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Hydroxyethyl Starch 130/04 (tetrastarch) and coagulation in cardiac surgery (Voluven)

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BACKGROUND

- Postoperative bleeding is a frequent and unpredictable complication of cardiopulmonary bypass (CPB) surgery.
- Post-CPB bleeding is associated with mortality, renal failure , prolonged mechanical ventilation and ICU stay, acute respiratory distress syndrome and sepsis.

Re-exploration in 3.6% - 4.2%

Dacey LJ
Reexploration for hemorrhage following coronary artery bypass surgery.
Arch Sur 1998;133;442-7

BLEEDING AFTER CARDIAC SURGERY

- Coagulopathy can cause post-CPB bleeding
- Fluid management may modify bleeding risk
- Studies indicate increased post-CPB bleeding risk with HES

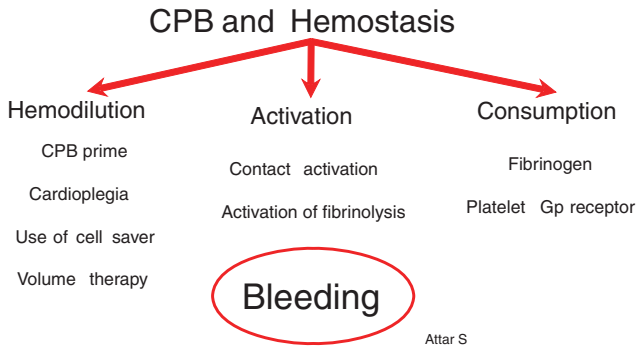
Woodman RC
Bleeding complication associated with CPB
Blood 1990;76:1680-1697

ETIOLOGY OF MICROVASCULAR BLEEDING AFTER CPB

- Qualitative platelet abnormalities
- Trombocytopenia
- Coagulation factor deficiency
- Residual heparin or heparin rebound
- Hypothermia
- Fibrinolysis
- Excessive protamine

Attar S
Hemostasis in cardiac surgery.
Futura Pub Co1999

Pathophysiology of anormalities in the hemostatic system related to CPB



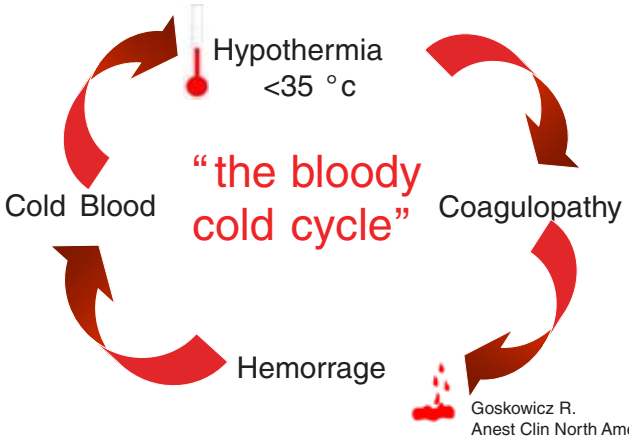
Attar S
Hemostasis in cardiac surgery.
Futura Pub Co1999

COAGULATION AND HES IN CARDIAC SURGERY

Several studies have documented the negative impact of HES on coagulation associated with increased bleeding tendency in cardiac surgery patients

Cope JT
Intraoperative HES infusion impairs hemostasis after cardiac surgery.
Ann Thorac Surg 1997;63:78-82

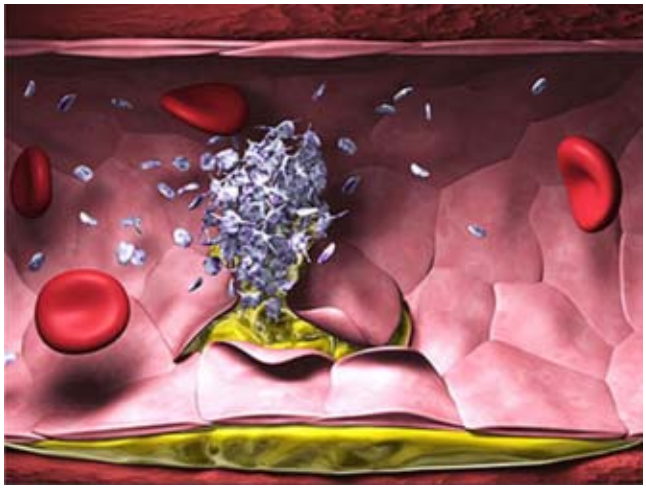
Kuitunen AH
HES as a priming solution for CPB impairs hemostasis afer cardiac surgery
Anesth Analg 2004;98:291-97



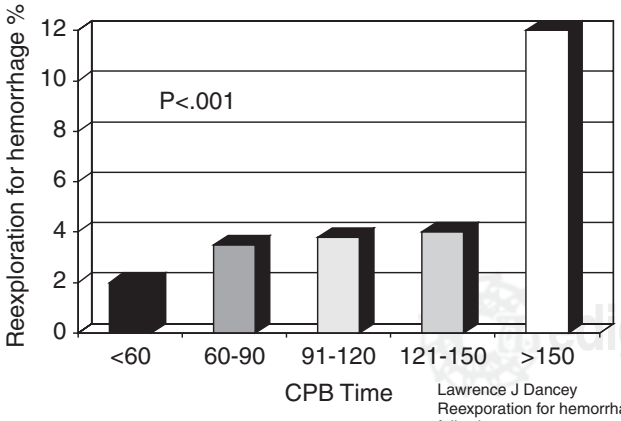
Goskowicz R.
Anest Clin North Amer
1999;17:959

COLLOIDS AND COAGULATION

- Decreases in coagulation factors
- Fibrinogen
- Coagulation factor VIII
- von Willebrand factor
- Platelet function
- Hemodilution

