Perioperative colloids: an update

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Conflicts of interest – financial disclosures

<table>
<thead>
<tr>
<th>Company</th>
<th>Nature of Affiliation</th>
<th>Unlabeled Product Usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
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Volume expansion: First choice in clinical routine - OR

Colloids vs. crystalloids: Background for the use of colloids

Rational fluid therapy: Different volume compartments should be addressed separately
Two opposing forces:
- Outward hydrostatic pressure (blood pressure)
- Inward oncotic pressure (COP)

Colloids:
COP → Net filtration ↓

### Physiology: The endothelial surface layer

- Crystalloids
- Vascular barrier
- Plasma proteins
- Endothelial glyocalyx
- Membrane-bound glycoproteins and proteoglycans (syndecan and glypican), with negatively charged side chains (heparan, dermatan, chondroitin sulfates, hyaluronan)

### Physiology: Starling's principle

- Interstitial space
- Endothelial cell layer
- Vascular lumens

### Colloids vs. crystalloids: Efficacy: Volume effects

<table>
<thead>
<tr>
<th>Model</th>
<th>Preparation</th>
<th>Blood volume before hemorrhage (ml)</th>
<th>Blood volume after hemorrhage (ml)</th>
<th>Infused amount (ml)</th>
<th>Blood volume after resuscitation (ml)</th>
<th>Volume effect (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEMO</td>
<td>6% HES 130/0.4</td>
<td>1.076 ± 0.257</td>
<td>1.034 ± 0.240</td>
<td>1.084 ± 0.247</td>
<td>1.034 ± 0.240</td>
<td>6% ± 0.16</td>
<td>[1]</td>
</tr>
<tr>
<td>HEMO</td>
<td>6% HES 200/0.5</td>
<td>1.049 ± 0.240</td>
<td>1.084 ± 0.247</td>
<td>1.034 ± 0.240</td>
<td>1.034 ± 0.240</td>
<td>6% ± 0.16</td>
<td>[2]</td>
</tr>
<tr>
<td>Plasma</td>
<td>Longest Range</td>
<td>1.097 ± 0.240</td>
<td>1.084 ± 0.247</td>
<td>1.034 ± 0.240</td>
<td>1.034 ± 0.240</td>
<td>6% ± 0.16</td>
<td>[3]</td>
</tr>
</tbody>
</table>

Efficacy: 1 L colloids = 4-5 L crystalloids

### Colloids vs. crystalloids: Efficacy

Are colloids always more efficient?

Infused volumes:
1 L colloids: 1.32 L crystalloids

- No Normalization of Central Venous Pressure
- No Normalization of Mean Arterial Pressure
- No Normalization of O2 Saturation
**Perioperative Colloids vs. Crystalloids: Efficacy**

Are colloids always more efficient?

**Infused volumes:**
- 1 (colloids) : 1.4 (crystalloids)

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**Infused volumes:**
- 1.0 (colloids) : 1.2-4 (crystalloids)

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**Perioperative Fluid Therapy With Tetrastarch and Gelatin in Cardiac Surgery—A Prospective Sequential Analysis**

Beyer O. et al.

**Crit Care Med 2013; 41:2532–2542**

**Perioperative patients**

- Hemodynamic stabilization

- Fluid intake

- Abnormal ScvO₂

- Abnormal CVP

- Abnormal lactate

- Ongoing vasopressor use
Colloids vs. crystalloids: Efficacy
Are colloids always more efficient?

Perioperative Colloids

Rapid 1L co-load of 6% HES vs. Hartmann solution (HS)

Shedding of the glyocalyx:
- Sepsis
- Surgical trauma / inflammation
- Ischaemia/reperfusion
- Diabetes / arteriosclerosis
- Trauma
- Iatrogenic intravascular hypervolaemia

