/kg	81%
	Pediatric	Fresh frozen plasma	10 mL/kg	21	8.7±3.9 mL/kg	7.6±6.2 mL/kg	81%
Boks et al.[67]	Cardiac	130/0.4	1000	90	1768±75	586±55 mL	NR
		MF gelatin	1300–1500	90	1921±89	582±57 mL	NR
Ooi et al.[68]	Cardiac	130/0.4	1942±1046	45	567±281	NR	89%
		MF gelatin	1973±729l	45	596±337	NR	93%
Vanhoonacker et al.[20]	Cardiac	130/0.4	1500	82	9.4±6.1 mL/kg	0.77±0.90 U	NR
		MF gelatin	1500	72	7.8±5.0 mL/kg	0.63±1.08 U	NR
Hanart et al.[21]	Cardiac	130/0.4	50 (37–50) mL/kg	60	19 (9–31) mL/kg[b]	18 (0–40) mL/kg	57%
	Pediatric	4% albumin	50 (45–50) mL/kg	59	25 (13–32) mL/kg[b]	29 (6–42) mL/kg	78%*
Lee et al.[69]	Cardiac	130/0.4	1458±465[c]	53	978±347	2.1±1.6 U	27%
	Off pump	Balanced crystalloid	8342±1794	53	1028±389	1.6±1.2 U	23%

Studies for which blood loss was the primary end point. All studies of randomly allocated patients. Author's name in italics indicates publications that specifically indicated that the trial was double blinded. All values are those from the published reports. Values are presented as mean ± SD, except those with parentheses, which are median (interquartile range). Data shown in italics indicate a statistically significant difference. Volume is the volume of tetrastarch or comparator administered. % Transfused is the percentage of patients transfused with allogeneic red cells.

U = units; NR = not reported; MF = modified fluid; HES = hydroxyethyl starch.

[a] MF gelatin also used: group HES 130, 500 (0–4000) mL; group HES 200/0.5, 1700 (0–4000) mL.

[b] Expressed as pure red cell volume (i.e., hematocrit of 100%) rather than blood volume.

[c] Crystalloids also used in the HES 130/0.4 group, 6694±1882 mL.

* $P = 0.019$ versus HES 130/0.4.

Table 2. Studies Using Ex Vivo Coagulation Variables as the Primary Objective and Reporting Blood Loss Data

Authors	Surgery	Starch/comparator	Volume (mL)	No. patients (*n*)	Blood loss (mL)	Volume PRBCs	% Transfused
Chen et al.[70]	Minor	130/0.4	20 mL/kg	20	56±23	NR	NR
		HES 200/0.5	20 mL/kg	20	60±17		
		Ringer lactate solution	20 mL/kg	20	65±19		
Kim et al.[22]	Cardiac	130/0.4	2.4±0.5 L	24	530±247	1 (0–4) U	NR
	Off pump	HES 200/0.5	2.3±0.6 L	24	*713±263**	1 (0–3) U	
Mittermayer et al.[28]	Major orthopedic	130/0.4	6–8 mL/kg/h	19	319 (4–1744)[a]	9 U[b]	3/19
	(spine)	MF gelatin	8–11 mL/kg/h	21	526 (7–1559)[a]	13 U[b]	8/21
		Ringer lactate solution	13–15 mL/kg/h	21	296 (47–1064)[a]	2 U[b]	1/20
Tiryakioglu et al.[53]	Cardiac	130/0.4	1500	70	430±150	2U[b]	NR
		Ringer acetate solution	1500	70	460±140	2U[b]	
Osthaus et al.[23]	Miscellaneous	130/0.42	10 mL/kg	25	2.9±4.9 mL/kg/h	NR	NR
	pediatric	MF gelatin	10 mL/kg	25	4.2±4.6 mL/kg/h		
Schramko et al.[71]	Cardiac	130/0.4	15 mL/kg	15	895 (619–1250)	NR	5/15
		HES 200/0.5	15 mL/kg	15	870 (680–1230)		11/15
		4% albumin	15 mL/kg	15	990 (773–1073		5/15
Schramko et al.[72]	Cardiac	130/0.4	28 mL/kg	15	951±336	15U[b]	NR
		MF gelatin	28 mL/kg	15	1099±420	21U[b]	
		Ringer lactate solution	28 mL/kg	15	921±367	8U[b]	
Muralidhar et al.[24]	Cardiac	130/0.4	1920±230	10	*550±125*	0	0
	Off pump	HES 200/0.5	2200±307	10	*856±131†*	0	0
		MF gelatin	2700±197†	10	582±159	0	0
Choi et al.[73]	Cardiac	130/0.4	500	18	471±187[c]	9[c]	7/18[c]
		5% albumin	500	18	573±201[c]	15[c]	11/18[c]
Choi et al.[25]	Major orthopedic	130/0.4	15 mL/kg	27	1422±688	960±584	*4/27*
	(spine)	HES 670/0.75	15 mL/kg	27	1373±517	800±289	*12/27‡*
Jin and Yu[74]	Gastric cancer	130/0.4	30 mL/kg	12	349±98	NR	NR
		MF gelatin	30 mL/kg	12	314±58		
		Ringer lactate solution	30 mL/kg	12	321±84		
Liang et al.[75]	Colon cancer	130/0.4	1490±280	18	190±50	0	0
		HES 200/0.5	1510±260	17	210±60	0	0
Zdolsek et al.[45]	Major ortho-	130/0.4	1023±188	22	511±228	NR	NR
	pedic (hip replacement)	130/0.42	886±198	18	539±422		
		HES 200/0.5	952±179	20	595±265		
		Dextran 70	861±230	18	524±200		

* $P = 0.016$ versus HES 130/0.4.

† $P < 0.05$ versus HES 130/0.4 and MF gelatin.

‡ $P = 0.03$ versus HES 130/0.4.

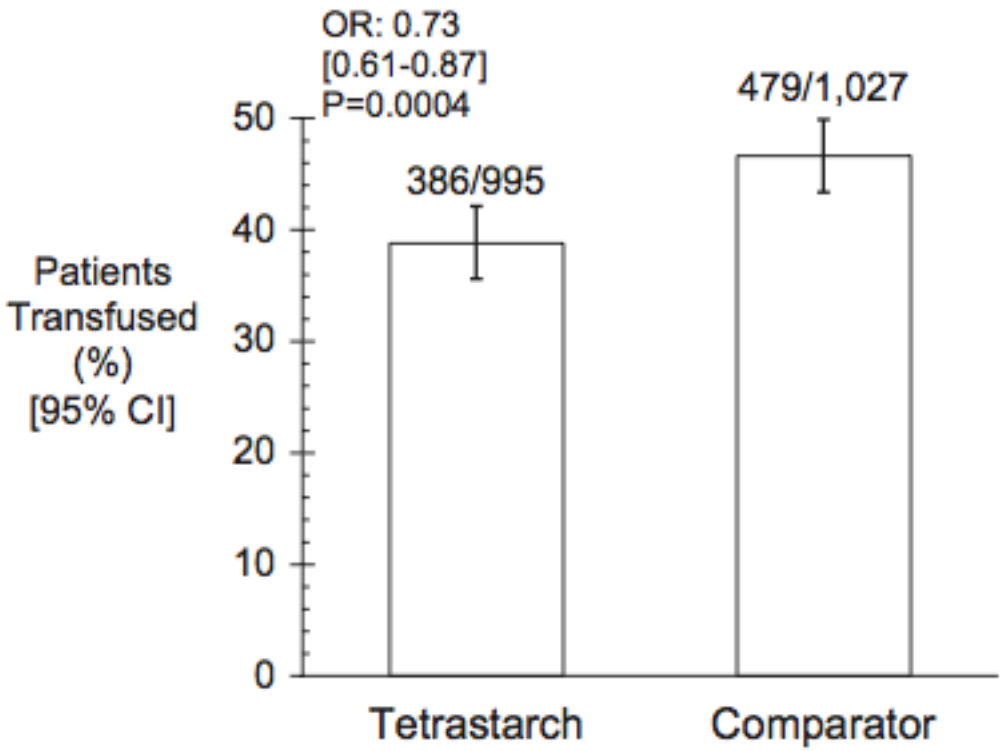


Figure 4. Fraction of patients transfused with allogeneic red cells comparing those given a tetrastarch versus all other comparators. Twenty trials reported allogeneic red cell transfusion (2151 patients); 2 reported no difference without actual data; 18 studies provided data for 2022 patients. Bars are 95% confidence intervals.

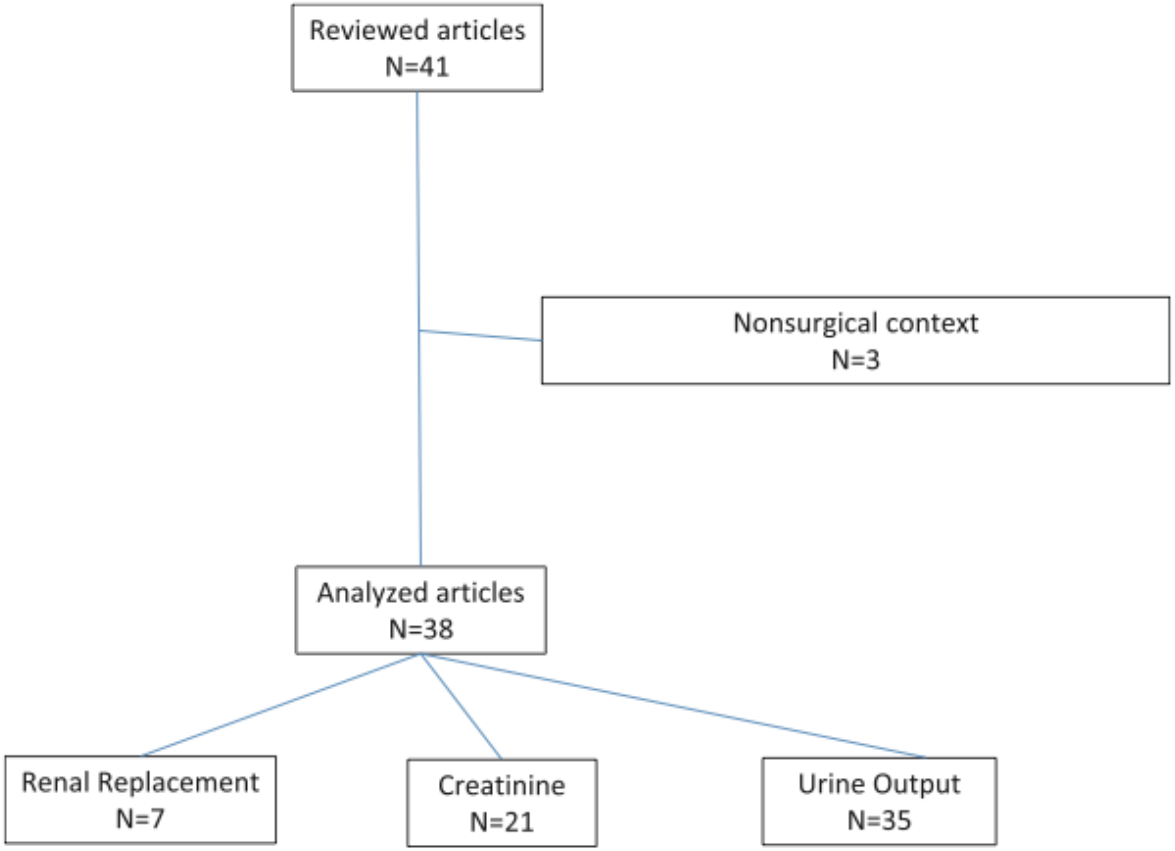


Figure 5. Flow chart of reviewed and analyzed publications related to renal function.

Table 4. Studies Evaluating Renal Function as the Primary Objective and Reporting Blood Loss Data

Authors	Surgery	Starch/comparator	Volume (mL)	No. patients (*N*)	Blood loss (mL)	Volume packed red blood cells	% Transfused
Harten et al.[42]	Major abdominal	130/0.4	750 (0–1750)	14	400 (0–2000)	NR	NR
		standard care[a]		15	250 (0–750)		
Mahmood et al.[41]	Major vascular	130/0.4	3911±783	21	1650 (1025–2630)	6 (4–8) U	NR
		Hydroxyethyl starch 200/0.62	3443±1769	21	1500 (1055–2050)	7 (5–10)	
		Modified fluid gelatin	4490±1499	20	1700 (800–3150)	7 (5–10)	

NR = not reported.

[a] Not defined in the publication.

Table 6. Studies Reporting Data for RRT

Author	Patient population	Starch, comparator	Volume (mL)	N (total)	RRT (N)
Godet et al.[51]	Abdominal aortic surgery	HES 130/0.4	2350±1355	32	0
		Gelatin	2136±1174	33	1
James et al.[46]	Trauma (blunt)	HES 130/0.4	6113±1919	20	2
		Saline solution	6295±2197	22	1
	Trauma (penetrating)	HES 130/0.4	*5093±2733*	36	0
		Saline solution	*7473±4321**	31	2
Kasper et al.[54]	Coronary artery bypass	HES 130/0.4	3500 (2000–4500)	59	2
		HES 200/0.5	2500 (1850–3250)	58	3
Lee et al.[69]	Coronary artery bypass	HES 130/0.4	1458±465	53	1
		Crystalloid	8342±1794	53	0
Mahmood et al.[41]	Aortic aneurysm surgery	HES 130/0.4	3911±1783	21	1
		HES 200/0.62	3443±1769	21	1
		Gelatin	4490±1499	20	3
Mukhtar et al.[40]	Liver transplantation	HES 130/0.4	9309±1557	20	1
		Human albumin	8136±2153	20	1
Olofsson et al.[35]	Primary hip arthroplasty	HES 130/0.4	250 or 500	184	0
		MP40X	250 or 500	180	1

Studies reporting data for RRT. All studies randomly allocated patients. Author's name in italics indicates publications that specifically indicated that the trial was double blinded. Data shown in italics indicate a statistically significant difference.

HES = hydroxyethyl starch; RRT = renal replacement therapy.

* $P < 0.05$ versus HES 130/0.4.