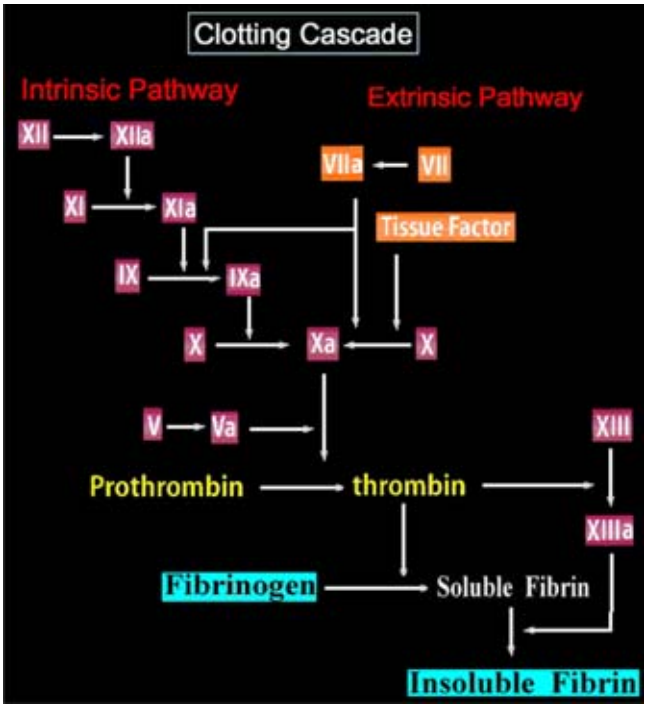


REEXPLORATION FOR HEMORRHAGE



Lawrence J Dancey
Reexporation for hemorrhage following coronary artery Bypass grafting.
Arch Surg 1998; 133:442-447

De Jonge E
Effects of different plasma substitutes on blood coagulation
Crit Care Med 2001,29,1261,7



HES CLASSIFICATION

Degree of hidroxyethylatión

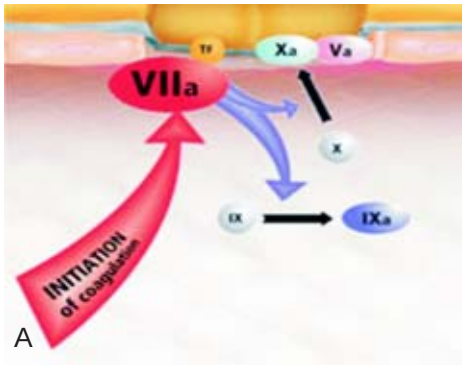
- 0.7 Hetastarch — Hespan
- 0.6 Hexastarch — Elohes
- 0.5 Pentastarch — Haes, Steril
- 0.4 Tetrastarch — Voluven

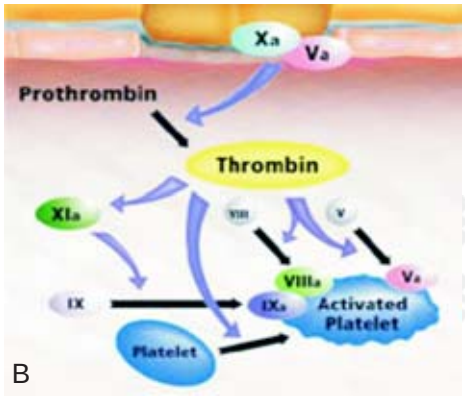
DOES INTRAOPERATIVE HES ADMINISTRATION INCREASE BLOOD LOSS AND TRANSFUSION REQUIREMENTS AFTER CARDIAC SURGERY?

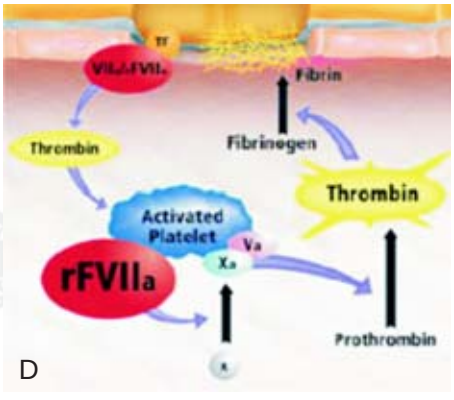
Postoperative blood loss (ml) (n = 444)

Time period hr	No hetastarch n = 234	hetastarch N = 210	p
0-4	377	518	< 0.001
0-12	681	979	< 0.001
0-24	924	1284	< 0.001

Knutson JE
Anesth Analg 2000;90:801-7
Mayo Clinic. Rochester

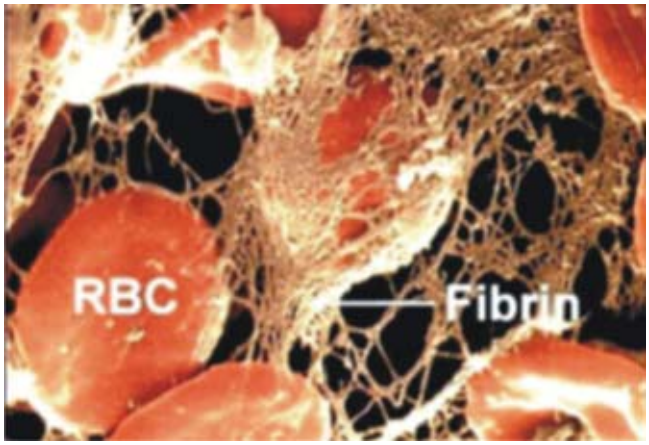






HETASTARCH AND BLEEDING COMPLICATIONS AFTER CORONARY SURGEY

HES use in patients undergoing CABG surgery may be associated with a significant risk of postop bleeding (Hetastarch) (n = 238)



Avorn J.
Hetastarch and bleeding complications after coronary surgery
CHEST 2003;124:1437-1442
Harvard Med School

BLOOD AND STARCH IN CARDIAC SURGERY TO THE EDITOR:

Most randomized studies on HES and bleeding have failed to show any clinically significant bleeding differences.