Table 1: Measured volume effects

<table>
<thead>
<tr>
<th>Model</th>
<th>Preparation</th>
<th>Blood volume before haemorrhage (ml)</th>
<th>Blood volume after haemorrhage (ml)</th>
<th>Blood volume at baseline (ml)</th>
<th>Volume effect (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>Human albumin</td>
<td>4.413 ± 0.398</td>
<td>1.576 ± 0.237</td>
<td>3.876 ± 0.486</td>
<td>85 ± 16</td>
<td>(SE)</td>
</tr>
<tr>
<td>6% HES 130/0.4</td>
<td>10%</td>
<td>4.412 ± 0.474</td>
<td>1.571 ± 0.297</td>
<td>3.841 ± 0.457</td>
<td>85 ± 16</td>
<td>(SE)</td>
</tr>
<tr>
<td>6% HES 130/0.5</td>
<td>10%</td>
<td>4.403 ± 0.481</td>
<td>1.569 ± 0.297</td>
<td>3.835 ± 0.457</td>
<td>85 ± 16</td>
<td>(SE)</td>
</tr>
<tr>
<td>Lactated Ringer</td>
<td>10%</td>
<td>4.958 ± 0.987</td>
<td>1.439 ± 0.235</td>
<td>3.463 ± 0.969</td>
<td>70 ± 10</td>
<td>(SE)</td>
</tr>
<tr>
<td>10%</td>
<td>Human albumin</td>
<td>4.497 ± 0.708</td>
<td>1.376 ± 0.129</td>
<td>3.761 ± 0.904</td>
<td>80 ± 19</td>
<td>(SE)</td>
</tr>
<tr>
<td>Lactated Ringer</td>
<td>10%</td>
<td>4.613 ± 0.725</td>
<td>1.376 ± 0.129</td>
<td>3.761 ± 0.904</td>
<td>80 ± 19</td>
<td>(SE)</td>
</tr>
</tbody>
</table>

Values are means [SE] (±). Arterial-venous lactate and Hb, pH, SOFA, Lactate was measured on admission and every 6 hours.
**Colloids vs. crystalloids: Safety**

**Nephrotoxicity**

Hydroxyethylstarch and cosmetic-nephrotoxic lesions in kidney transplantation

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**ICU**


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**Colloids vs. crystalloids: Safety**

**Nephrotoxicity**

Perioperative patients

Effect of Waxy Maize-derived Hydroxyethyl Starch 130/0.4 on Renal Function in Surgical Patients

Claude Martin, M.D.,*† Matthias Jacob, M.D.,† Eric Vicaut, M.D.,† Bertrand Guldet, M.D.,§ Hugo Van Aken, M.D., Ph.D.,† Andrea Kurtz, M.D.†

Perioperative Fluid Therapy With Tetrastarch and Gelatin in Cardiac Surgery—A Prospective Sequential Analysis. Crit Care Med 2013; 41:2532–2542

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**Colloids vs. crystalloids: Safety**

**Nephrotoxicity**

Perioperative patients

<table>
<thead>
<tr>
<th>HES vs. Gelatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>HES</td>
</tr>
<tr>
<td>Gelatin</td>
</tr>
<tr>
<td>p-value</td>
</tr>
</tbody>
</table>

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*Funding: None.*
Colloids vs. colloids: Safety
Nephrotoxicity

HES vs. albumin

Replacement of albumin by hydroxyethyl starch could increase the risk for acute kidney injury in patients with severe ARDS.

Colloids vs. crystalloids: Safety
Mortality

6% HES 130/0.4
(Tetraspan®, potato HES, max. 33ml/kg/d)

90d-Mortality:
HES 51% vs. RA 43% (RR 1.17; 95% CI: 1.01 to 1.36; P = 0.03)

90d-Mortality:
HES 41% vs. RL 33.9% (P = 0.09)

Colloids vs. crystalloids: Safety
Mortality

6% HES 130/0.4
(waixy-maize HES, Voluven®, max. 50ml/kg/d)

ICU
Colloids vs. crystalloids: Safety

Mortality

ICU: Albumin

A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit

Perioperative patients

Safety of Modern Starches Used During Surgery

Philipe Van Der Linden, MD, PhD, * Michael James, MB ChB, PhD, FRCA, TCRA, FICSA;1 Michael Mythen, MD, FRCA, (S) and Richard B. Wescott, MD1

Perioperative patients: HES vs. Gelatin

Status-1: Adjusted Effects of Treatment Periods (Crystallloid Period as Reference Group)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted HR (95% CI)</th>
<th>P</th>
<th>Adjusted HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HES 1st 9·25/54</td>
<td>1.07 (0.98, 1.20)</td>
<td>0.091</td>
<td>0.08 (0.048, 1.275)</td>
<td>0.816</td>
</tr>
<tr>
<td>Gelatin 47</td>
<td>1.68 (0.94, 2.296)</td>
<td>0.097</td>
<td>1.29 (0.024, 1.886)</td>
<td>0.154</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HES 1st 9·25/54</td>
<td>1.12 (0.96, 1.293)</td>
<td>0.162</td>
<td>1.13 (0.057, 1.886)</td>
<td>0.889</td>
</tr>
<tr>
<td>Gelatin 47</td>
<td>1.15 (0.85, 1.558)</td>
<td>0.326</td>
<td>1.18 (0.024, 1.886)</td>
<td>0.708</td>
</tr>
</tbody>
</table>