Renal Replacement Therapy

Seven studies reported the need for RRT (Table 6). 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).[46]

Table 7. Studies Reporting Serum Creatinine or Creatinine Clearance Data

Author	Patient population	Starch, comparator	Volume (mL)	No. patients per group (N)	Creatinine baseline (mg/dL)	Creatinine peak (mg/dL)
Boldt et al.[55]	Cardiac surgery	HES 130/0.4	795±75	10	0.88±0.15	1.01±0.26
		HES 200/0.5	820±90	10	0.91±0.17	1.04±0.22
Fenger-Eriksen et al., 2005[61]	Major spine surgery	HES 130/0.4	4000 (3000–6000)	6	0.83 (0.61–1.01)	0.74 (0.58–0.82)
		Saline	7000 (700–10,000)	5	0.87 (0.57–1.11)	0.81 (0.73–0.85)
Gallandat Huet et al.[36]	Cardiac surgery	HES 130/0.4	2550±561	30	1.10±0.16	1.23±0.20
		HES 200/0.5	2466±516	29	1.12±0.16	1.07±0.23
Godet et al.[51]	Abdominal aortic surgery	HES 130/0.4	2350±1355	32	*1.23±0.33*	1.40±0.70
		Gelatin	2136±1174	33	*1.26 ±.0.28*	1.44±0.70
Hanart et al.[21]	Pediatric cardiac surgery	HES 130/0.4	Intraoperative, 50 (45–50)/kg	60	0.32 (0.27–0.39)	0.31 (0.25–0.40)
		Human albumin	Intraoperative, 50 (37–50)/kg	59	0.27 (0.24–0.35)	0.30 (0.23–0.36)
Harten et al.[42]	Emergency abdominal surgery	HES 130/0.4	750 (0–1750)	14	0.97 (0.62–1.82)	0.97 (0.68–1.70)
		"Standard care"		15	1.14 (0.80–2.95)	1.08 (0.68–3.41)
Heinze et al.[39]	Major urological surgery	HES 130/0.42	2540±1232	46	0.85±0.19	0.89±0.19
		HES 200/0.5	2290±1040	47	0.83±0.26	0.86±0.28
Ickx et al.[49]	Major abdominal surgery	HES 130/0.4	1825±245	20	1.05±0.13	0.95±0.19
		HES 200/0.5	1925±183	20	1.15±0.12	1.02±0.12
Jover et al.[56]	Laparoscopic cholecystectomy	HES 130/0.4	500	14	CrCl: 116±28	*CrCl: 176±14*
		Ringer lactate solution	500	15	CrCl: 109.± 21	*CrCl:* 62±6.6*
Kasper et al.[62]	Major surgery	HES 130/0.4	500	30	Creatinine: normal; no significant change	Creatinine: normal; no significant change
		HES 200/0.5	500	30		
Kasper et al.[54]	Coronary artery bypass	HES 130/0.4	3500 (2000–4500)	59	0.9±0.2	1.0±0.3
		HES 200/0.5	2500 (1850- 3250)	58	0.9±0.2	1.1±0.4
Kim et al.[22]	Coronary artery bypass surgery	HES 130/0.4	2400±500	24	0.96±0.2	1.0±0.2
		HES 200/0.5	2300±600	24	1.0±0.2	0.9±0.2
Mahmood et al.[41]	Aortic aneurysm surgery	HES 130/0.4	3911±1783	21	1.1±0.01	*1.0±0.01*
		HES 200/0.62	3443±1769	21	1.2±0.03	1.2±0.1
		Gelatin	4490±1499	20	1.1±0.01	*1.6±0.2**
Mukhtar et al.[40]	Liver transplantation	HES 130/0.4	9309±1557	20	1.1±0.1	1.5±0.3
		Human albumin	8136±2153	20	1.1±0.3	1.3±0.4
Olofsson et al.[35]	Primary hip arthroplasty	HES 130/0.4	250 or 500	184	CrCl: 82 (62–100) mL/min	CrCl: 96 (78–122) mL/min
		MP4OX	250 or 500	180	CrCl: 82 (70–100) mL/min	CrCl: 94 (72–114) mL/min
Shabazi et al.[43]	Cardiopulmonary bypass	HES 130/0.4	1500	35	0.96±0.18	1.25±0.35
		Ringer lactate solution	1500	35	1±0.15	1.21±0.45
Tiryakioglu et al.[53]	Cardiopulmonary bypass priming	HES 130/0.4	1500	70	1.1±0.1	*1.4±0.24*
		Ringer lactate solution	1500	70	1.0±0.2	*1.1±0.22**
Van der Linden et al.[52]	Cardiac surgery	HES 130/0.4	48.8±20.9/kg	65	1.05±0.23	1.02±0.29
		Gelatin	48.9±19.3/kg	68	1.09±0.29	1.17±0.74
Van der Linden et al.[34]	Primary hip arthroplasty	HES 130/0.4	250 or 500	201	CrCl: no differences between groups	CrCl: no differences between groups
		MP4OX	250 or 500	198		
Wu et al.[57]	Living-related kidney transplantation	HES 130/0.4	1107±308	38	8.17±2.47	0.86±0.23
		Gelatin	1178±320	39	8.27±2.42	1.03±0.41
Yang et al.[44]	Hepatectomy	HES 130/0.4	4500 + crystalloid	26	Normal, no significant differences between groups	Normal, no significant differences between groups
		Human albumin	1800 + crystalloid	30		
		Ringer lactate solution	12,924	25		
Yap et al.[79]	Coronary artery bypass surgery	HES 130/0.4	500	21		1.09±0.25
		Gelatin	500	21		1.35±0.57

Peak Kreatinin
HES vs diğer sıvılar
0,85 -1,08 %95 CI:1
p>0,05

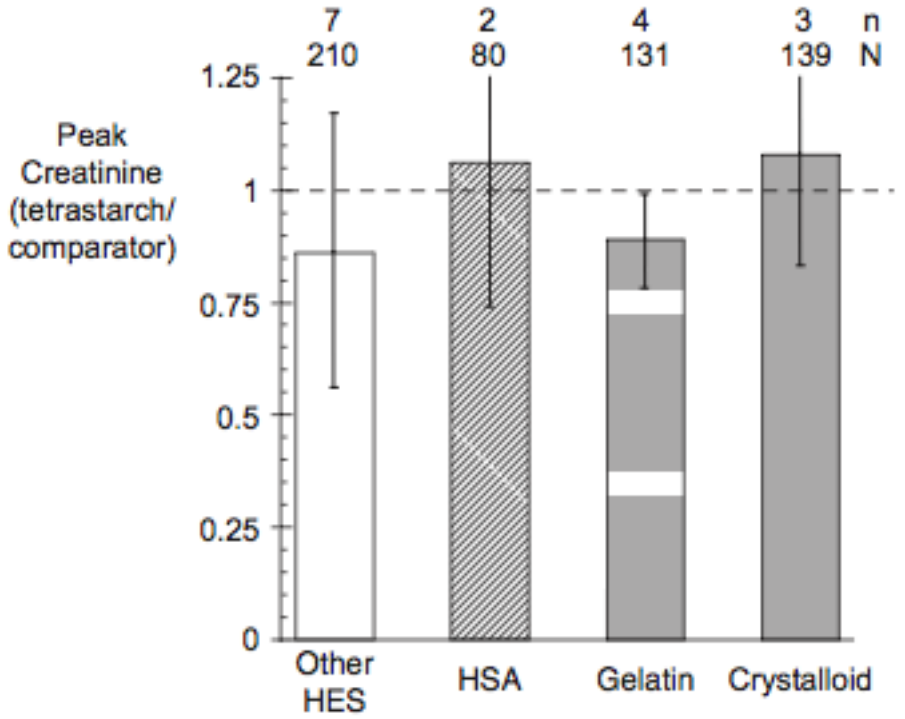


Figure 6. Ratio of peak postoperative serum creatinine concentration for patients given a tetrastarch to the peak postoperative serum creatinine for patients given comparators. The bars are mean values (with 95% confidence intervals) of the mean or median group data reported in all publications providing serum creatinine data. *n* = number of publications providing data; *N* = number of patients in those trials who were given a tetrastarch; HSA = human serum albumin. No statistical analyses were performed.

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 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.

In summary, we conclude that data in the peer-reviewed literature do not suggest an adverse safety signal when tetrastarches are used intraoperatively or in the immediate postoperative period or both. We did

Original Article

http://dx.doi.org/10.3349/ymj.2014.55.3.625
pISSN: 0513-5796, eISSN: 1976-2437

Yonsei Med J 55(3):625-634, 2014

YMJ

Effect of 6% Hydroxyethyl Starch 130/0.4 as a Priming Solution on Coagulation and Inflammation Following Complex Heart Surgery

Jang-Eun Cho,[1] Jae-Kwang Shim,[2] Jong-Won Song,[2] Hye-Won Lee,[1]
Dong-Hwan Kim,[1] and Young-Lan Kwak[2]

- Grup 1: Albumin+ HES (18 hasta)
  - (500ml %5 albumin) + (1000ml Plasmalyte)
  - İnf: 20 mL/kg/gün 6% HES 130/0.4
- Grup 2: HES + HES (18 hasta)
  - (500 mL 6% HES 130/0.4 + (1000 mL of plasmalyte)
    İnf: 20 mL/kg/gün 6% HES 130/0.4
- Grup 3:Albumin + non HES (18 hasta)
  - (500ml %5 albumin) +(1000ml Plasmalyte)
  - İnf: Plasmalyte

Table 2. ROTEM before [Pre] and 24 h after [Post] CPB

	HA-HES	HES-HES	HA-nonHES	*p* value
InTEM				
Coagulation time (s)				
PreCPB	187 [173-224]	204 [148-289]	200 [172-271]	0.75
PostCPB	242 [187-268]	228 [162-283]	274 [219-344]	0.428
Clot formation time (s)				
PreCPB	91 [75-114]	88 [71-132]	70 [68-92]	0.124
PostCPB	115 [92-193]*	121 [80-208]	119 [101-138]*	0.972
α angle (°)				
PreCPB	73 [68-75]	73 [69-76]	76 [73-77]	0.109
PostCPB	72 [61-73]	70 [54-76]	69 [65-71]*	0.977
Maximum clot firmness (mm)				
PreCPB	60 [57-64]	63 [58-65]	61 [56-65]	0.602
PostCPB	54 [45-58]*	52 [45-56]*	57 [51-59]*	0.085
ExTEM				
Coagulation time (s)				
PreCPB	57 [49-75]	55 [49-67]	50 [45-52]	0.123
PostCPB	58 [50-80]	55 [45-70]	52 [45-60]	0.234
Clot formation time (s)				
PreCPB	104 [79-124]	99 [82-112]	85 [73-112]	0.514
PostCPB	114 [106-165]	105 [86-144]	120 [93-126]*	0.482
α angle (°)				
PreCPB	71 [65-74]	72 [68-74]	74 [71-78]	0.130
PostCPB	69 [64-72]	72 [67-76]	74 [70-76]	0.093
Maximum clot firmness (mm)				
PreCPB	59 [54-61]	63 [58-65]	62 [57-66]	0.057
PostCPB	56 [50-62]	59 [56-63]	58 [55-61]*	0.314
FibTEM				
Maximum clot firmness (mm)				
PreCPB	14 [11-17]	17 [14-25]	18 [15-20]	0.052
PostCPB	16 [13-20]	17 [11-20]	18 [15-25]	0.658

preCPB, before cardiopulmonary bypass; postCPB, after cardiopulmonary bypass; ROTEM, rotation thromboelastography; HA, 5% human albumin; HES, 6% hydroxyethyl starch 130/0.4; InTEM, intrinsic ROTEM; ExTEM, extrinsic ROTEM; FibTEM, fibrinogen ROTEM.
Values are median [interquartile range].
*$p<0.05$ between pre- and postCPB within group.

Table 3. Blood Loss, Transfusion Requirement, Coagulation Variables, and Fluid Balance

	Intraoperative	Postoperative 24 h
Blood loss (mL)		
HA-HES	500 [480-720]	450 [380-740]
HES-HES	583 [420-700]	495 [410-1220]
HA-nonHES	500 [485-665]	430 [280-685]
Transfused pRBC (units)/patients number (%)		
HA-HES	1 [0-1]/10 (56)	0 [0-1]/8 (44)
HES-HES	1 [0-2]/11 (61)	0 [0-1.5]/8 (44)
HA-nonHES	0 [0-1]/7 (39)	0 [0-1]/7 (39)
Transfused FFP (units)/patients number (%)		
HA-HES	0 [0-3]/5 (28)	0 [0-0]/3 (17)
HES-HES	0 [0-3]/5 (28)	0 [0-0.5]/4 (22)
HA-nonHES	0 [0-3]/5 (28)	0 [0-0]/3 (17)
Transfused Plts (units)/patients number (%)		
HA-HES	0 [0-0]/2 (11)	0 [0-0]/1 (6)
HES-HES	0 [0-0]/3 (17)	0 [0-0]/1 (6)
HA-nonHES	0 [0-0]/1 (6)	0 [0-0]/2 (11)

HA, 5% human albumin; HES, 6% hydroxyethyl starch 130/0.4; pRBC, packed red blood cells; FFP, fresh frozen plasma; Plt, platelet concentrations; PT, prothrombin time; aPTT, activated partial thromboplastin time.

Values are median [interquartile range] or mean±standard deviation or number of patients. Total, combined data of intraoperative and postoperative 24 h.

*$p<0.005$ compared with HA-HES and HES-HES group.

†$p<0.005$ compared with HA-HES and HA-nonHES group.

Table 4. Postoperative Datas

	HA-HES (n=18)	HES-HES (n=18)	HA-nonHES (n=18)	*p* value
Hemofiltration (mL)	1200 [800-1875]	1000 [850-2200]	1000 [100-1650]	0.417
AKI (n)	4	4	5	0.629
ICU day (day)	3.3±0.9	3.2±1.0	2.7±0.9	0.196
Hospital day (day)	13.2±4.4	11.2±5.5	12.4±3.4	0.671
Mortality (n)	0	1	0	0.981

HA, 5% human albumin; HES, 6% hydroxyethyl starch 130/0.4; AKI, acute kidney injury by RIFLE (R-risk, I-injury, F-failure, LE-loss and end stage renal disease) criteria; ICU, intensive care unit.

Values are number of patients or median [interquartile range].

In conclusion, 6% HES 130/0.4, when used for priming and perioperative fluid therapy up to 20 mL/kg, seemed to yield similar influence on the ensuing coagulopathy and inflammatory response following complex valvular heart surgery requiring prolonged duration of CPB, compared with conventional fluid regimen including albumin and plasmalyte.

Gurbuz *et al. Journal of Cardiothoracic Surgery* 2013, **8**:71
http://www.cardiothoracicsurgery.org/content/8/1/71

JOURNAL OF CARDIOTHORACIC SURGERY

RESEARCH ARTICLE Open Access

Hydroxyethyl starch 6%, 130/0.4 vs. a balanced crystalloid solution in cardiopulmonary bypass priming: a randomized, prospective study

Hasan Alper Gurbuz[1,2], Ahmet Baris Durukan[1,2*], Nevriye Salman[3], Murat Tavlasoglu[4], Elif Durukan[5], Halil İbrahim Ucar[1] and Cem Yorgancioglu[1]

Table 1 Comparison of the two groups by preoperative and intraoperative characteristics

Factor	Isolyte-M® group (n:100)	Voluven® 6% group (n:100)	p value*
	Mean ± SD	Mean ± SD	
Age	61.81 ± 10.12	61.52 ± 9.29	0.833
BMI (kg/m^2)	27.88 ± 3.96	29.02 ± 4.61	0.063
LVEF (%)	53.72 ± 10.81	52.33 ± 11.08	0.370
Cross-clamp time (min)	53.57 ± 20.12	55.58 ± 17.22	0.449
CPB time (min)	79.69 ± 27.93	82.57 ± 23.98	0.435
Graft #	3.22 ± 1.06	3.10 ± 0.90	0.390
	n:%	n:%	p value**
Patient Total	100	100	
Male sex	77	74	0.622
Current/Ex-smoker	67	63	0.553
Diabetes Mellitus	46	42	0.569
Hypertension	65	62	0.659
Dyslipidemia	79	76	0.611
Preoperative β-blocker use	40	47	0.318
Peripheral Arterial Disease[a]	1	6	0.118***
Stroke	-	1	1.000***
Carotid Disease[b]	7	5	0.552***
COPD/Asthma	14	15	0.841

*independent samples *t*-test.
**chi-square test.
***Fisher's exact test.