Shander A.
CHEST 2004;125:2369-70

ALBUMIN *VS* HES IN CPB SURGERY: A META-ANALYSIS OF POSTOPERATIVE BLEEDING

Mean blood loss

Albumin group	HES group
693 ± 350 ml	789 ± 487

REOPERATION WAS LOWER IN ALBUMIN THAN HES
3.7% *VS* 8.4%

A difference of 96 ml only

Sixteen trials involving 653 randomized patients were included

Wilkes MM.
Ann Thorac Surg
2001;72:527-533

EFFECTS OF TWO DIFFERENT HES SOLUTIONS (HES 200/0.5 *VS* HES 130/0.4) ON THE EXPRESSION OF PLATELET MEMBRANE GLYCOPROTEIN

(N = 60)

15 min after infusion

- Group L = Ringer lactated 20 ml/kg
- Group H = HES 200/0.5 20 ml/kg
- Group V = HES 130/0.4 20ml/kg

Both HES can inhibit platelet coagulation, experienced faster recovery after HES 130/0.4

Cheng G.
Acta Anest Scand
2006;50:1089-94

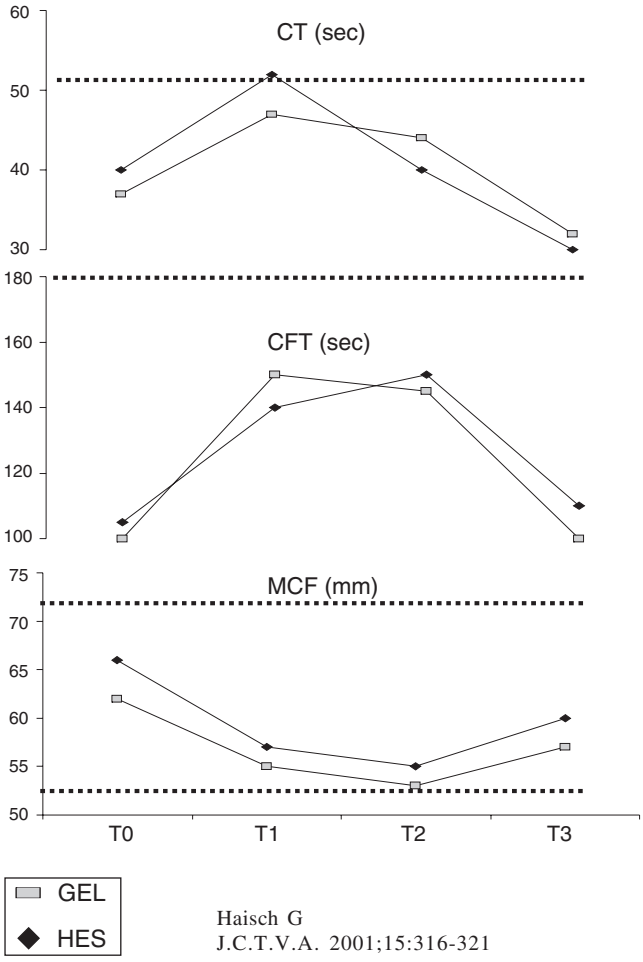
INFLUENCE OF A NEW HYDROXYETHYL STARCH PREPARATION (HES 130/0.4) ON COAGULATION IN CARDIAC SURGICAL PATIENTS

(n=42)

GEL (N = 21)	HES (130/0.4) (N = 21)
3.310 ± 810 ml	3.070 ± 570 ML

PVC = 10-14 mmHg

Volume replacement with HES was as safe as GEL with regard to coagulation in cardiac surgical patients



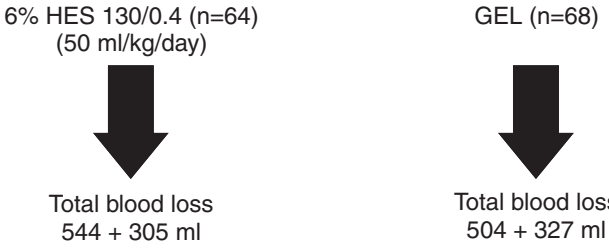
Haisch G
J.C.T.V.A. 2001;15:316-321

CONCLUSION

Six percent HES 130/0.4 at a median dose of 49 ml/kg did not increase blood loss and transfusion requirements in coronary artery bypass surgery compared with 6% HES 200/0.5 at a dose of 33 ml/kg.

Kasper SM
Anesthesiology 2003;99:42-7

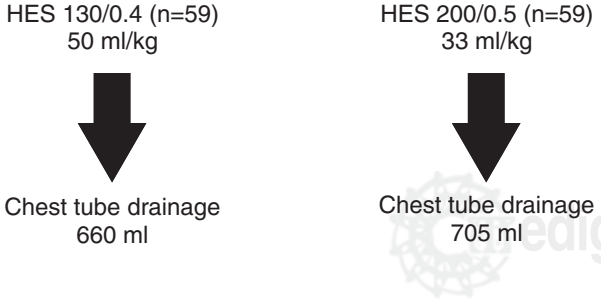
HYDROXYETHYL STARCH 130/0.4 *VERSUS* MODIFIED GELATIN FOR VOLUME EXPANSION IN CARDIAC SURGERY PATIENTS



HES 130/0.4 up to 50 ml/kg is a valuable alternative to modified fluid gelatin for plasma volume expansion during and after cardiac surgery

