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

Revista Mexicana de Anestesiología
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

Kuitunen AH

COLLOIDS AND COAGULATION

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

REEXPLORATION FOR HEMORRHAGE

Lawrence J Dancey

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
- 0.6 Hexastarch
- 0.5 Pentastarch
- 0.4 Tetrastarch

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

Postoperative blood loss (ml) (n = 444)

<table>
<thead>
<tr>
<th>Time period</th>
<th>No hetastarch</th>
<th>Hetastarch</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>377</td>
<td>518</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>0-12</td>
<td>681</td>
<td>979</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>0-24</td>
<td>924</td>
<td>1284</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Knutson JE
Anesth Analg 2000;90:801-7
Mayo Clinic, Rochester
HETASTARCH AND BLEEDING COMPLICATIONS AFTER CORONARY SURGERY

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


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

<table>
<thead>
<tr>
<th></th>
<th>Albumin group</th>
<th>HES group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean blood loss</td>
<td>693 ± 350 ml</td>
<td>789 ± 487</td>
</tr>
</tbody>
</table>

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


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
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

**CONCLUSION**

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

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

6% HES 130/0.4 (n=64) (50 ml/kg/day)

- Total blood loss 544 ± 305 ml

GEL (n=68)

- Total blood loss 504 ± 327 ml

**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**

HES 130/0.4 (n=59) 50 ml/kg

- Chest tube drainage 660 ml

HES 200/0.5 (n=59) 33 ml/kg

- Chest tube drainage 705 ml

Kasper SM
Anesthesiology 2003;99:42-47

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

HES 130/0.4 (n=12) 1,000 ml/prime, 50 ml/kg/day

- Transfusion requirement 587.5 ± 346.5 ml

Ringer’s solution (n=18)

- Transfusion requirement 736.1 ± 545.8 ml

Tempe DK
Annals of Cardiac Anesthesia 2006;9:144-149
THE EFFECTS OF HYDROXYETHYL STARCHES OF VARYING MOLECULAR WEIGHTS ON PLATELET FUNCTION

![Bar graph showing the effects of different molecular weights of hydroxyethyl starches on platelet function.](image)

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

![Graph showing the relative changes of tpO2 (%) over time for HES 70, HES 130, and HES 200.](image)

**EFFECT OF HES ON HEMOSTASIS**

![Diagram illustrating the effects of HES on hemostasis.](image)

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

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>S</th>
<th>H 130</th>
<th>H 200</th>
<th>H 450</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT(s)</td>
<td>30.4 ± 1.9</td>
<td>33.8 ± 2.1</td>
<td>32.7 ± 2.3</td>
<td>32.8 ± 2.1</td>
<td>33.2 ± 2.2</td>
</tr>
<tr>
<td>PT(s)</td>
<td>10.2 ± 0.3</td>
<td>13.2 ± 0.6</td>
<td>11.9 ± 0.5</td>
<td>11.3 ± 0.6</td>
<td>11.7 ± 0.6</td>
</tr>
</tbody>
</table>

We could demonstrate 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

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

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
Anesthesiol 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
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 high molecular HES with molar substitution of 0.4 and C2/C6 ratio has the lowest effect on in vitro human blood coagulation.

VOLUME THERAPY WITH A HES IN CARDIAC SURGICAL PATIENTS BEFORE CPB

<table>
<thead>
<tr>
<th></th>
<th>6% HES 130/0.4 (n = 10)</th>
<th>6% HES 200/0.5 (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of PRBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No of units</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>PRBC = packed red blood cells</td>
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<td></td>
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</table>

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

HYDROXYETHYL STARCH: SAVE OR NOT?

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

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

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.
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)
- Maintain adequate plasma colloid osmotic pressure COP (colloid)
- Prevent/moderate activation of cascade systems and trauma induced enhancement of coagulation (colloid)
- Prevent reperfusion injury caused by generation of free radicals (colloid)
- Adequate transport of oxygen to tissue cells (colloid+RBC)
- Promote diuresis (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
Anesthesiol Intensivmed Notfallmed Schmerzther 1998;33:397