Table 2 Comparison of the two groups by postoperative variables

	Isolyte-M® group	Voluven® 6% group	
	Mean ± SD	Mean ± SD	p value*
ICU intubation time, hours	10.38 ± 9.04	9.38 ± 2.64	0.290
Length Of Stay			
ICU, hours	47.93 ± 12.01	45.25 ± 5.86	0.046
Postoperative, days	6.14 ± 2.55	5.47 ± 1.20	0.019
Drainage tubes removed, hours	36.36 ± 10.39	36.12 ± 13.32	0.886
Total amount of drainage, ml	741.75 ± 448.58	680.30 ± 332.92	0.273
Number of FFP used	1.05 ± 1.32	1.02 ± 1.40	0.877
Number of packed RBC used	1.82 ± 1.65	1.63 ± 1.50	0.397
Number of PC used	0.61 ± 1.92	0.15 ± 0.98	0.035
	n:%	n:%	p value**
Postoperative exploration for hemorrhage	2	5	0.445
Postoperative AF	15	19	0.451***
Renal Dysfunction[a]	6	9	0.421
Postoperative Stroke	1	1	1.000

*Independent samples t-test.
** Fisher's exact test.
***chi-square test.

Conclusions

- In this prospective randomized study,
- we did not document any difference between HES and crystalloid solutions used for CPB priming regarding postoperative outcomes like postoperative bleeding, renal functions and the use of blood and FFP.
- The number of used PC was less and the hospital length of stay and ICU stay were shorter in HES group.

Jacob et al. Critical Care (2014) 18:656
DOI 10.1186/s13054-014-0656-0

CRITICAL CARE

RESEARCH Open Access

The impact of hydroxyethyl starches in cardiac surgery: a meta-analysis

Matthias Jacob[1], Jean-Luc Fellahi[2,3*], Daniel Chappell[4] and Andrea Kurz[5]

Introduction: Recent studies in septic patients showed that adverse effects of hydroxyethyl starches (HESs) possibly outweigh their benefits in severely impaired physiological haemostasis. It remains unclear whether this also applies to patient populations that are less vulnerable. In this meta-analysis, we evaluated the impact of various HES generations on safety and efficacy endpoints in patients undergoing cardiac surgery.

Methods: We searched the PubMed, Embase and Cochrane Central Register of Controlled Trials databases for randomised controlled trials (RCTs) in the English or German language comparing the use of HES to any other colloid or crystalloid during open heart surgery.

Results: Blood loss and transfusion requirements were higher for older starches with mean molecular weights more than 200 kDa compared to other volume substitutes. In contrast, this effect was not observed with latest-generation tetrastarches (130/0.4), which performed even better when compared to albumin (blood loss of tetrastarch versus albumin: standardised mean difference (SMD), −0.34; 95% CI, −0.63, −0.05; $P = 0.02$; versus gelatin: SMD, −0.06; 95% CI, −0.20, 0.08; $P = 0.39$; versus crystalloids: SMD, −0.05; 95% CI, −0.20, 0.10; $P = 0.54$). Similar results were found for transfusion needs. Lengths of stay in the intensive care unit or hospital were significantly shorter with tetrastarches compared to gelatin (intensive care unit: SMD, −0.10; 95% CI, −0.15, −0.05; $P = 0.0002$) and crystalloids (hospital: SMD, −0.52; 95% CI, −0.90, −0.14; $P = 0.007$).

Conclusions: In this meta-analysis of RCTs, we could not identify safety issues with tetrastarches compared with other colloid or crystalloid solutions in terms of blood loss, transfusion requirements or hospital length of stay in patients undergoing cardiac surgery. The safety data on coagulation with older starches raise some issues that need to be addressed in future trials.

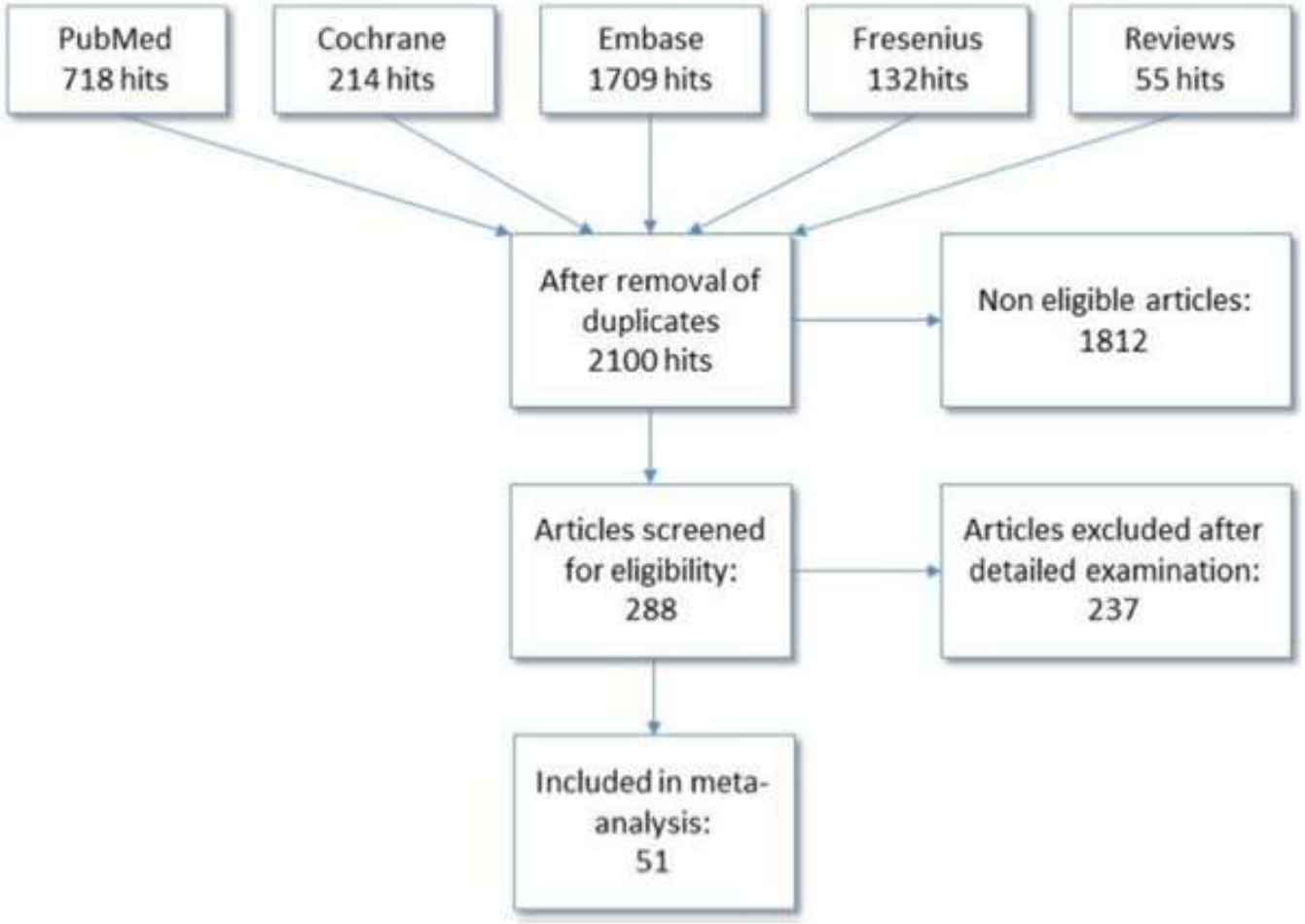


Figure 1 Overview of study selection.

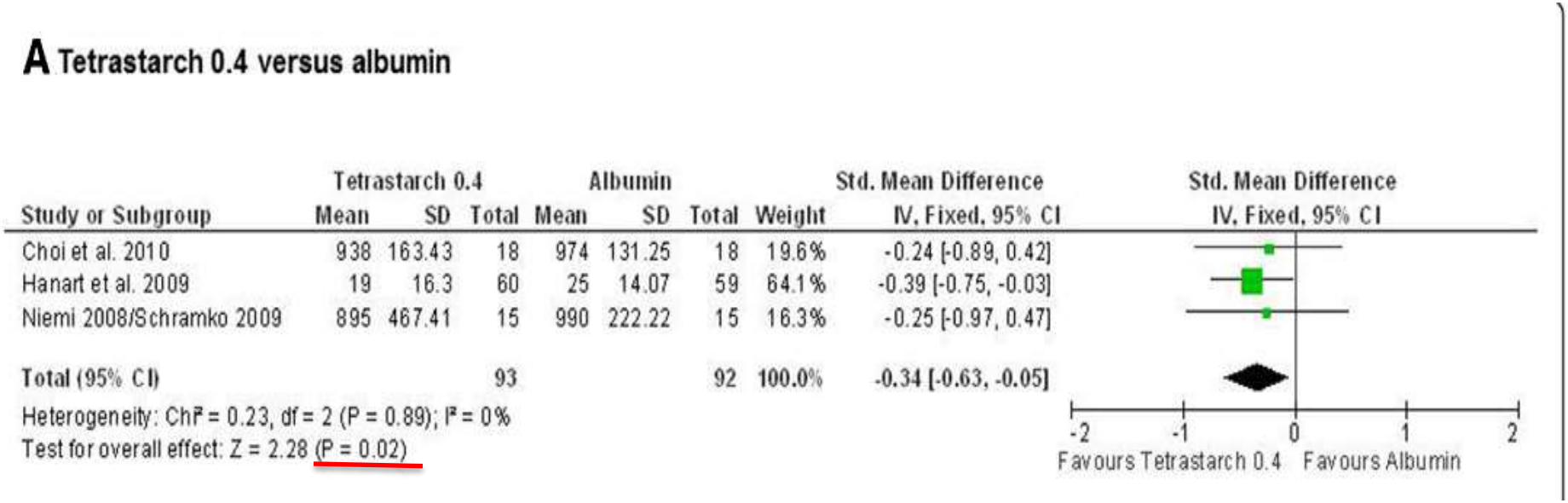


Figure 2 Blood loss with tetrastarch compared to albumin, gelatin or crystalloids. Units of blood loss were expressed in millilitres (ml), except for Hanart *et al.* [43] and Van der Linden *et al.* [52], where the units were millilitres per kilogram body weight, and Lee *et al.* [47], where no unit was indicated. The standardised mean difference (Std. mean difference) of the mean for the tetrastarch groups minus the mean for the albumin **(A)**, gelatin **(B)** and crystalloid **(C)** groups was used as effect size. Fixed-effects models were applied to calculate a common effect estimate using the inverse-variance method (IV). SD, standard deviation; CI, Confidence interval.

B Tetrastarch 0.4 versus gelatin

Study or Subgroup	Tetrastarch 0.4 Mean	SD	Total	Gelatin Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Alavi et al. 2012	1,280	280	32	1,350	270	31	7.7%	-0.25 [-0.75, 0.24]
Boks et al. 2007	1,768	711.51	90	1,921	844.33	90	22.1%	-0.20 [-0.49, 0.10]
Kimenai et al. 2013	500	311.11	30	465	288.89	30	7.4%	0.12 [-0.39, 0.62]
Mulavisala et al. 2012	76	74	28	109	108	21	5.8%	-0.36 [-0.93, 0.21]
Muralidhar et al. 2010	550	124.9	10	582	159	10	2.4%	-0.21 [-1.09, 0.67]
Ooi et al. 2009	567.3	281.2	45	596.4	336.6	45	11.1%	-0.09 [-0.51, 0.32]
Schramko et al. 2010	951	336	15	1,099	420	15	3.6%	-0.38 [-1.10, 0.34]
Van der Linden et al 2005	19.4	12.3	64	19.2	14.5	68	16.3%	0.01 [-0.33, 0.36]
Vanhoonacker et al. 2009	695.79	368.82	82	592.43	347.89	72	18.7%	0.29 [-0.03, 0.60]
Yap et al. 2007	507	183	20	561	227	20	4.9%	-0.26 [-0.88, 0.37]
Total (95% CI)			**416**			**402**	**100.0%**	**-0.06 [-0.20, 0.08]**

Heterogeneity: Chi² = 8.92, df = 9 (P = 0.44); I² = 0%

Test for overall effect: Z = 0.87 (P = 0.39)

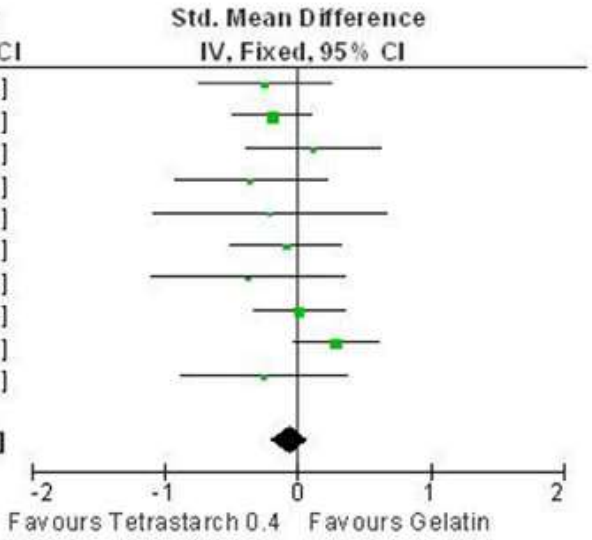


Figure 2 Blood loss with tetrastarch compared to albumin, gelatin or crystalloids. Units of blood loss were expressed in millilitres (ml), except for Hanart *et al.* [43] and Van der Linden *et al.* [52], where the units were millilitres per kilogram body weight, and Lee *et al.* [47], where no unit was indicated. The standardised mean difference (Std. mean difference) of the mean for the tetrastarch groups minus the mean for the albumin **(A)**, gelatin **(B)** and crystalloid **(C)** groups was used as effect size. Fixed-effects models were applied to calculate a common effect estimate using the inverse-variance method (IV). SD, standard deviation; CI, Confidence interval.

C Tetrastarch 0.4 versus crystalloid

Study or Subgroup	Tetrastarch 0.4 Mean	SD	Total	Crystalloid Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Akkucuk et al. 2013	236.6	127.2	12	192.1	109.1	12	3.5%	0.36 [-0.45, 1.17]
Alavi et al. 2012	1,280	280	32	1,300	260	29	9.0%	-0.07 [-0.58, 0.43]
Chakravarthy et al. 2012	1,589	390	25	1,381	357	23	6.8%	0.55 [-0.03, 1.12]
Gurbuz et al. 2013	680.3	332.92	100	741.75	448.58	100	29.6%	-0.15 [-0.43, 0.12]
Lee et al. 2011	978	347	53	1,028	389	53	15.7%	-0.13 [-0.52, 0.25]
Schramko et al. 2010	951	336	15	921	367	15	4.4%	0.08 [-0.63, 0.80]
Shahbazi et al. 2011	934.9	591	35	853.4	552.5	35	10.3%	0.14 [-0.33, 0.61]
Tiryakioglu et al. 2008	430	150	70	460	140	70	20.6%	-0.21 [-0.54, 0.13]
Total (95% CI)			342			337	**100.0%**	**-0.05 [-0.20, 0.10]**

Heterogeneity: $Chi^2 = 7.45$, $df = 7$ ($P = 0.38$); $I^2 = 6\%$

Test for overall effect: $Z = 0.62$ ($P = 0.54$)

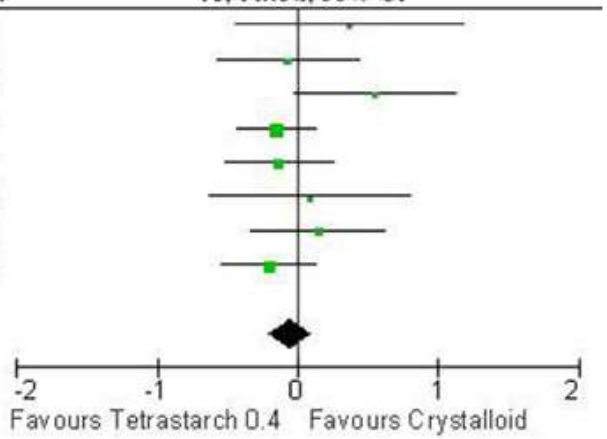


Figure 2 Blood loss with tetrastarch compared to albumin, gelatin or crystalloids. Units of blood loss were expressed in millilitres (ml), except for Hanart *et al.* [43] and Van der Linden *et al.* [52], where the units were millilitres per kilogram body weight, and Lee *et al.* [47], where no unit was indicated. The standardised mean difference (Std. mean difference) of the mean for the tetrastarch groups minus the mean for the albumin **(A)**, gelatin **(B)** and crystalloid **(C)** groups was used as effect size. Fixed-effects models were applied to calculate a common effect estimate using the inverse-variance method (IV). SD, standard deviation; CI, Confidence interval.