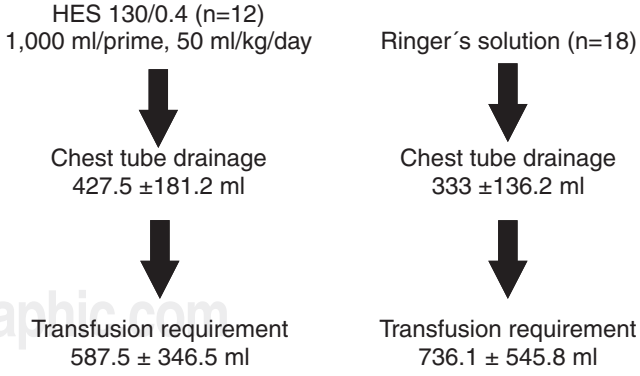
Van der Linden PJ
Anesth Analg:2005;101:629-34

LARGE-DOSE HYDROXYETHYL STARCH 130/0.4 DOES NOT INCREASE BLOOD LOSS AND TRANSFUSION REQUIREMENTS IN CORONARY ARTERY BYPASS SURGERY COMPARED WITH HES 200/0.5 AT RECOMMENDED DOSES



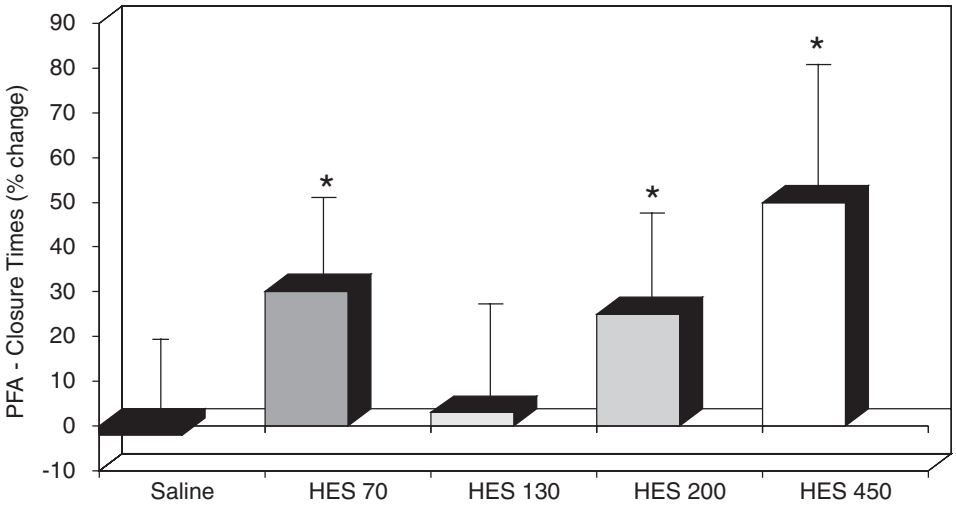
Kasper SM
Anesthesiology 2003;99:42-47

HES 130/0.4 (TETRASTARCH) AS A PRIME AND SOLE COLLOID DURING VALVULAR HEART SURGERY



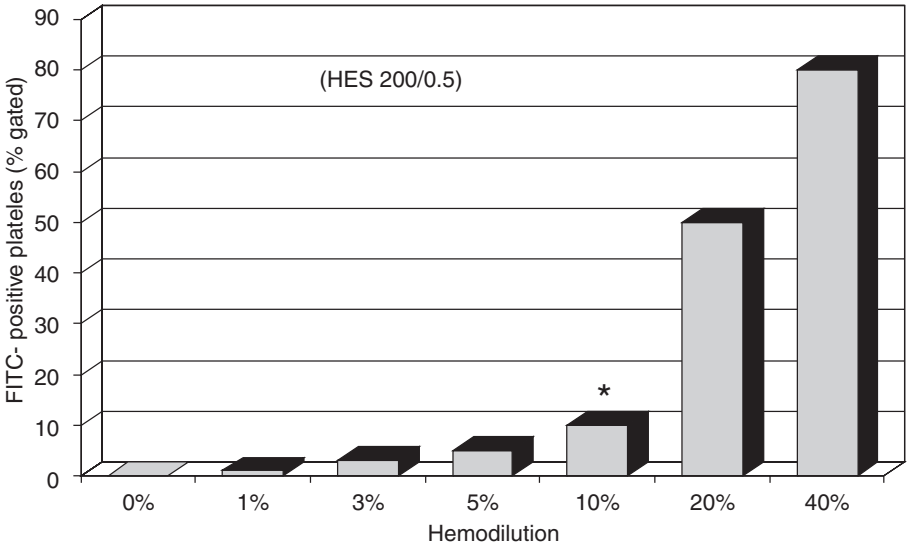
Tempe DK
Annals of Cardiac Anesthesia 2006,9:144-149