Colloids vs. crystalloids: Safety

Bleeding

• VISEP trial:
  - HES-patients received more units of PRBC than patients in the Ringer's lactate group (p = 0.06)
• 6S trial:
  - 10% of HES patients had severe bleeding (≥3 PRBC/24h) versus 6% of RA patients (RR, 1.52; P=0.09)
  - More patients in the HES-group than in the RA-group received PRBC (RR, 1.28: 95% CI, 1.12 to 1.47; P<0.001)
• CHEST trial:
  - significantly higher use of blood products in the HES group compared to the saline group (78±250 ml vs. 60±110 ml, P<0.001)
Colloids vs. crystalloids: Safety

### Perioperative patients: HES vs. Gelatin

**Table 1. Fluids and Blood Products Administered During Surgery for Cardiopulmonary Bypass: A prospective comparison of HES and Gelatin**

<table>
<thead>
<tr>
<th>Fluids and Blood Products</th>
<th>Hydroxyethyl starch</th>
<th>Gelatin</th>
<th>Expiration Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depot: HES 130/0.4</td>
<td>3.5% (0.5%)</td>
<td>0.5% (0.5%)</td>
<td>3.5% (0.5%)</td>
</tr>
<tr>
<td>Depot: HES 130/0.3</td>
<td>3.5% (0.5%)</td>
<td>0.5% (0.5%)</td>
<td>3.5% (0.5%)</td>
</tr>
<tr>
<td>Depot: Gelatin</td>
<td>3.5% (0.5%)</td>
<td>0.5% (0.5%)</td>
<td>3.5% (0.5%)</td>
</tr>
<tr>
<td>Depot: Gelatin</td>
<td>3.5% (0.5%)</td>
<td>0.5% (0.5%)</td>
<td>3.5% (0.5%)</td>
</tr>
</tbody>
</table>

**Perioperative Colloids**

**Colloids vs. crystalloids: Safety**

**Bleeding**

- **Perioperative patients: HES vs. Gelatin**
- **Pruritus**

**References**

- Perioperative Fluid Therapy With Tetrastarch and Gelatin in Cardiac Surgery—A Prospective Sequential Analysis
  *Crit Care Med* 2013; 41:2532–2542

**Artificial colloid administration was consistently associated with coagulopathy and clinical bleeding, most frequently in cardiac surgery patients receiving hydroxyethyl starch.**

**HES deposit in Schwann cell of cutaneous nerve**

**British Journal of Dermatology** 2005 152, 3–12

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**Figure**

**Safety of Modern Starches Used During Surgery**

- Philippe Van Der Linden, MD, PhD, Michael I. James, MB ChB, PhD, FRCA, FACA(SA); [and Richard B. Wessely, MD](#)

There were no indications that the use of tetrasaccharides during surgery induces adverse renal effects as assessed by change of absolute or percentage concentrations of serum creatinine or need for renal replacement therapy (59 patients, 329 patients), increased intrarenal loss (39 patients, 329 patients), and adjusted eGFR (39 patients, 329 patients), respectively. Few complications were reported (0.5% patients, 0.1% patients). No adverse events were reported in patients with HES (0.5% patients, 0.1% patients). (Am J Med 2015;138:55–48)

**Conflicts of Interest:** See Disclosures at the end of the article.

Fresenius-Kabi requested us to undertake the research described. No one received any compensation.

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**Pruritus**

- **Incidence:**
  - ICU patients: 13-34%
  - Cardiac Surgery: 22%
  - Stroke: 3-54%
- **Hallmark:** delayed onset (1-6 weeks after exposure), long duration (9-15 weeks)
- **Unresponsive to treatment**

**Perioperative Colloids**
### Conclusion

**Colloids vs. crystalloids: Safety**

Colloids vs. crystalloids for fluid resuscitation in critically ill patients (Review)

Perioperative Care

**Conclusions**

- There is no evidence from randomised controlled trials that resuscitation with colloids reduces the risk of death, compared to resuscitation with crystalloids, in patients with trauma, burns or following surgery.
- Furthermore, the use of hydroxyethyl starch might increase mortality.
- As colloids are not associated with an improvement in survival and are considerably more expensive than crystalloids, it is hard to see how their continued use in clinical practice can be justified.