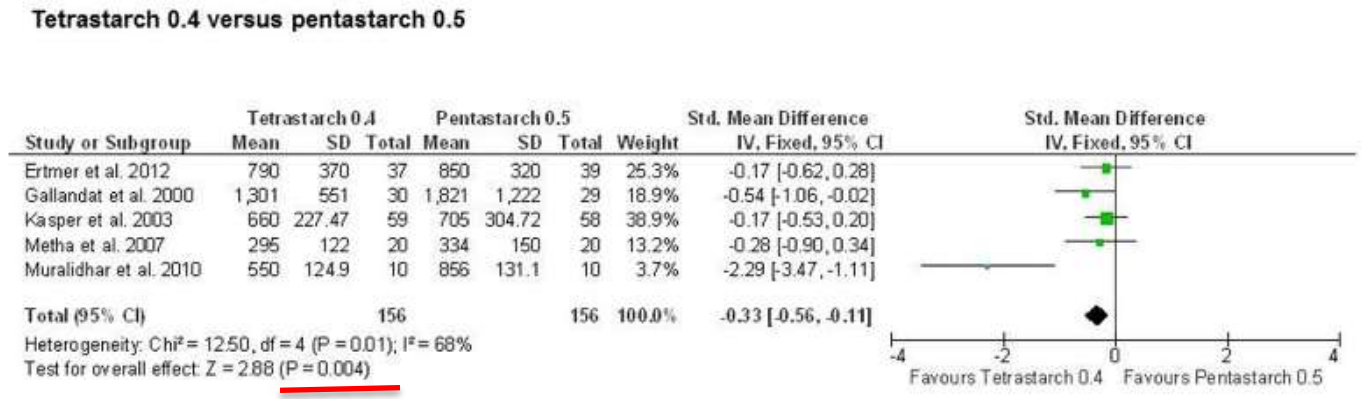


Figure 3 Blood loss with tetrastarch compared to pentastarch. Units of blood loss were millilitres (ml). The standardised mean difference (Std. mean difference) of the mean for the tetrastarch groups minus the mean for the pentastarch 0.5 group was used as effect size. A fixed-effects model was applied to calculate a common effect estimate using the inverse-variance method (IV). SD, Standard deviation; CI, Confidence interval.

A **Tetrastarch 0.4 versus albumin**

Study or Subgroup	Tetrastarch 0.4 Events	Total	Albumin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Choi et al. 2010	8	18	14	18	21.1%	0.57 [0.32, 1.01]
Hanart et al. 2009	34	60	46	59	69.9%	0.73 [0.56, 0.94]
Schramko et al. 2009	5	15	6	15	9.0%	0.83 [0.32, 2.15]
Total (95% CI)		**93**		**92**	**100.0%**	**0.70 [0.56, 0.89]**
Total events	47		66			

Heterogeneity: Chi² = 0.69, df = 2 (P = 0.71); I² = 0%

Test for overall effect: Z = 2.95 (P = 0.003)

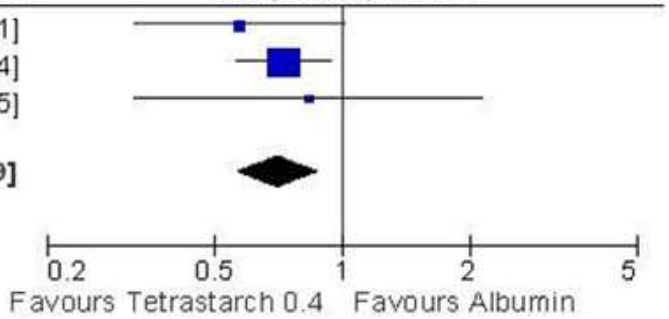


Figure 4 Transfusion requirements after tetrastarch compared to albumin, gelatin or crystalloids. The risk ratio was used as effect size (transfusion risk for the hydroxyethyl starch groups divided by transfusion risk for the albumin **(A)**, gelatin **(B)** and crystalloid **(C)** groups). Fixed-effects models were applied to calculate a common effect estimate using the Mantel-Haenszel (M-H) approach. CI, confidence interval.

B Tetrastarch 0.4 versus gelatin

Study or Subgroup	Tetrastarch 0.4 Events	Total	Gelatin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kimenai et al. 2013	4	30	3	30	2.9%	1.33 [0.33, 5.45]
Lou et al. 2012	8	35	8	35	7.8%	1.00 [0.42, 2.36]
Muralidhar et al. 2010	0	10	0	10		Not estimable
Ooi et al. 2009	40	45	42	45	41.1%	0.95 [0.84, 1.08]
Van der Linden et al 2005	24	64	21	68	19.9%	1.21 [0.75, 1.95]
Vanhoonacker et al. 2009	37	82	27	72	28.2%	1.20 [0.82, 1.76]
Total (95% CI)		**266**		**260**	**100.0%**	**1.09 [0.91, 1.30]**
Total events	113		101			

Heterogeneity: $Chi^2 = 4.75$, $df = 4$ ($P = 0.31$); $I^2 = 16\%$

Test for overall effect: $Z = 0.95$ ($P = 0.34$)

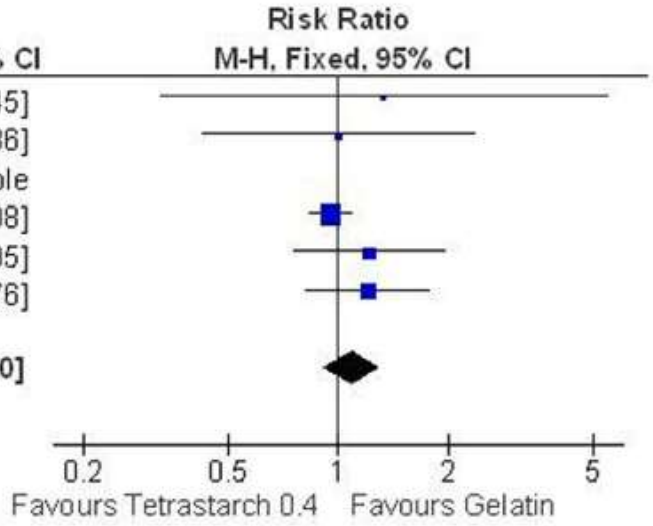


Figure 4 Transfusion requirements after tetrastarch compared to albumin, gelatin or crystalloids. The risk ratio was used as effect size (transfusion risk for the hydroxyethyl starch groups divided by transfusion risk for the albumin **(A)**, gelatin **(B)** and crystalloid **(C)** groups). Fixed-effects models were applied to calculate a common effect estimate using the Mantel-Haenszel (M-H) approach. CI, confidence interval.

C Tetrastarch 0.4 versus crystalloid

Study or Subgroup	Tetrastarch 0.4 Events	Total	Crystalloid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chakravarthy et al. 2012	8	25	6	23	34.2%	1.23 [0.50, 3.00]
Lee et al. 2011	14	53	12	53	65.8%	1.17 [0.60, 2.28]
Total (95% CI)		**78**		**76**	**100.0%**	**1.19 [0.69, 2.03]**
Total events	22		18			

Heterogeneity: $Chi^2 = 0.01$, df = 1 (P = 0.93); $I^2 = 0\%$

Test for overall effect: Z = 0.63 (P = 0.53)

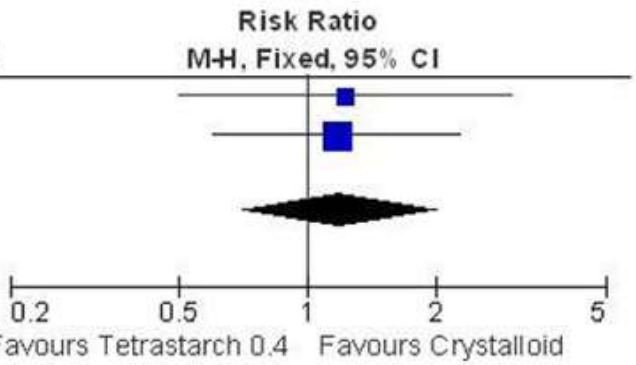


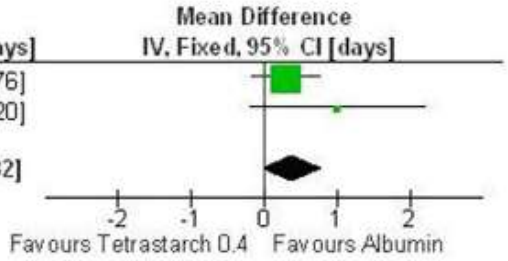
Figure 4 Transfusion requirements after tetrastarch compared to albumin, gelatin or crystalloids. The risk ratio was used as effect size (transfusion risk for the hydroxyethyl starch groups divided by transfusion risk for the albumin **(A)**, gelatin **(B)** and crystalloid **(C)** groups). Fixed-effects models were applied to calculate a common effect estimate using the Mantel-Haenszel (M-H) approach. CI, confidence interval.

A Tetrastarch 0.4 versus albumin

ICU

Study or Subgroup	Tetrastarch 0.4 Mean [days]	SD [days]	Total	Albumin Mean [days]	SD [days]	Total	Weight	Mean Difference IV, Fixed, 95% CI [days]
Choi et al. 2010	1.7	0.8	18	1.4	0.6	18	87.1%	0.30 [-0.16, 0.76]
Hanart et al. 2009	5	3.7	60	4	2.96	59	12.9%	1.00 [-0.20, 2.20]
Total (95% CI)			78			77	**100.0%**	**0.39 [-0.04, 0.82]**

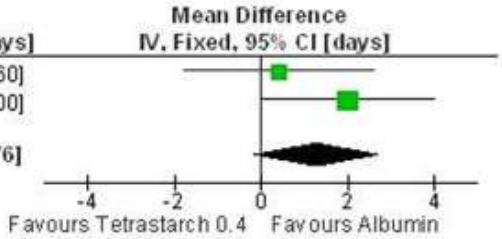
Heterogeneity: Chi² = 1.13, df = 1 (P = 0.29); I² = 12%
Test for overall effect: Z = 1.77 (P = 0.08)



Hospital

Study or Subgroup	Tetrastarch 0.4 Mean [days]	SD [days]	Total	Albumin Mean [days]	SD [days]	Total	Weight	Mean Difference IV, Fixed, 95% CI [days]
Choi et al. 2010	12	3.7	18	11.6	3	18	45.3%	0.40 [-1.80, 2.60]
Hanart et al. 2009	14	5.93	60	12	5.19	59	54.7%	2.00 [-0.00, 4.00]
Total (95% CI)			78			77	**100.0%**	**1.28 [-0.20, 2.76]**

Heterogeneity: Chi² = 1.11, df = 1 (P = 0.29); I² = 10%
Test for overall effect: Z = 1.69 (P = 0.09)



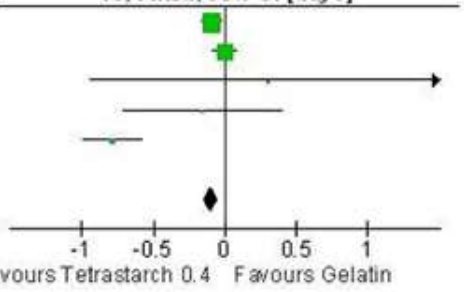
B Tetrastarch 0.4 versus gelatin

ICU

Study or Subgroup	Tetrastarch 0.4 Mean [days]	SD [days]	Total	Gelatin Mean [days]	SD [days]	Total	Weight	Mean Difference IV, Fixed, 95% CI [days]
Alavi et al. 2012	1.87	0.19	32	1.96	0.09	31	51.3%	-0.09 [-0.16, -0.02]
Boks et al. 2007	0.95	0.28	90	0.95	0.28	90	40.9%	0.00 [-0.08, 0.08]
Mulavisala et al. 2012	3.7	2.6	28	3.4	1.8	21	0.2%	0.30 [-0.93, 1.53]
Ooi et al. 2009	2.44	1.36	45	2.6	1.31	45	0.9%	-0.16 [-0.71, 0.39]
Van der Linden et al 2005	1	0.47	64	1.79	0.7	68	6.7%	-0.79 [-0.99, -0.59]
Total (95% CI)			259			255	100.0%	**-0.10 [-0.15, -0.05]**

Heterogeneity: Chi² = 50.93, df = 4 (P < 0.00001); I² = 92%

Test for overall effect: Z = 3.74 (P = 0.0002)

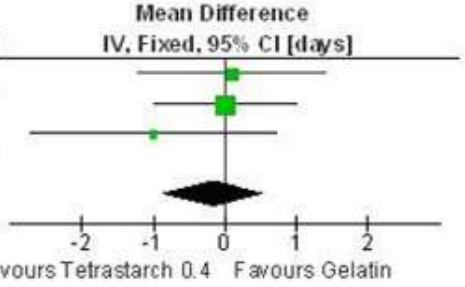


Hospital

Study or Subgroup	Tetrastarch 0.4 Mean [days]	SD [days]	Total	Gelatin Mean [days]	SD [days]	Total	Weight	Mean Difference IV, Fixed, 95% CI [days]
Mulavisala et al. 2012	6.8	1.9	28	6.7	2.6	21	29.9%	0.10 [-1.22, 1.42]
Ooi et al. 2009	6	2.6	45	6	2.2	45	52.4%	0.00 [-1.00, 1.00]
Van der Linden et al 2005	8	3.86	64	9	6.01	68	17.7%	-1.00 [-2.71, 0.71]
Total (95% CI)			137			134	100.0%	**-0.15 [-0.87, 0.57]**

Heterogeneity: Chi² = 1.17, df = 2 (P = 0.56); I² = 0%

Test for overall effect: Z = 0.40 (P = 0.69)



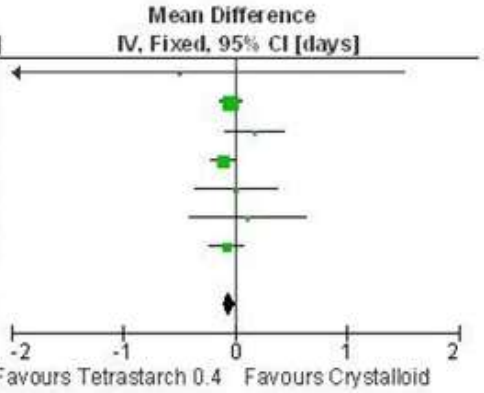
C **Tetrastarch 0.4 versus crystalloid**