THE EFFECTS OF HYDROXYETHYL STARCHES OF VARYING MOLECULAR WEIGHTS ON PLATELET FUNCTION



Franz A.
Anesth Analg 2001;92:14o2-7

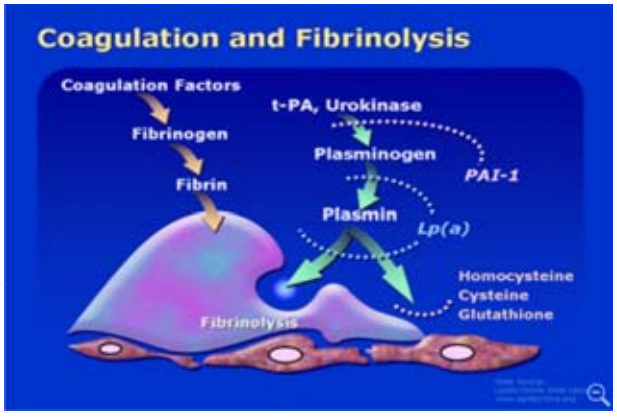
BINDING OF HYDROXYETHYL STARCH MOLECULES TO THE PLATELET SURFACE



Deusch E.
Anesth Analg
2003;97:680-3
Viena, Austria

THE EFFECT OF COLLOIDS ON FIBRINOLYSIS

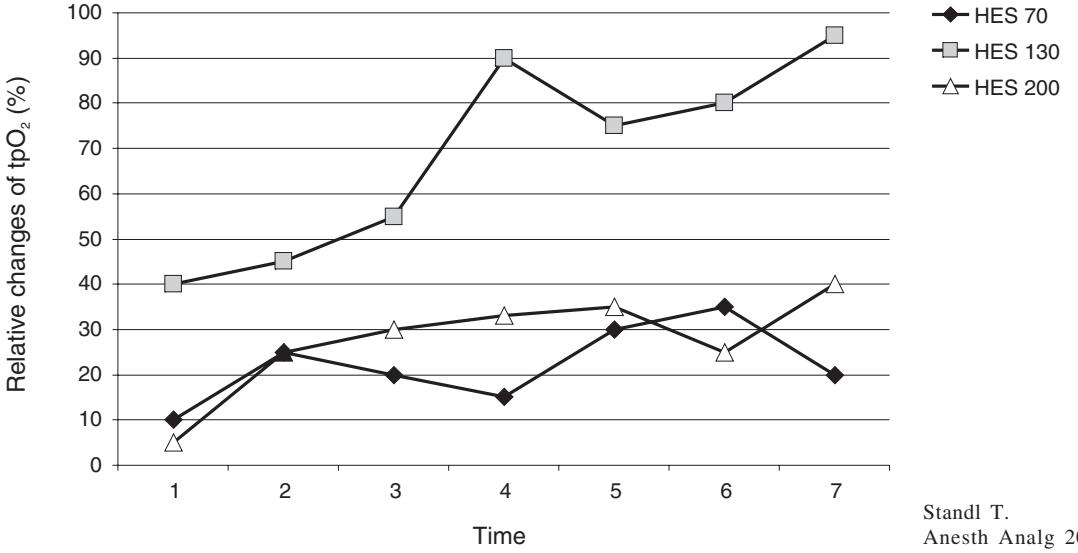
- The effect of HES on fibrinolysis seems not to be of predominant clinical importance



Strauss RG
Pentastarch may cause fewer effects on coagulation than hetastarch.
Transfusion 1988;28:257-60

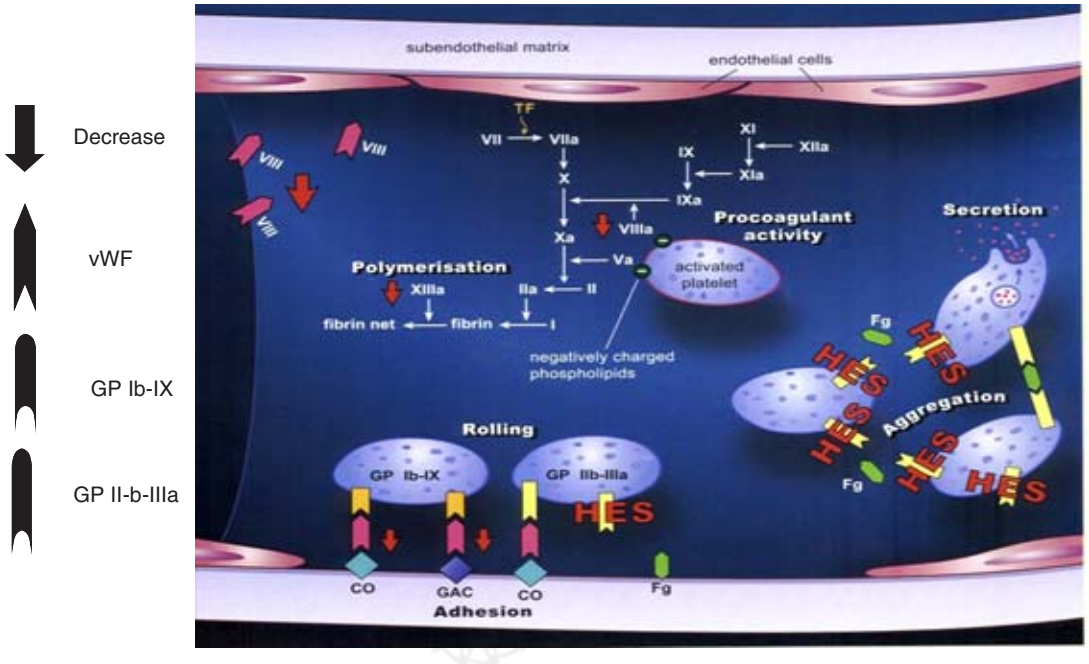
Kapiotis S
Effect of HES on the activity of blood coagulation and fibrinolysis in healthy volunteers. Crit Care Med 1994;22:606-12