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**Colloids vs. crystalloids: Costs**

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Voluven (Hayman)</th>
<th>Voluven (Non Hayman)</th>
<th>Mannitol</th>
<th>0.9% NaCl</th>
<th>Ringer’s lactate</th>
<th>Plasma-Lyte</th>
<th>Hartmann</th>
<th>Bellco</th>
</tr>
</thead>
<tbody>
<tr>
<td>Price (€500ml)</td>
<td>1.24</td>
<td>0.5</td>
<td>0.5</td>
<td>1.52</td>
<td>1.23</td>
<td>7.19</td>
<td>1.87</td>
<td>1.41</td>
</tr>
</tbody>
</table>

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**Conclusion**

- Because of the risk of kidney injury and mortality, HES solutions must no longer be used in patients with sepsis, burn injuries or critically ill patients.
- HES solutions should only be used for the treatment of hyperoncemia due to acute blood loss when crystalloids alone are not considered sufficient.
- There is a lack of robust long-term safety data in patients undergoing surgical procedures and in patients with trauma. The expected benefit of treatment should be carefully weighed against the uncertainties with regard to long-term safety, and other available treatment options should be considered. Additional studies will be performed with HES solutions in patients with trauma and in elective surgery.
- HES solutions should be used at the lowest effective dose for the shortest period of time. Treatment should be guided by continuous haemodynamic monitoring so that the infusion is stopped as soon as appropriate haemodynamic goals have been achieved.
- HES solutions are now contraindicated in patients with renal impairment or renal replacement therapy. The use of HES must be discontinued at the first sign of renal injury. An increased need for renal replacement therapy has been reported up to 90 days after HES administration. Patients’ kidney function should be monitored after HES administration.
- HES solutions are contraindicated in severe coagulopathy. HES solutions should be discontinued at the first sign of coagulopathy. Blood coagulation parameters should be monitored carefully in case of repeated administration.
**Conclusion**

- Do not use HES solutions in critically ill adult patients including those with sepsis, and those admitted to the ICU.
- Avoid use in patients with pre-existing renal dysfunction.
- Discontinue use of HES at the first sign of renal injury.
- Need for renal replacement therapy has been reported up to 90 days after HES administration. Continue to monitor renal function for at least 90 days in all patients.
- Avoid use in patients undergoing open heart surgery in association with cardiopulmonary bypass due to excess bleeding.
- Discontinue use of HES at the first sign of coagulopathy.

**Personal conclusion**

**Colloids**

- Volume effects are dependent upon clinical condition and frequently over-estimated
- Expensive
- Until now, no evidence for any benefit!

- Artificial colloids:
  - Nephrotoxic
  - Probable increase in mortality
  - Increase in bleeding complications, pruritus, anaphylactoid reactions

- Strong recommendations of EMA/FDA against the use of HES
- „Revival“ of albumin?

- Necessary precautions:
  - Not in patients with capillary leak (sepsis, burn injuries, CPB?)
  - Not in patients with risk for renal dysfunction
  - Only in hypovolemic, hemodynamic treatment algorithm
  - Only in the acute situation
  - Maximal doses!

Thank you very much for your attention
Volume expansion: First choice in clinical routine - ICU

First line

- Isotonic crystalloids: 81%
- HES: 55%
- Gelatin: 35%
- Albumin: 7%
- Plasma: 6%
- Dextrane: 4%
- Hypertone crys.: 2%

Volume expansion: Why do clinicians opt for a specific fluid?

Colloids vs. crystalloids: Efficacy

Volume effects

Colloids vs. colloids: Safety

Mortality

Perioperative patients: Albumin vs. HES

Study | Type | n | Setting | Treatment | Mortality
--- | --- | --- | --- | --- | ---
Sedrakyan Retro 19576 CABG | Albumin vs. non-protein colloids (HES, Dextran, and others) | OR 0.80 (CI 0.67-0.94); Exposure to non-protein-collodids independent RF for mortality
Trowbridge NCT 576 CPB | „Enhanced perfusion“: Maintain serum albumin > 3.5 g/dl or COP > 14 mmHg | OR 0.31 (CI 0.13-0.73)
Conclusion: Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients

- “We recommend not to use HES with molecular weight ≥ 200 kDa and/or degree of substitution > 0.4 in patients with severe sepsis and recommend not to use these HES solutions in other intensive care patients with increased risk for AKI (advanced age, sepsis, cardiovascular surgery, contrast nephropathy).”
- “We suggest that HES 130/0.4 be used in severe sepsis and other ICU patients with increased risk for AKI or bleeding only in the context of clinical trials rather than in routine clinical practice.”
- “We suggest that albumin may be included in the resuscitation of severe sepsis patients.”
- “We suggest not to use gelatin in ICU patients who are at increased risk for renal failure or bleeding outside the context of clinical trials.”
- “We recommend reassessment of existing dose limits for HES and an assessment of whether dose limitations should apply for gelatins.”