ICU

Study or Subgroup	Tetrastarch 0.4 Mean [days]	SD [days]	Total	Crystalloid Mean [days]	SD [days]	Total	Weight	Mean Difference IV, Fixed, 95% CI [days]
Akkucuk et al. 2013	2.5	2.2	12	3	2.8	12	0.1%	-0.50 [-2.51, 1.51]
Alavi et al. 2012	1.87	0.19	32	1.92	0.19	29	41.7%	-0.05 [-0.15, 0.05]
Chakravarthy et al. 2012	1.92	0.5	25	1.75	0.42	23	5.6%	0.17 [-0.09, 0.43]
Gurbuz et al. 2013	1.89	0.24	100	2	0.5	100	32.2%	-0.11 [-0.22, -0.00]
Lee et al. 2011	2.7	0.8	53	2.7	1.1	53	2.8%	0.00 [-0.37, 0.37]
Shahbazi et al. 2011	3.04	0.84	35	2.94	1.32	35	1.4%	0.10 [-0.42, 0.62]
Tiryakioglu et al. 2008	1.88	0.42	70	1.96	0.5	70	16.2%	-0.08 [-0.23, 0.07]
Total (95% CI)			327			322	100.0%	**-0.06 [-0.12, 0.00]**

Heterogeneity: $Chi^2 = 4.57$, $df = 6$ ($P = 0.60$); $I^2 = 0\%$

Test for overall effect: $Z = 1.87$ ($P = 0.06$)

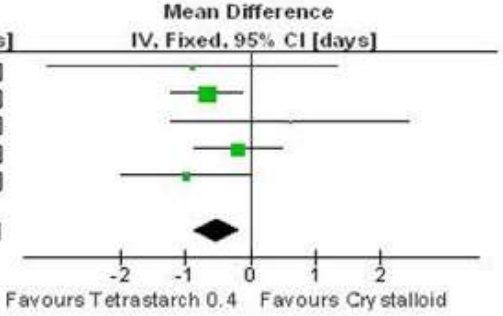


Hospital

Study or Subgroup	Tetrastarch 0.4 Mean [days]	SD [days]	Total	Crystalloid Mean [days]	SD [days]	Total	Weight	Mean Difference IV, Fixed, 95% CI [days]
Akkucuk et al. 2013	5	2.3	12	5.9	3.2	12	2.9%	-0.90 [-3.13, 1.33]
Gurbuz et al. 2013	5.47	1.2	100	6.14	2.55	100	46.7%	-0.67 [-1.22, -0.12]
Lee et al. 2011	10.9	5.7	53	10.3	3.7	53	4.3%	0.60 [-1.23, 2.43]
Shahbazi et al. 2011	5.23	0.94	35	5.43	1.79	35	31.8%	-0.20 [-0.87, 0.47]
Tiryakioglu et al. 2008	8	3	70	9	3	70	14.4%	-1.00 [-1.99, -0.01]
Total (95% CI)			270			270	100.0%	**-0.52 [-0.90, -0.14]**

Heterogeneity: $Chi^2 = 3.61$, $df = 4$ ($P = 0.46$); $I^2 = 0\%$

Test for overall effect: $Z = 2.70$ ($P = 0.007$)



gure 5 (See legend on next page.)

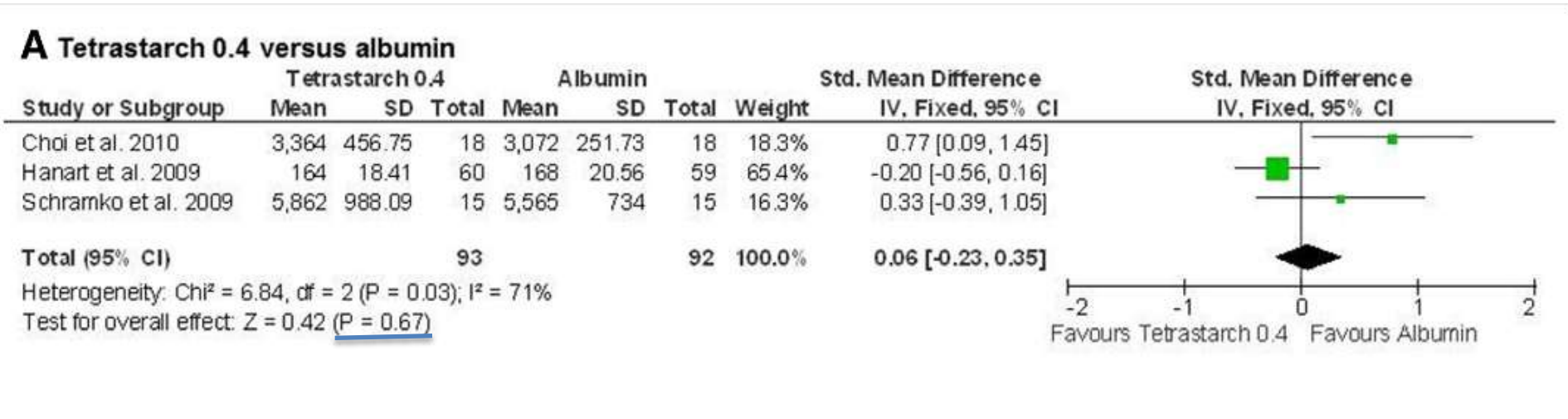


Figure 6 Efficacy of tetrastarch compared to albumin, gelatin or crystalloids as judged by total volume infusion. Units of total combined volume of colloids and crystalloids were expressed in millilitres (ml), except for Hanart *et al.* [43] and Van der Linden *et al.* [38,52], where units were expressed as millilitres per kilogram body weight (ml/kg). **(A)** Albumin. **(B)** Gelatin. **(C)** Crystalloid. The standardised mean difference (Std. mean difference) of the mean for the hydroxyethyl starch group minus the mean for the albumin group was used as effect size. Fixed-effects models were applied to calculate a common effect estimate using the inverse variance method (IV). SD, standard deviation; CI, confidence interval.

B Tetrastarch 0.4 versus gelatin

Study or Subgroup	Tetrastarch 0.4 Mean	SD	Total	Gelatin Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Alavi et al. 2012	4,820	230.87	32	7,225	338.01	31	1.1%	-8.23 [-9.80, -6.67]
Kimenai et al. 2013	6,275	840.88	30	6,130	764.08	30	10.8%	0.18 [-0.33, 0.69]
Mulavisala et al. 2012	566	145.84	28	654	173.07	21	8.4%	-0.55 [-1.13, 0.03]
Muralidhar et al. 2010	1,920	229.9	10	2,700	197.2	10	1.3%	-3.49 [-4.98, -2.00]
Ooi et al. 2009	1,942.3	1,046.1	45	1,973.3	728.8	45	16.3%	-0.03 [-0.45, 0.38]
Schramko et al. 2010	2,724	908.06	15	3,735	854.79	15	4.6%	-1.12 [-1.89, -0.34]
Van der Linden et al 2005	100.6	14.51	64	102.5	12.97	68	23.9%	-0.14 [-0.48, 0.20]
Vanhoonacker et al. 2009	676	467	82	1,035	613	72	26.4%	-0.66 [-0.99, -0.34]
Yap et al. 2007	2,674	722	20	2,510	769	20	7.2%	0.22 [-0.41, 0.84]
Total (95% CI)			326			312	100.0%	**-0.41 [-0.58, -0.25]**

Heterogeneity: Chi² = 132.74, df = 8 (P < 0.00001); I² = 94%

Test for overall effect: Z = 4.84 (P < 0.00001)

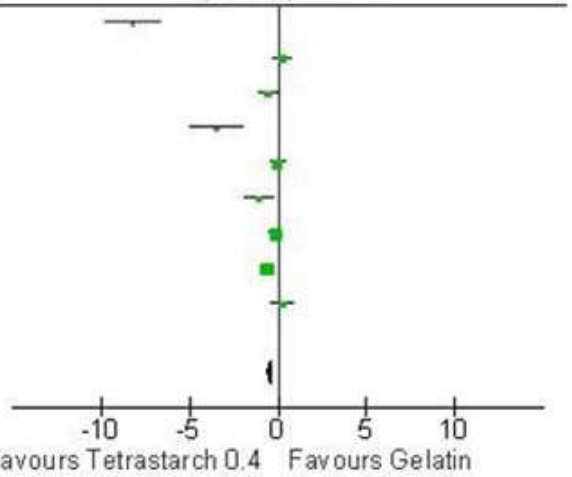


Figure 6 Efficacy of tetrastarch compared to albumin, gelatin or crystalloids as judged by total volume infusion. Units of total combined volume of colloids and crystalloids were expressed in millilitres (ml), except for Hanart *et al.* [43] and Van der Linden *et al.* [38,52], where units were expressed as millilitres per kilogram body weight (ml/kg). **(A)** Albumin. **(B)** Gelatin. **(C)** Crystalloid. The standardised mean difference (Std. mean difference) of the mean for the hydroxyethyl starch group minus the mean for the albumin group was used as effect size. Fixed-effects models were applied to calculate a common effect estimate using the inverse variance method (IV). SD, standard deviation; CI, confidence interval.

C Tetrastarch 0.4 versus crystalloid

Study or Subgroup	Tetrastarch 0.4 Mean	SD	Total	Crystalloid Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Akkucuk et al. 2013	1,804.97	282.63	12	2,187.22	646.51	12	13.8%	-0.74 [-1.57, 0.09]
Alavi et al. 2012	4,820	230.87	32	8,250	371.21	29	2.2%	-11.08 [-13.17, -8.99]
Lee et al. 2011	8,152	1,370.79	53	8,342	1,794	53	65.6%	-0.12 [-0.50, 0.26]
Schramko et al. 2010	2,724	908.06	15	2,924	762.22	15	18.5%	-0.23 [-0.95, 0.49]
Tiryakioglu et al. 2008	0	0	70	1,360	360	70		Not estimable
Total (95% CI)			**182**			**179**	**100.0%**	**-0.46 [-0.77, -0.15]**

Heterogeneity: Chi² = 102.72, df = 3 (P < 0.00001); I² = 97%

Test for overall effect: Z = 2.94 (P = 0.003)

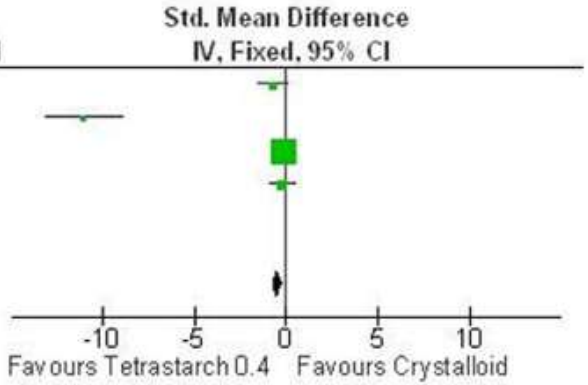


Figure 6 Efficacy of tetrastarch compared to albumin, gelatin or crystalloids as judged by total volume infusion. Units of total combined volume of colloids and crystalloids were expressed in millilitres (ml), except for Hanart *et al.* [43] and Van der Linden *et al.* [38,52], where units were expressed as millilitres per kilogram body weight (ml/kg). **(A)** Albumin. **(B)** Gelatin. **(C)** Crystalloid. The standardised mean difference (Std. mean difference) of the mean for the hydroxyethyl starch group minus the mean for the albumin group was used as effect size. Fixed-effects models were applied to calculate a common effect estimate using the inverse variance method (M). SD, standard deviation; CI, confidence interval.

- We conclude that tetrastarches are improved compared to older starches in regards to blood loss or need for transfusions.
- On the basis of the available data, tetrastarches seem to be efficient and safe volume substitutes which can be recommended for cardiac surgery.

British Journal of Anaesthesia **112** (1): 25–34 (2014)
Advance Access publication 17 September 2013 · doi:10.1093/bja/aet303

BJA

REVIEW ARTICLES

Incidence of postoperative death and acute kidney injury associated with i.v. 6% hydroxyethyl starch use: systematic review and meta-analysis

M. A. Gillies[1*], M. Habicher[2], S. Jhanji[3], M. Sander[2], M. Mythen[4], M. Hamilton[5] and R. M. Pearse[6]

[1] Department of Critical Care, Royal Infirmary of Edinburgh, Little France Crescent, Edinburgh EH16 4SA, UK
[2] Charité-Universitätsmedizin Berlin, Campus Charité Mitte, Charitéplatz 1, Berlin D-10117, Germany
[3] Royal Marsden Hospital, London SW3 6JJ, UK
[4] University College Hospital, London NW1 2BU, UK
[5] St George's Healthcare NHS Trust, London SW17 0QT, UK
[6] Barts and the London School of Medicine and Dentistry, Queen Mary's University of London, London EC1M 6BQ, UK

* Corresponding author. E-mail: michael.gillies@ed.ac.uk

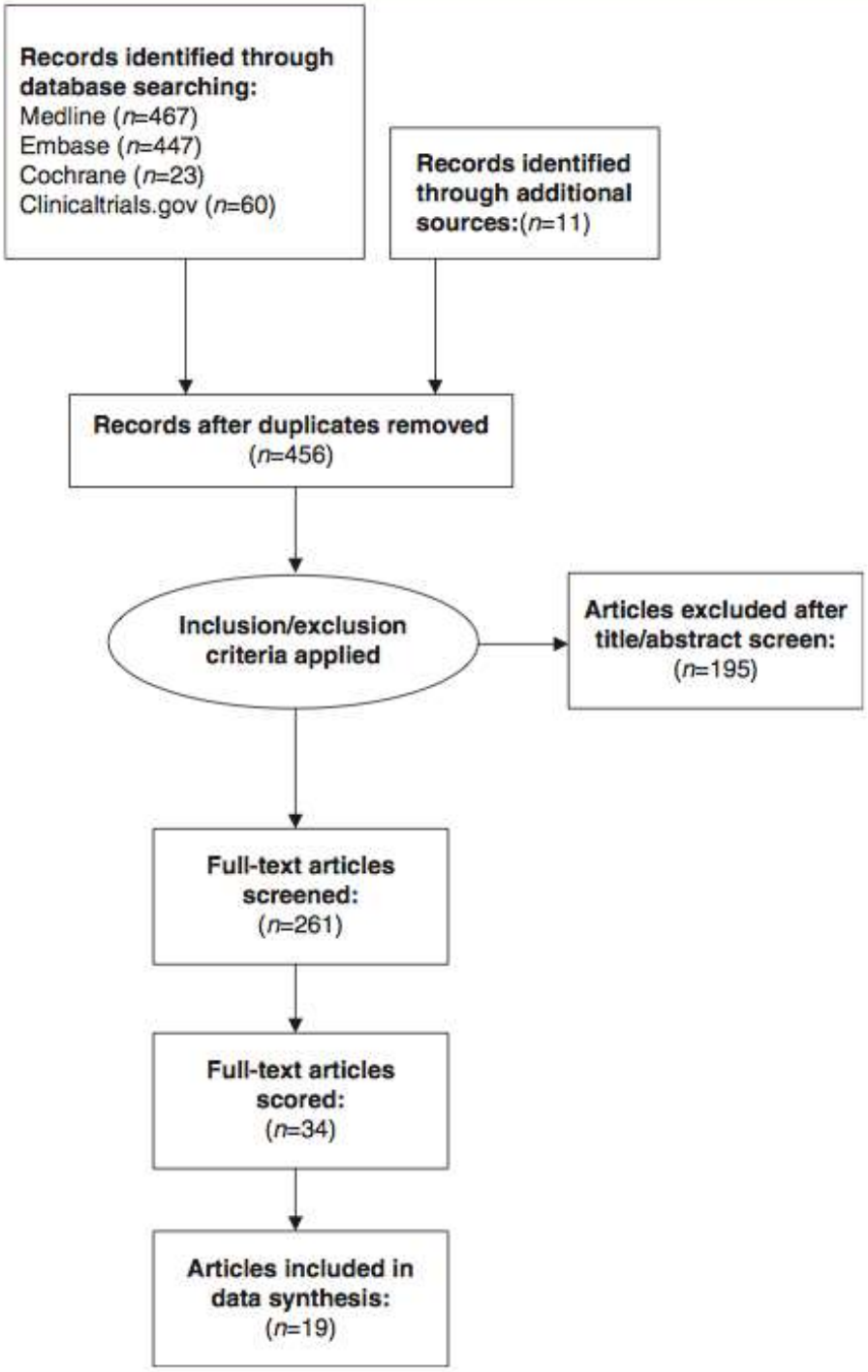

Records identified through database searching:
Medline (n=467)
Embase (n=447)
Cochrane (n=23)
Clinicaltrials.gov (n=60)
Records identified through additional sources:(n=11)
Records after duplicates removed (n=456)
Inclusion/exclusion criteria applied
Articles excluded after title/abstract screen: (n=195)
Full-text articles screened: (n=261)
Full-text articles scored: (n=34)
Articles included in data synthesis: (n=19)