HYDROXYETHYL STARCH 130/04 PROVIDES LARGER AND FASTER INCREASES IN TISSUE OXYGEN TENSION



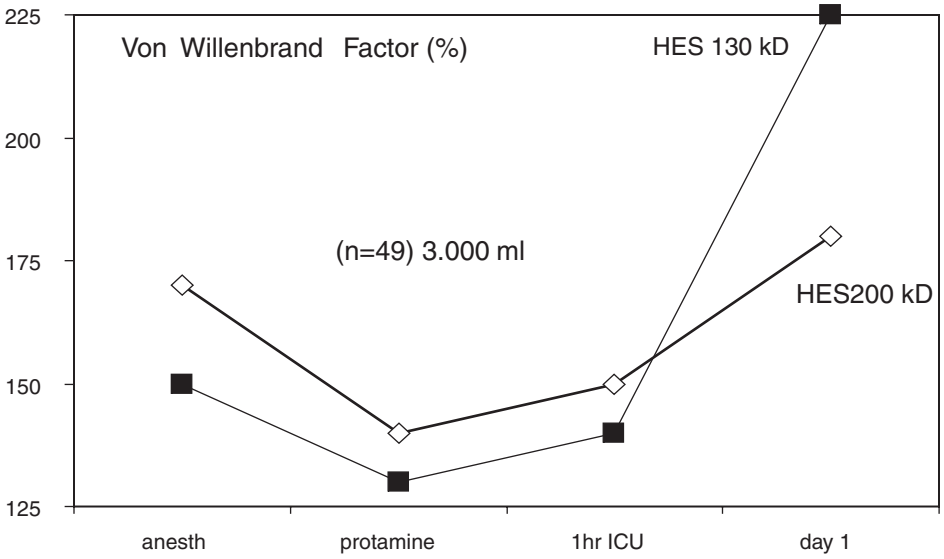
Standl T.
Anesth Analg 2003;96:936-943

EFFECT OF HES ON HEMOSTASIS



Kozek-Langernecker SA
Anesthesiology 2005;103:654-660

INCREASED VON WILLEBRAND FACTOR AFTER LOW MOLECULAR WEIGHT HES PRIMING SOLUTION IN CPB



HES 130/0.4 has no negative effect on hemostatic function when used in large quantities during CPB
Blood loss was lower in the HES 130

van Oeveren W
B J A 1998;80:A267

COAGULATION EFFECTS OF A HES 130/0.4 COMPARED TO HES WITH HIGHER MOLECULAR WEIGHT

Effect of 30% *in vitro* dilution on activated partial thromboplastin time (aPTT) and prothrombin time (PT)

	C	S	H 130	H 200	H 450
aPTT(s)	30.4 ± 1.9	33.8 ± 2.1	32.7 ± 2.3	32.8 ± 2.1	33.2 ± 2.2
PT(s)	10.2 ± 0.3	13.2 ± 0.6	11.9 ± 0.5	11.3 ± 0.6	11.7 ± 0.6

We could demostrate that HES 130/0.4 had a significantly lower impact on maximal amplitude (strength of the clot) compared to HES 450/0.7 , no additional adverse effects on clot polymerization should be expected.

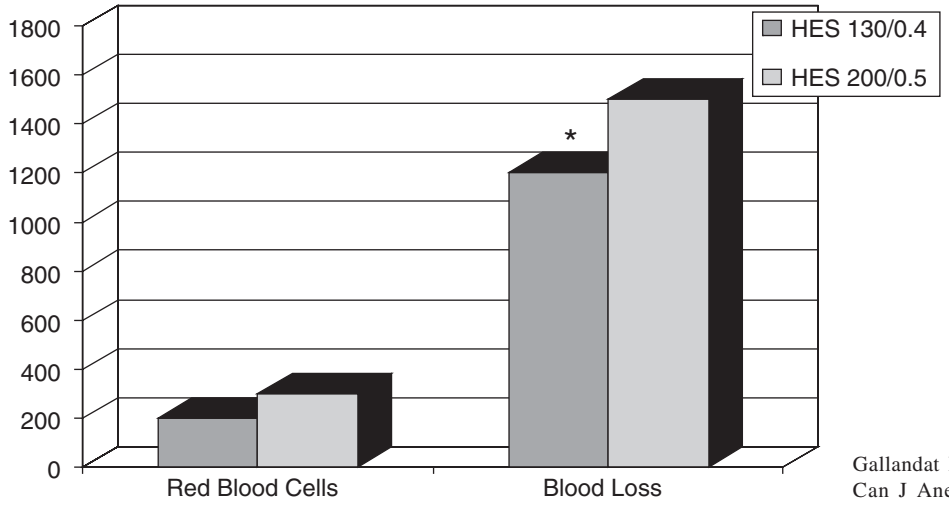
Entholzner EK
Acta Anesthesiol Scand 2000;44:1116-1121

VOLUVEN FOR EFFECTIVE PERIOPERATIVE PLASMA VOLUME SUBSTITUTION IN CARDIAC SURGERY

OR + ICU data (means)	HES 130	HES200
Total HES use (ml)	2,550	2,466
Total HES use (ml/kg)	31	31
Total crystalloids (ml)	5,482	5,586
Total fluid balance (ml)	3,292	3,212
Blood loss (ml)	1,301	1,821
No blood donor use (% of pats)	60	51
Platelet # po. Day 1 (median x 10)	178	153
% increase vWF po. day 1	48	8

Gallandat Huet RCG
Can J Anesth 2000;47:1207-1215

VOLUVEN FOR EFFECTIVE PERIOPERATIVE PLASMA VOLUME SUBSTITUTION IN CARDIAC SURGERY



Gallandat Huet RCG
Can J Anesth 2000;47:1207-1215

EFFECTS OF VOLUME THERAPY USING HES (130/0.4) ON POST-OPERATIVE BLEEDING AND TRANSFUSION REQUIREMENTS IN CHILDREN UNDERGOING CARDIAC SURGERY

(n = 42 children)

- (FFP) n = 21
- (HES 130/0.4) n = 21 10 ml/kg
- Results: INR was prolonged after HES ($p < 0.05$)
- Conclusions: HES (130/0.4) in children undergoing cardiac surgery does not cause more bleeding or a higher transfusion requirement than FFP, 10 ml/kg.