Table 1 Characteristics of included studies. RRT, renal replacement therapy; AKI, acute kidney injury; SCr, serum creatine; AKIN, Acute Kidney Injury Network

Study	Design	Type of surgery	*n*	Starch	Comparator	Jadad score	Reports mortality	Reports RRT	Reports AKI	Author-defined AKI	Commercial support
Alavi and colleagues[20]	RCT	Cardiac	92	6% HES 130/0.4	4% gelatin, RL	3	Yes	No	No	–	Not stated
Dehne and colleagues[21]	RCT	ENT	60	6% HES-200/0.5: 6% HES-200/0.62: 6% HES-450/0.7	RL	4	Yes	No	No	–	Fresenius
Diehl and colleagues[22]	RCT	Cardiac	60	6% HES-450/0.7	5% albumin	3	Yes	No	Yes	SCr >1.5 mg dl^{-1}	Not stated
Feldheiser and colleagues[23]	RCT	Gynaecological	50	6% HES 130/0.4	Balanced crystalloid	4	Yes	No	No	–	Fresenius-Kabi
Godet and colleagues[24]	Multicentre RCT	Vascular	65	6% HES 130/0.4	3% gelatin	4	Yes	Yes	Yes	Increase in SCr from baseline of >0.5 mg dl^{-1}	Fresenius-Kabi
Gondos and colleagues[25]	Multicentre RCT	Mixed	200	6% HES 130/0.4	RL, 4% gelatin, 5% albumin	3	Yes	No	No	–	Fresenius-Kabi
Guo and colleagues[26]	RCT	Gynaecological	42	6% HES-200/0.5	RL	3	Yes	Yes	No	–	Not stated
Hecht-Dolnik and colleagues[9]	RCT	Cardiac	156	6% hetastarch	5% albumin	4	Yes	No	No	–	None
Hung and colleagues[27]	RCT	Vascular	84	6% HES 130/0.4	RL	4	Yes	Yes	Yes	Not specified	Edwards
Kultunen and colleagues[28]	RCT	Cardiac	45	6% HES 120/0.7: 6% HES 400/0.7	4% albumin	4	Yes	No	No	–	Not stated
Lee and colleagues[29]	RCT	Cardiac	106	6% HES 130/0.4	RL	3	No	Yes	Yes	AKIN criteria	None
Mahmood and colleagues[30]	RCT	Vascular	62	6% HES 200/0.6: 6% HES 130/0.4	4% gelatin	4	Yes	Yes	No	–	Fresenius-Kabi
Marik and colleagues[31]	RCT	Vascular	30	6% hetastarch	RL	4	Yes	No	No	–	Not stated
Munsch and colleagues[32]	RCT	Cardiac	40	6% HES-450/0.7	Plasma protein fraction	3	Yes	No	No	–	Not stated
Ooi and colleagues[33]	RCT	Cardiac	90	6% HES 130/0.4	4% gelatin	4	Yes	Yes	Yes	Not specified	Not stated
Sirvinskas and colleagues[34]	RCT	Cardiac	80	NaCl 0.72%/6% HES	RL	3	Yes	No	No	–	Not stated
Van der Linden and colleagues[35]	RCT	Cardiac		6% HES-200/0.5	3.5% gelatin	3	Yes	No	No	–	Not stated
van der Linden and colleagues[36]	RCT	Cardiac	132	6% HES 130/0.4 (Voluven)	3% gelatin	3	Yes	No	No	–	Not stated
Verheij and colleagues[37]	RCT	Cardiac or major vascular	67	6% HES 200/0.5	4% gelatin, NaCl 0.9%	4	Yes	No	No	–	Braun

Study or subgroup	HES Events	HES Total	Control Events	Control Total	Weight	Risk difference M–H, fixed, 95% CI
Cardiac surgery						
Alavi and colleagues[20]	0	32	0	60	6.1%	0.00 [–0.05, 0.05]
Diehl and colleagues[22]	0	33	0	27	4.4%	0.00 [–0.06, 0.06]
Hecht-Dolnik and colleagues[9]	0	78	0	78	11.5%	0.00 [–0.02, 0.02]
Kuitunen and colleagues[28]	0	30	0	15	2.9%	0.00 [–0.10, 0.10]
Munsch and colleagues[32]	0	20	0	20	2.9%	0.00 [–0.09, 0.09]
Ooi and colleagues[33]	0	45	0	45	6.6%	0.00 [–0.04, 0.04]
Sirvinskas and colleagues[34]	0	40	0	40	5.9%	0.00 [–0.05, 0.05]
Van der Linden and colleagues[35]	0	55	0	55	8.1%	0.00 [–0.03, 0.03]
Van der Linden and colleagues[36]	0	64	1	68	9.7%	–0.01 [–0.06, 0.03]
Verheij and colleagues[37]	0	17	2	50	3.7%	–0.04 [–0.14, 0.06]
Subtotal (95% CI)		**414**		**458**	**62.0%**	**–0.00 [–0.02, 0.01]**
Total events	0		3			
Heterogeneity: χ^2=1.12, df=9 (P=1.00); I^2=0%						
Test for overall effect: Z=0.58 (P=0.56)						
Non-cardiac/mixed surgery						
Dehne and colleagues[21]	0	45	0	15	3.3%	0.00 [–0.09, 0.09]
Feldheiser and colleagues[23]	1	26	0	24	3.7%	0.04 [–0.06, 0.14]
Godet and colleagues[24]	2	32	2	33	4.8%	0.00 [–0.11, 0.12]
Gondos and colleagues[25]	15	50	38	150	11.1%	0.05 [–0.10, 0.19]
Guo and colleagues[26]	0	20	0	22	3.1%	0.00 [–0.09, 0.09]
Hung and colleagues[27]	0	41	0	39	5.9%	0.00 [–0.05, 0.05]
Mahmood and colleagues[30]	1	42	3	20	4.0%	–0.13 [–0.29, 0.04]
Marik and colleagues[31]	0	15	0	15	2.2%	0.00 [–0.12, 0.12]
Subtotal (95% CI)		**271**		**318**	**38.0%**	**0.00 [–0.12, 0.12]**
Total events	19		43			
Heterogeneity: χ^2=3.27, df=7 (P=0.86); I^2=0%						
Test for overall effect: Z=0.16 (P=0.87)						
Total (95% CI)		**685**		**776**	**100.0%**	**–0.00 [–0.02, 0.02]**
Total events	19		46			
Heterogeneity: χ^2=4.33, df=17 (P=1.00); I^2=0%						
Test for overall effect: Z=0.12 (P=0.91)						
Test for subgroup differences: χ^2=0.11, df=1 (P=0.74); I^2=0%						

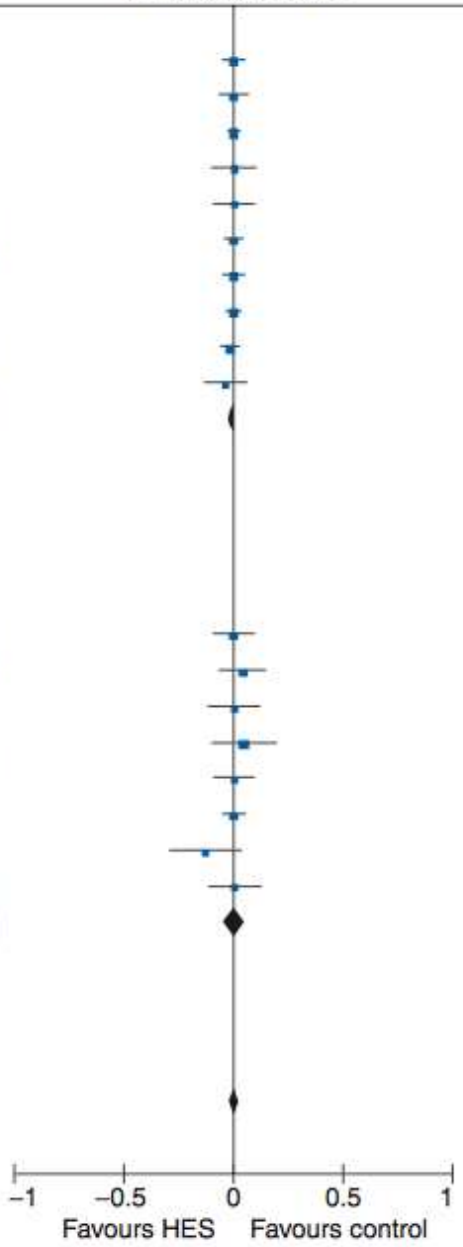


Fig 2 Forest plot of hospital mortality.

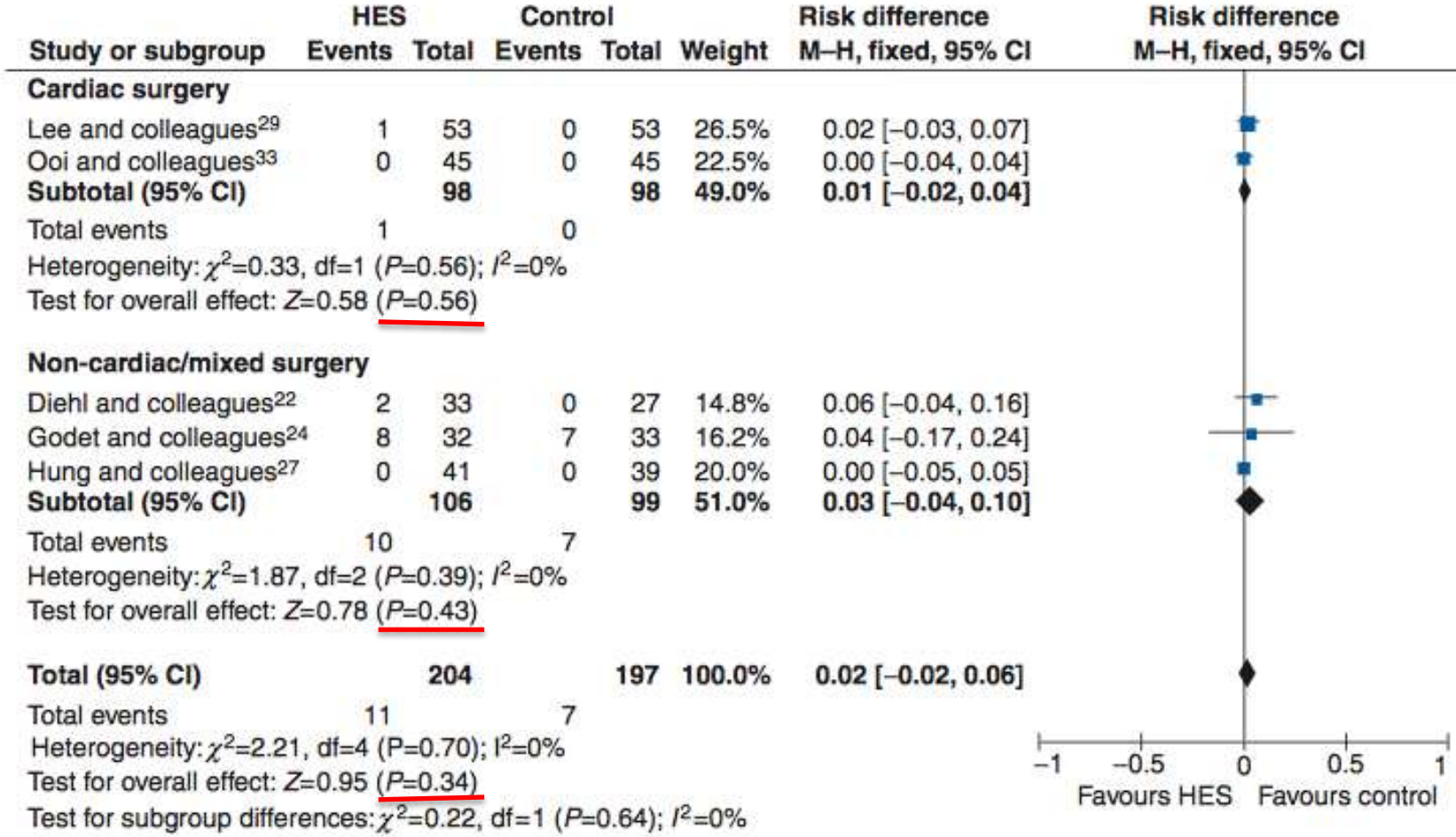


Fig 3 Forest plot of acute kidney injury.