Sung KC
Acta Anesthesiol Scand 2006;50:108-111

THROMBELASTOGRAPHIC COAGULATION ANALYSIS FOLLOWING *IN VITRO* AND *IN VIVO* HEMODILUTION WITH HES

- HES 130/04 and HES 200/0.5-6%
- Volunteers 1.000 ml infusion 30 min

- Conclusion. The effects of *in vitro* hemodilution with HES on coagulation differ qualitatively and quantitatively from the effects of in vivo hemodilution.

Asskali F
Anasthesiol Intensivmed Notfallmed Schmerzther 2002;37:258-266
Frankfurt

INFLUENCE OF COLLOID INFUSION ON COAGULATION DURING OFF-PUMP CABG

(n = 30)

- Group I = 6% HES 200/.5
- Group II = 6% HES 130/.4
- Group III = 4 % Suc GEL

7 a 8 ml/kg PVC 10 mmHg

Results: Chest tube drainage 24 Hrs
Group I (856 ± 131ml)
Group II (550 ± 124 ml)
Group III (582 ± 159 ml)

Conclusion:
HES 130/0.4 is a good choice for maintenance of intravascular volume during off pump CABG with relative lack of impairment of coagulation

Kanchi M
Anesth Analg 2003;96,SCA 141 India

COMPARISON OF HES (130/0.4)AND HES (200/0.5) IN OFF PUMP CORONARY ARTERY SURGERY

(n = 40)
20 ml/kg
Coagulation parameters

- Platelet count, prothrombin time (PT), partial thromboplastin time (PTT)
- Conclusion. Voluven showed less derangement in PT, and less blood loss

Mehta YP
Anesth Analg 2004;98:SCA1-134 Abstract 63

MOLAR SUBSTITUTION AND C2/C6 RATIO OF HES :INFLUENCE ON BLOOD COAGULATION

(n = 30 patients)

- 700 kD differing in their molar substitution(0.4 and 0.5) and C2/C6 ratio to achieve 20,40 and 60% dilution
- Blood coagulation assessed by TEG analysis and plasma coagulation test .
- Results. The lowest C2/C6 ratio was associated with the lowest effect on blood coagulation .
- Conclusions. TEG analysis indicates that hight molecular HES with molar substitution of 0.4 and C2/C6 ratio has the lowest effect on in vitro human blood coagulation

Brit J Anesth 2006;96:455-463
Von Roten I. Zurich , Switzerland

VOLUME THERAPY WITH A HES IN CARDIAC SURGICAL PATIENTS BEFORE CPB

	6% HES 130/0.4 (n = 10)	6% HES 200/0.5 (n = 10)
Use of PRBC (total No of units)	3	3

PRBC = packed red blood cells

HES 130/0.4 6% may become an alternative strategy for volume therapy in cardiac surgery

Boldt J
J Cardiothorac Vasc Anesth 2000;14:264-268

HYDROXYETHYL STARCH: SAVE OR NOT?

Table studies of the effect of hydroxyethyl starch on coagulation, grouped by result

Author (ref.)	Size	Population	Coagulation effects
No effects			
Dieh et al[36]	60	Postoperative	None
Claes et al[38]	40	Intraoperative	None
Falk et al[40]	12	Sepsis	None
Munsch et al[37]	40	Postoperative	None
Halonen et al[39]	15	Intraoperative	None
Gold et al[31]	40	Intraoperative	None
Effects on laboratory values only			
Muller et al[1]	20	Intraoperative	↓I, VII, PA
Stump et al[3]	30	Volunteers	↓I, VIII, ↑PTT
Kuitunen et al[2]	45	Intraoperative	↓VIII, xWF, ↑PTT
Korttilla et al[4]	6	Volunteers	↓VIII
Kupiotis et al[5]	10	Volunteers	↓VIII
Lucas et al[6]	34	Animals	↓I, II, VIII, ↑PT, PTT
Strauss et al[7]	30	Volunteers	↓I
Popov-Cenic et al[16]	30	Intraoperative	↓VII, IX, PA
Clinically significant effects			
Bold et al[8]	75	Intraoperative	↑CT drainage, ↓PA
Villarino et al[9]	28	Intraoperative	↑Transfusions, reoperations, PT, PTT
Cope and tribble[41]	127	Intraoperative	↑CT Drainage, transfusions, reoperations, PT
Trumble et al (10)	26	Postoperative, Vasospasm	↑PTT, trend for transfusions, reoperations

Warren B. Anesth Analg 1997;84:206-12

ACUTE NORMOVOLEMIC HEMODILUTION (ANH) IN CARDIAC SURGERY WITH HES 130/0.4 EFFECTS ON COAGULATION

- 20 patients scheduled for cardiac surgery
- ANH with HES 130/0.4 (n = 10)
- ANH with L Ringer's (n = 10)
- Tromboelastography TEG measurements
- TEG was measured after induction, before CPB during CPB, and at the end of surgery.
- Reaction time R, coagulation time K, maximal amplitude MA.