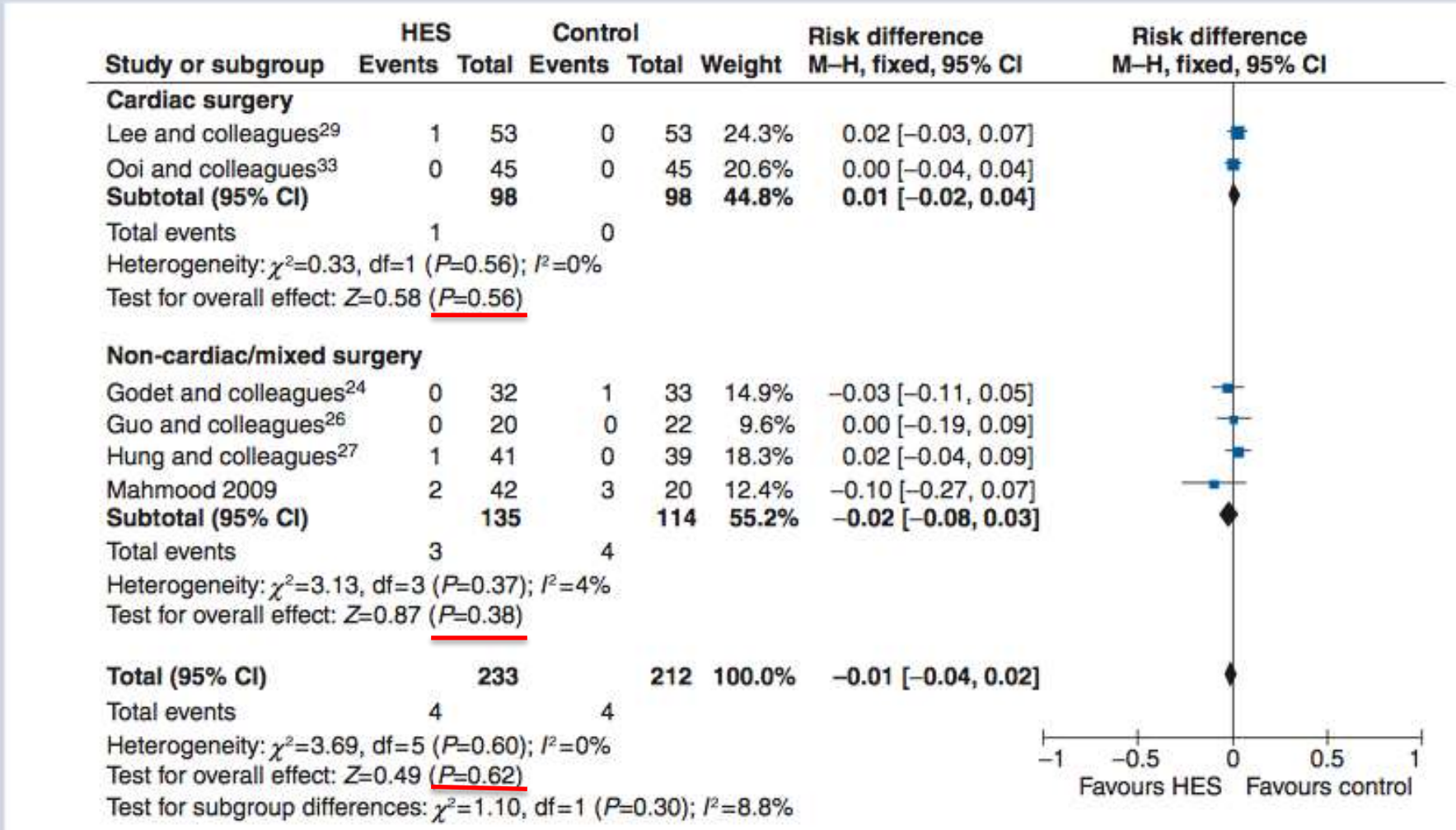


Fig 4 Forest plot of renal replacement therapy.

Conclusion

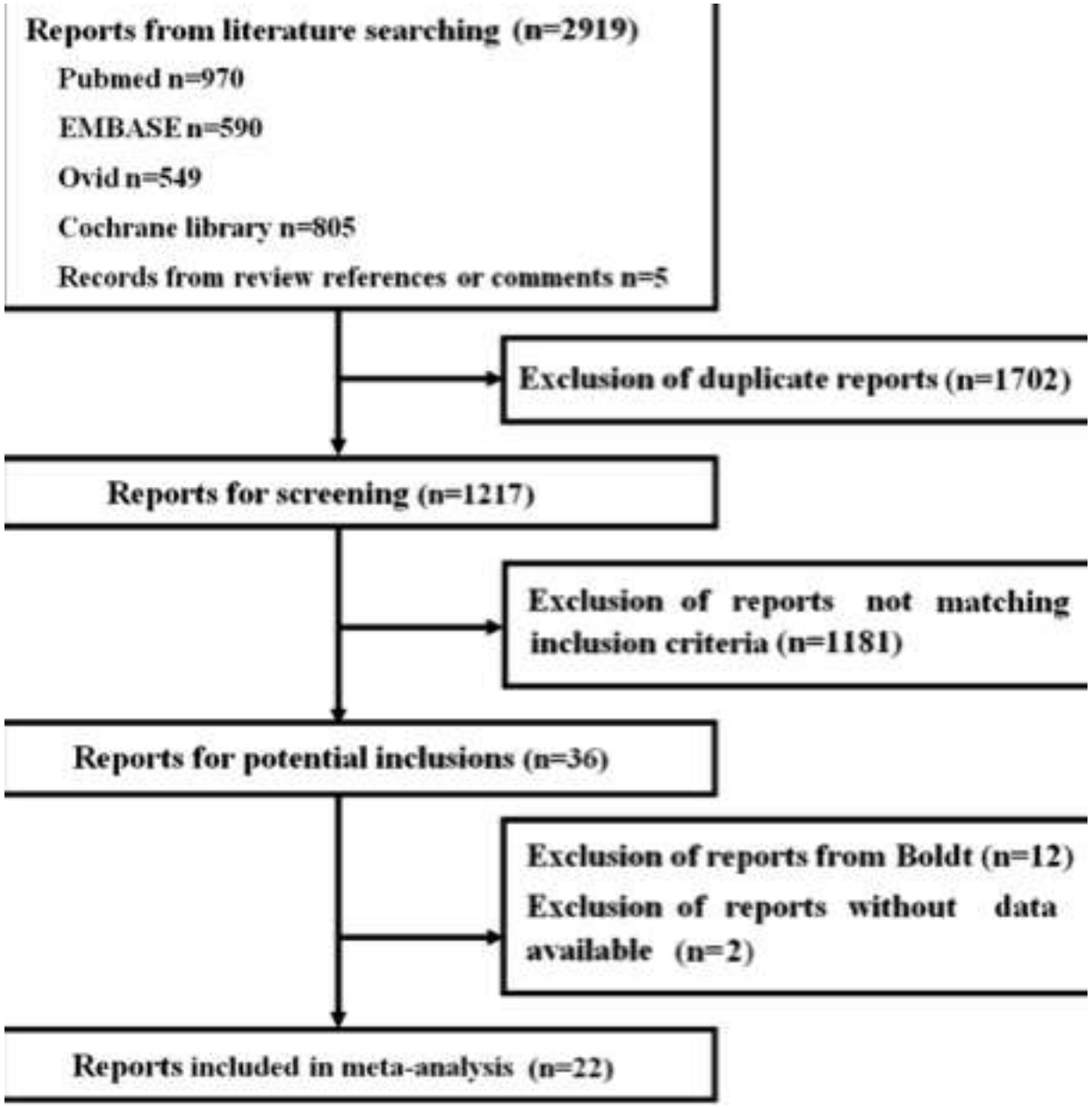
- The principal finding of this study was that there was no difference in hospital mortality, requirement for RRT, or author defined AKI associated with perioperative use of i.v. 6% HES solutions.

Critical Care

BioMed Central
The Open Access Publisher

6% Hydroxyethyl starch versus other fluids for non-septic patients in the intensive care unit: a meta-analysis of randomized controlled trials

Critical Care (2015) 19:92

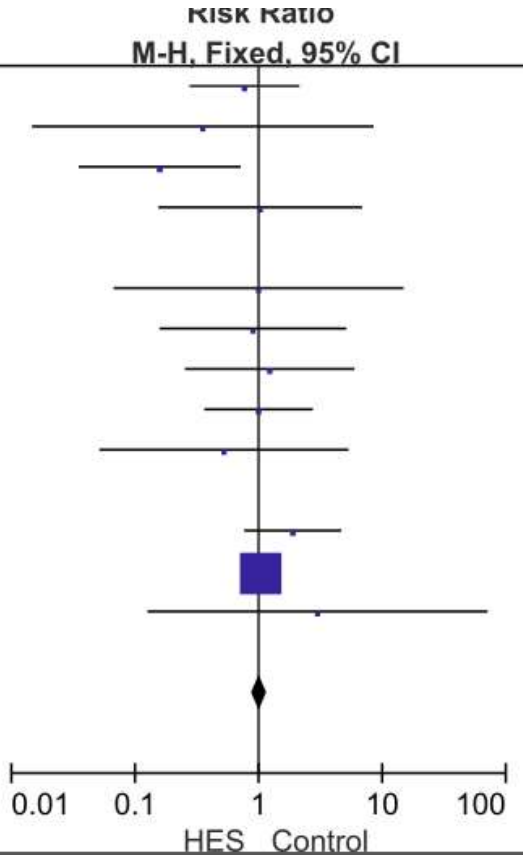

Reports from literature searching (n=2919)
Pubmed n=970
EMBASE n=590
Ovid n=549
Cochrane library n=805
Records from review references or comments n=5
Exclusion of duplicate reports (n=1702)
Reports for screening (n=1217)
Exclusion of reports not matching inclusion criteria (n=1181)
Reports for potential inclusions (n=36)
Exclusion of reports from Boldt (n=12)
Exclusion of reports without data available (n=2)
Reports included in meta-analysis (n=22)

Mortalite

Study or Subgroup	Experimental-HES Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Beards 1994	4	13	6	15	1.5%	0.77 [0.28, 2.14]	1994
Van der Linden 2005	0	64	1	68	0.4%	0.35 [0.01, 8.53]	2005
Mahmood 2007	2	42	6	20	2.2%	0.16 [0.04, 0.72]	2007
Godet 2008	2	32	2	33	0.5%	1.03 [0.15, 6.89]	2008
Ooi 2009	0	45	0	45		Not estimable	2009
Mukhtas 2009	1	20	1	20	0.3%	1.00 [0.07, 14.90]	2009
Heradstveit 2010	2	10	2	9	0.6%	0.90 [0.16, 5.13]	2010
Gondos 2010	2	26	5	80	0.7%	1.23 [0.25, 5.97]	2010
Inal 2010	5	15	5	15	1.3%	1.00 [0.36, 2.75]	2010
Du 2011	1	20	2	21	0.5%	0.53 [0.05, 5.35]	2011
Yang 2011	0	26	0	55		Not estimable	2011
James 2011	12	56	6	53	1.6%	1.89 [0.77, 4.68]	2011
Myburgh 2012	349	2337	342	2383	90.3%	1.04 [0.91, 1.19]	2012
Nagpal 2012	1	35	0	35	0.1%	3.00 [0.13, 71.22]	2012
Total (95% CI)		**2741**		**2852**	**100.0%**	**1.03 [0.90, 1.17]**	
Total events	381		378				

Heterogeneity: $Chi^2 = 9.24$, $df = 11$ ($P = 0.60$); $I^2 = 0\%$

Test for overall effect: $Z = 0.42$ ($P = 0.67$)

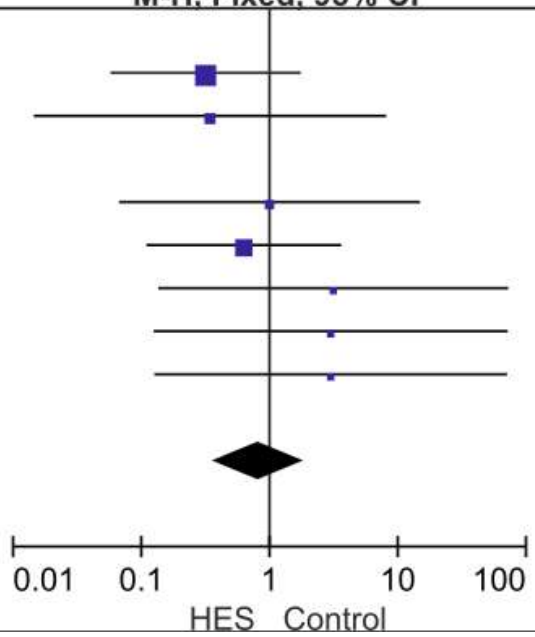


RRT

Study or Subgroup	HES Events	HES Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Chen 2006	0	33	0	33		Not estimable	2006
Mahmood 2007	2	42	3	20	36.6%	0.32 [0.06, 1.75]	2007
Godet 2008	0	32	1	33	13.3%	0.34 [0.01, 8.13]	2008
Ooi 2009	0	45	0	45		Not estimable	2009
Mukhtas 2009	1	20	1	20	9.0%	1.00 [0.07, 14.90]	2009
James 2011	2	56	3	53	27.7%	0.63 [0.11, 3.63]	2011
Du 2011	1	20	0	21	4.4%	3.14 [0.14, 72.92]	2011
Lee 2011	1	53	0	53	4.5%	3.00 [0.12, 72.02]	2011
Nagpal 2012	1	35	0	35	4.5%	3.00 [0.13, 71.22]	2012
Total (95% CI)		**336**		**313**	**100.0%**	**0.83 [0.36, 1.91]**	
Total events	8		8				

Heterogeneity: $Chi^2 = 3.58$, $df = 6$ ($P = 0.73$); $I^2 = 0\%$

Test for overall effect: $Z = 0.43$ ($P = 0.67$)



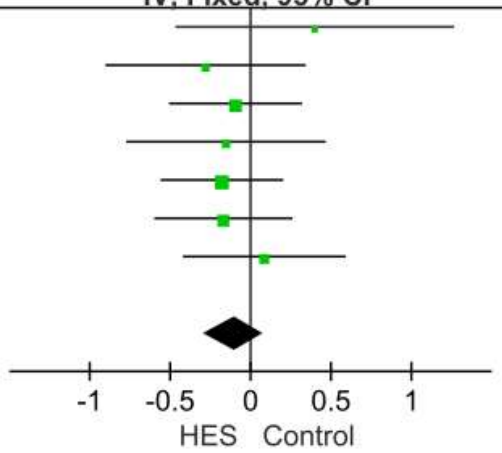
A: Bleeding, B: RBC Transfusion

A

Study or Subgroup	HES Mean	HES SD	HES Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Ley 1990	1,070	448	11	896	383	10	4.7%	0.40 [-0.47, 1.27]	1990
Schramko 2009	883	431	30	990	222	15	9.0%	-0.28 [-0.90, 0.34]	2009
Ooi 2009	567.3	281.2	45	596.4	336.6	45	20.5%	-0.09 [-0.51, 0.32]	2009
Schramko 2010	951	336	15	1,010	398	30	9.1%	-0.15 [-0.77, 0.47]	2010
Lee 2011	753	313	53	810	322	53	24.1%	-0.18 [-0.56, 0.20]	2011
Alavi 2012	1,280	280	32	1,326	264	60	19.0%	-0.17 [-0.60, 0.26]	2012
Kimenai 2013	500	420	30	465	390	30	13.7%	0.09 [-0.42, 0.59]	2013
Total (95% CI)			**216**			**243**	**100.0%**	**-0.10 [-0.29, 0.08]**	

Heterogeneity: Chi² = 2.40, df = 6 (P = 0.88); I² = 0%

Test for overall effect: Z = 1.08 (P = 0.28)

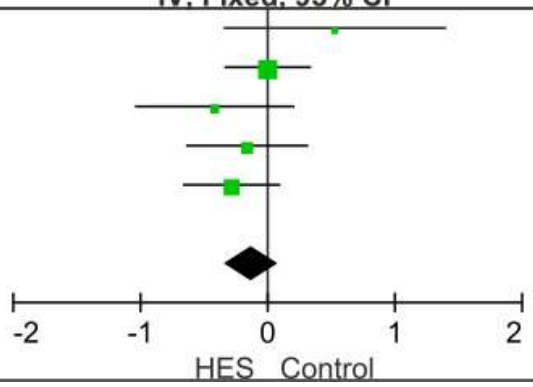


B

Study or Subgroup	HES Mean	HES SD	HES Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Ley 1990	0.9	1	11	0.4	0.8	10	5.5%	0.53 [-0.35, 1.40]	1990
Van der Linden 2005	1.5	1.8	64	1.5	1.8	68	36.4%	0.00 [-0.34, 0.34]	2005
Mukhtas 2009	3	2.4	20	4	2.3	20	10.8%	-0.42 [-1.04, 0.21]	2009
James 2011	5.2	5.2	36	6	4.5	31	18.3%	-0.16 [-0.64, 0.32]	2011
Lee 2011	0.6	1.1	53	0.9	1	53	29.0%	-0.28 [-0.67, 0.10]	2011
Total (95% CI)			**184**			**182**	**100.0%**	**-0.13 [-0.33, 0.08]**	

Heterogeneity: Chi² = 4.16, df = 4 (P = 0.38); I² = 4%

Test for overall effect: Z = 1.21 (P = 0.23)



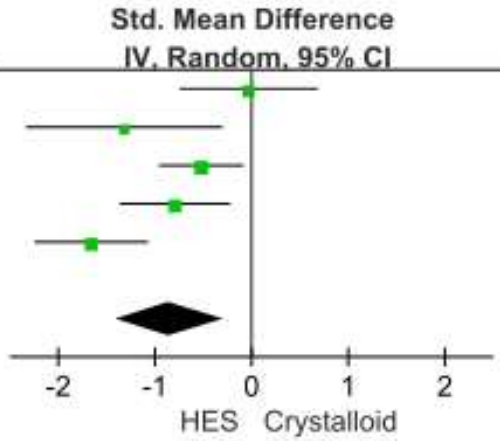
A:HES-Crytaloid, B:HES-GEL C:HES Alb ICU sıvı ted

A

Study or Subgroup	HES Mean	HES SD	HES Total	Crystalloid Mean	Crystalloid SD	Crystalloid Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Schramko 2010	2,587	633	15	2,606	564	15	19.0%	-0.03 [-0.75, 0.68]	2010
Heradstveit 2010	5,499	2,047	10	8,678	2,565	9	14.3%	-1.32 [-2.33, -0.30]	2010
James 2011	5,457	2,402	56	6,984	3,621	33	23.9%	-0.52 [-0.96, -0.08]	2011
Yang 2011	2,047	79	26	2,145	154	25	21.5%	-0.79 [-1.37, -0.22]	2011
Alavi 2012	3,500	2,100	32	6,100	400	29	21.3%	-1.66 [-2.25, -1.07]	2012
Total (95% CI)			**139**			**111**	**100.0%**	**-0.84 [-1.39, -0.30]**	

Heterogeneity: Tau² = 0.28; Chi² = 15.22, df = 4 (P = 0.004); I² = 74%

Test for overall effect: Z = 3.02 (P = 0.003)

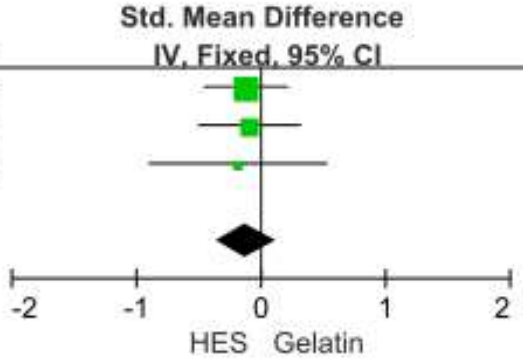


B

Study or Subgroup	HES Mean	HES SD	HES Total	Gelatin Mean	Gelatin SD	Gelatin Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Van der Linden 2005	3,570	678	64	3,654	707	69	52.5%	-0.12 [-0.46, 0.22]	2005
Ooi 2009	717	910	45	794	712	45	35.6%	-0.09 [-0.51, 0.32]	2009
Schramko 2010	2,587	633	15	2,820	1,605	15	11.8%	-0.19 [-0.90, 0.53]	2010
Total (95% CI)			**124**			**129**	**100.0%**	**-0.12 [-0.37, 0.13]**	

Heterogeneity: Chi² = 0.05, df = 2 (P = 0.98); I² = 0%

Test for overall effect: Z = 0.94 (P = 0.35)

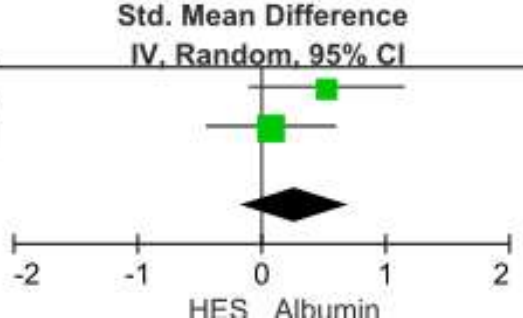


C

Study or Subgroup	HES Mean	HES SD	HES Total	Albumin Mean	Albumin SD	Albumin Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Schramko 2009	3,006	879	30	2,565	705	15	42.2%	0.52 [-0.11, 1.15]	2009
Yang 2011	2,047	79	26	2,042	51	30	57.8%	0.08 [-0.45, 0.60]	2011
Total (95% CI)			**56**			**45**	**100.0%**	**0.26 [-0.17, 0.70]**	

Heterogeneity: Tau² = 0.01; Chi² = 1.15, df = 1 (P = 0.28); I² = 13%

Test for overall effect: Z = 1.19 (P = 0.23)



Conclusion

Although volume expansion with 6% HES did not seem to increase the mortality or RRT incidence in non-septic ICU patients, the sample sizes of our meta-analysis were small and the studies generally were of poor quality.

Cytokine xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.journals.elsevier.com/cytokine

Review Article

Immune and inflammatory role of hydroxyethyl starch 130/0.4 and fluid gelatin in patients undergoing coronary surgery

Tülün Öztürk [a,*,1], Ece Onur [b,1], Mustafa Cerrahoğlu [c,1], Mehmet Çalgan [b,1], Funda Nizamoglu [a,1], Melek Çivi [a,1]

[a] Department of Anaesthesiology and Reanimation, Celal Bayar University, Faculty of Medicine, Manisa 45020, Turkey
[b] Department of Biochemistry, Celal Bayar University, Faculty of Medicine, Manisa 45020, Turkey
[c] Department of Cardiovascular Surgery, Celal Bayar University, Faculty of Medicine, Manisa 45020, Turkey

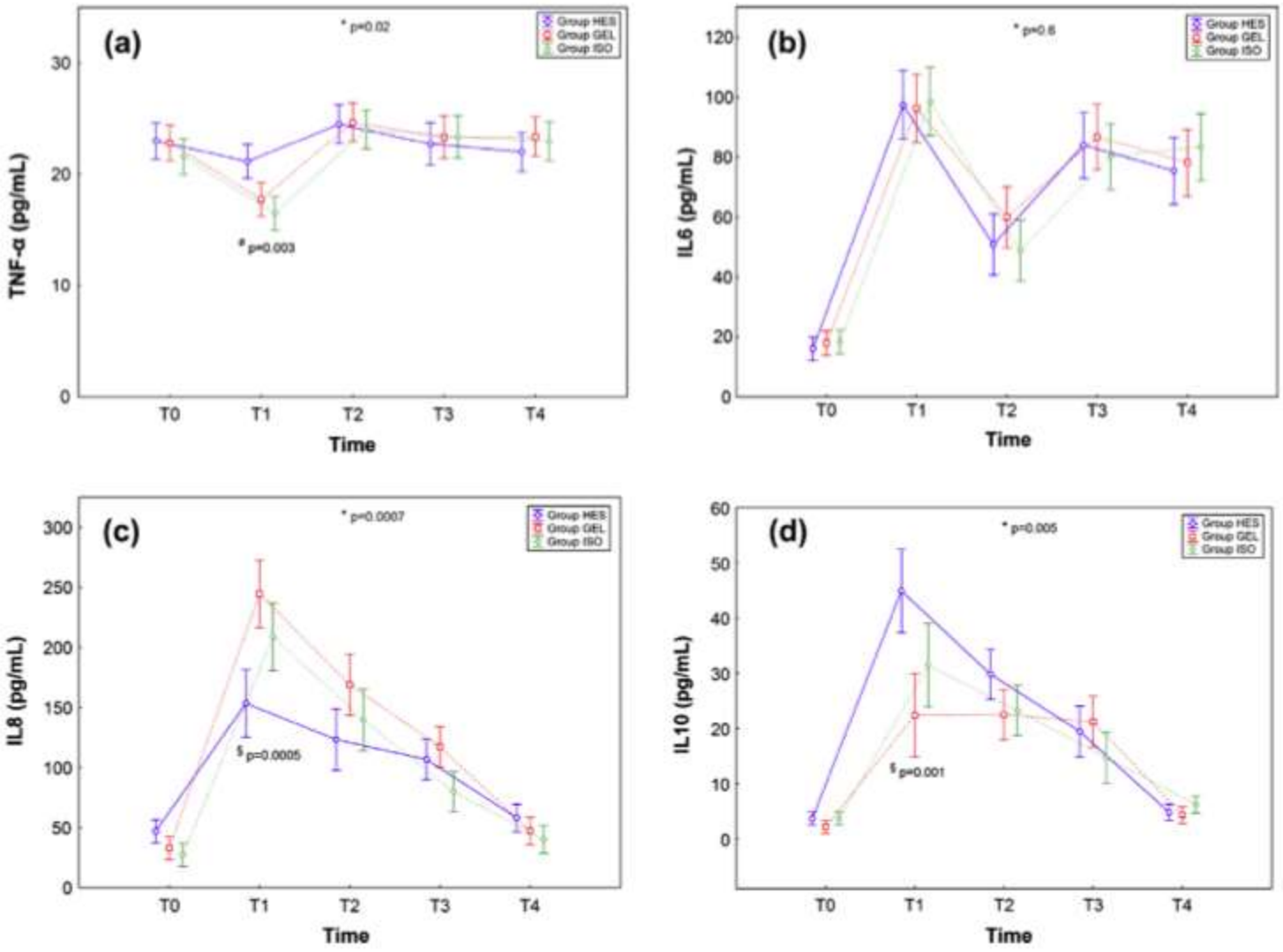
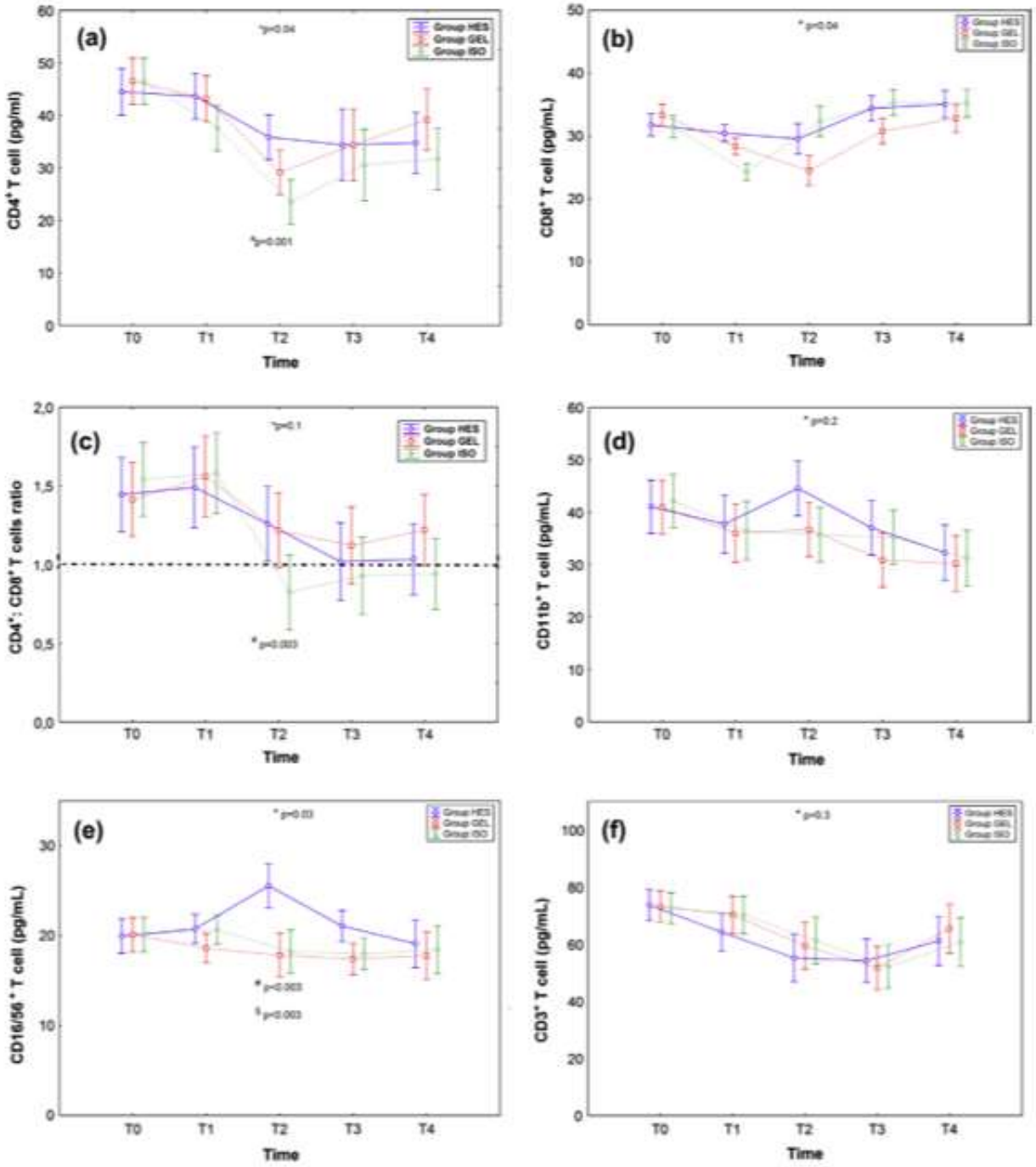


Fig. 1. (a-d) plasma levels of tumor necrosis factor-α (TNF-α, a), interleukin-6 (IL-6, b), interleukin-8 (IL-8, c) and interleukin-10 (IL-10, d) at baseline (T0), and 2 h (T1), 12 h (T2), 24 h (T3) and 48 h (T4) after separation from cardiopulmonary bypass after patients were randomly given hydroxyethyl starch 130/0.4 (HES, $n = 10$), gelatin (GEL, $n = 10$) or crystalloid (ISO, $n = 10$) for acute normovolemic hemodilution. Data are given as means and vertical bars denote 95% confidence intervals. *Repeated measures of ANOVA design, overall two-way (group and time) interaction. #Kruskal–Wallis ANOVA by rank test, multivariate analysis with Bonferroni correction (Group HES vs. Group ISO at T1). §Kruskal–Wallis ANOVA by rank test, multivariate analysis with Bonferroni correction (Group HES vs. Group GEL at T1).


(a)
CD4+ T cell (pg/ml)
Group HES
Group GEL
Group ISO
T0
T1
T2
T3
T4
Time
(b)
CD8+ T cell (pg/mL)
(c)
CD4+: CD8+ T cells ratio
(d)
CD11b+ T cell (pg/mL)
(e)
CD16/56+ T cell (pg/mL)
(f)
CD3+ T cell (pg/mL)

Discussion

- In an in vivo system, the balance of pro- and anti-inflammatory reactions determines the extent of the overall inflammatory response.
  - In our study,
  - The HES group showed ;
    - less pro-inflammatory (as measured by IL-8) and
    - more anti-inflammatory response (as measured by IL-10) than GEL, and
    - less pro-inflammatory (as measured by TNF-a) response than ISO 2 h after weaning from CPB.