Conclusion: During ANH in cardiac surgery, HES 130/0.4 was associated with similar changes than Ringer's Lactated .on TEG measurements

Perez Franco R, Rojas Peres E, Luna Ortiz P
Instituto Nacional de Cardiologia Ignacio Chavez
Mexico DF

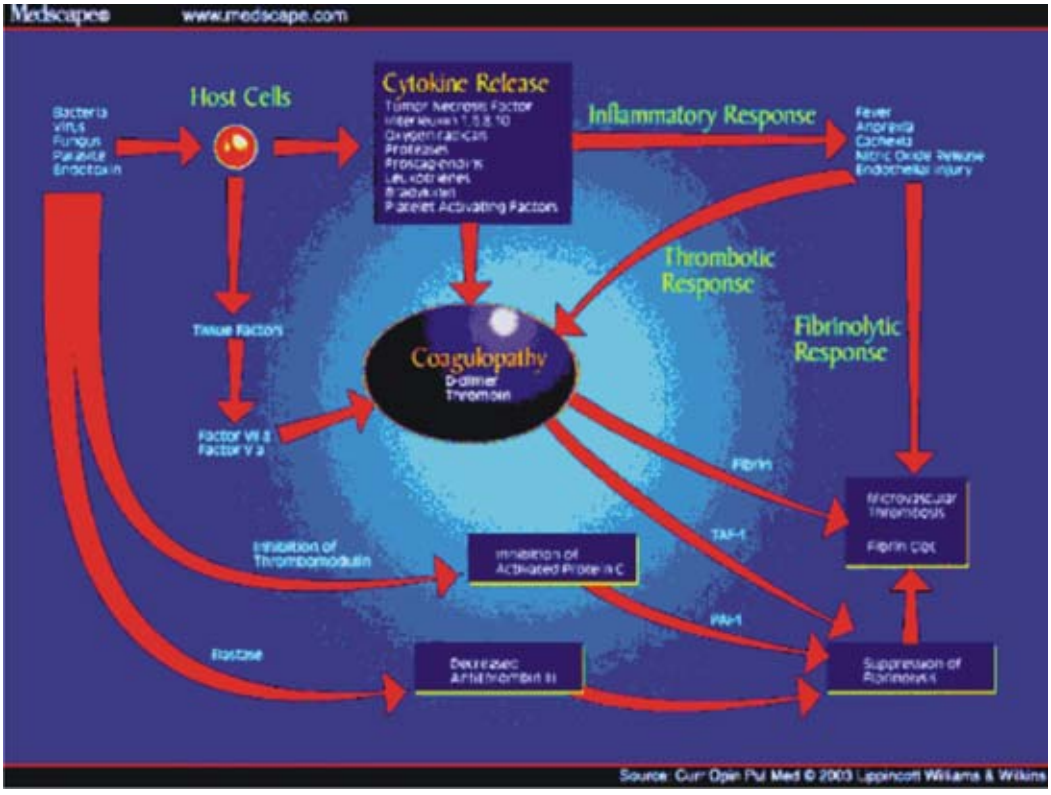
WHY INCLUDE COLLOID FOR PLASMA VOLUME SUPPORT? - MAIN ARGUMENTS

- To avoid "overhydrated" patients
- To promote cardiac output and systemic blood flow
- To improve microcirculation and blood-tissue exchange
- To promote clinical outcome
  - The quality?
  - Morbidity, mortality?

Haljamae Hengo MD
Perioperativ Advances in colloid therapy
Intensivdag, OSLO, 2005

HES 130/0.4 – REDUCES INFLAMMATORY RESPONSE

- Lang et al . Volume replacement with HES 130/0.4 may reduce the inflammatory response in major abdominal surgery. Can J Anesth 2003;50:1009-1016
- RL *vs* HES and release of pro-inflammatory cytokines . n = 36
- IL-6, IL-8 lower in HES treated patient
- Soluble adhesion molecules(sELAM-1 and sICAM-1) higher in RL group.
- Volume replacement with HES 130/0.4 – may reduce the inflammatory response in major surgery .
- Boldt et al . Influence of different volume replacement strategies on inflammation and endothelial activation in the elderly undergoing major abdominal surgery . Intensive Care Med 2004;30:416-422 n = 66



WHY DO WE PREFER HES 130/0.4 (VOLUVEN) ?

Because:
- Well characterized plasma volume expansion
- Large volume (50 ml/kg b.w./ day)
- Minor effects on hemostasis
- Minor influence on renal function
- Relative rapid elimination
- Reduction of endothelial cell activation and inflammatory response
- Minimal risk of anaphylactic reactions

Haljamae Hengo MD
Int J Intens Care 1999;6:20-30
Goteborg, Sweden

WHAT DO WE WANT TO ACHIEVE IN CLINICAL PRACTICE?

- Provide daily basal fluid requirements (crystalloid)
- Maintain normovolaemia and haemodynamic stability (colloid)
- Compensate for internal fluid fluxes from interstitial and intracellular spaces (Crystalloid)
- Enhance microvascular blood flow (colloid)
- Mantain adecuate plasma colloid osmotic pressure COP (colloid)
- Prevent/moderate activation of cascade systems an trauma induced enhancement of coagulation (colloid)
- Prevent reperfusion injury caused by generation of free radicals (colloid)
- Adecuate transport of oxygen to tissue cells (colloid+RBC)
- Promote diuesis (crystalloid).
- Reduced inflammatory response. (colloid)

USE OF COLLOID CLEARLY INDICATED !

Haljamae H.
Int J Intens Care 1999;6 (1) 20-30

THE PROS AND CONS OF HES SOLUTIONS

- HES solutions could reduce microvascular permeability, leading to the concept that they could “plug” the leaks created in the endothelium during various disease processes, including CPB, sepsis and burn. (Capillary leak syndrome)

Vincent JL
Plugging the leaks? New insights into synthetic colloids.
Crit Care Med 1991;19:316-8 Jean-Louis Vincent Editorial
Anesth Analg 2007;104.484-486

Jean-Louis Vincent Editorial
Anesth Analg 2007;104:484-486

Feng X
Hydroxyethyl starch, but not modified fluid gelatin, affects inflammatory response in a rat model
Anesth Analg 2007;104:624-630

HES (130/0.4) THE STARCH FOR TOMORROW’S CARDIAC SURGERY?

Huet Gallandat
Anasthesiol Intensivmed Notfallmed Schmerzther 1998;33:397