NEW COLLOID
6% HYDROXYETHYL
STARCH (130/0.4)

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CLINICAL USE
OF THIRD
GENERATION
NEW COLLOID
HES 130/0.4
HYPOVOLEMIC CONDITION

HYPOVOLEMIC SHOCK
With/without VASCULAR LEAKAGE

SEPTIC SHOCK
DSS
HEMORRHAGIC

TYPE OF FLUIDS:
CRYSTALOID COLLOIDS

GELATINE, HYDROXYETHYL STARCH (HES), ALBUMIN, PPF

RL
RA
NaCl

HES
HES
HES

LOW MW
MED MW
HIGH MW

< 130.000 MW
200.000-300.000 MW
> 300.000 MW
**Effects of Synthetic Colloids**

- Retaining of fluid in the IVS
- Increased IV volume
- Venous flow back (preload)
- Cardiac output
- Oncotic pressure
- Hemodilution
- Improved theology
- Hematocrit
- Flow resistance
- Arterial oxygen concentration
- CO
- DO2
- CaO2

**Ideal Colloid**

- Less coagulopathy, hemolysis, red cell hemolysis, cross-match disturbances
- Rapid volume replacement
- Good hemodynamic restoration
- Improvement of Microcirculation
- Improvement of plasma oncotic pressure
- Increase DO2 and organ function
- Fast metabolism / excretion and good tolerance
DISADVANTAGE EFFECTS OF SYNTHETIC COLLOID

- **Coagulation dilution**: (decrease vWF; platelet adhesion ↓) ➔ Dextran, HMW. HES & high dose/multiple
- **Renal function**: Dextran, HMW. HES and high DS (450 kD/0.7)
- **Tissue Accumulation**: HMW. HES / high DS (RES, skin, nerve)

HES = Hydroxethylstarch
(Not all HES are the same!)

1. (Based on degree of substitution)

<table>
<thead>
<tr>
<th>Tetrastarch (0.4)</th>
<th>Pentastarch (0.5)</th>
<th>Hetastarch (0.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TETRAHES</td>
<td>HES 130 /0.4</td>
<td>HES 200 /0.5</td>
</tr>
<tr>
<td></td>
<td>HES 450 /0.7</td>
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</tbody>
</table>

2. (Based on Molecular weight)

<table>
<thead>
<tr>
<th>High molecular weight HES</th>
<th>Medium Molecular weight HES</th>
<th>Low molecular weight HES</th>
</tr>
</thead>
<tbody>
<tr>
<td>HES 450 /0.7</td>
<td>HES 200 /0.5</td>
<td>HES 40 /0.5</td>
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<tr>
<td>HES 470 /0.7</td>
<td>HES 200 /0.62</td>
<td>HES 70 /0.5</td>
</tr>
<tr>
<td>Hespan, Plasmasteril</td>
<td>Hemohes, Haes-steril</td>
<td>HES 110 /0.5</td>
</tr>
<tr>
<td></td>
<td>Elohes</td>
<td>HES 130 /0.4</td>
</tr>
<tr>
<td></td>
<td>Pentaspan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TETRAHES</td>
<td></td>
</tr>
</tbody>
</table>
Effects of PVR solutions on haemostasis and coagulation

<table>
<thead>
<tr>
<th></th>
<th>Gelatins</th>
<th>HMW. HES</th>
<th>Dextran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VIII, vWF</td>
<td>No effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adhesion</td>
<td>No effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggregation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombus formation</td>
<td>No clinical effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood typing</td>
<td>No effect</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In emergency situation blood typing prior to infusion

Tetrahes structure

- HES ➔ similar to glycogen ➔ consists of:
  - D-glucose units linked via linear alpha – 1,4 bonds and branching off from about one in every 17 glucose units via alpha-1,6 bonds
  - Hydroxyethyl groups ➔ more resistant to enzymatic degradation and the longer its intravascular residence time
Characteristics of 6% HES 130/0.4

- 6% HES 130/0.4 in 0.9% sodium chloride sol.
- Mean Molecular Weight: 130,000 ± 20,000 Da
- Molecular DS: 0.38 - 0.45
- C2/C6 substitution pattern: ≥ 8
- Sealing effect: Positive
- Water binding capacity: 21 ml H2O/g HES
- Colloid Osmotic Pressure: 36 mmHg
- Theoretical osmolarity: 308 mosm/l
- pH value: 4.0 - 5.5
- Titration acidity: < 1.0 mmol/l NaOH
Extent and Duration of Volume expansion (Tetrahes)

- Concentration: 6%

- Degree of molar substitution (MS): 0.4
- 4 hydroxyethyl group per 10 glucose unit

- Substitution pattern (site of hydroxyethylation): position 2, 3, and 6 of the glucose unit. Ratio C2/C6 > 8

Structural formula of HES and mode of steric interference with degradation by amylase
HES 130/0.4 ( TETRAHES )

- HES 130/0.4 ➔ 130,000 MW, DS 0.4 and improved C2/C6 ratio ( > 8 )
- Advantages
  - No tissue storage; Quickly excreted;
  - Improve safety profil (hemostasis);
  - Comparable macro/microcirculatory efficacy
  - Initial volume efficacy
  - Good hemorrhheology
  - Complete elimination
  - Maximal Dose: 50 ml/kg/day

Pharmacodynamic Studies
On Volume Effect

- **12 Volunteers:** 500 ml blood letting 30 ’; single inf.500 ml HES 130/0.4 15’. Results: Reduction in Ht, Increase in plasma volume/ blood volume; Volume effect 100%; Plateau effect 4 hours; Volume effect 6 hours
- **RCT of HES 130/0.4** in variety of clinical situation ➔ HES 130/0.4 is a comparable in efficacy to HES 200/0.5 (Kapser, Boldt, Langeron, Huet, Vogt)
Volume Therapy
With HES 130/0.4

- The extent & Duration of the Volume Effect → Vital for macro & microcirculation
- A fast & effective replacement of the intravascular volume → optimize capillary perfusion; improve blood rheology & its \(O_2\) transport capacity → prevent excessive release of mediators & MOF (Bold, 1998)
Influence On Macro and Microcirculation

- Effective volume replacement \(\rightarrow\) improved acute and chronic macro & microcirculation disturbances
- \(\uparrow\) perfusion pressure and \(\downarrow\) blood / plasma viscosity improve rheological properties \(\rightarrow\) improvement in the microcirculation

Stimulation of Pro-inflammatory Process

- No cytokines release in vitro
- No affecting on various surface antigens
- No affecting on adhesion molecules on monocytes and endothelial cells (Dietrich et al 1998)
- Slightly reduce plasma concentration of adhesion molecules (Boldt et al, 1998)
Problems in Colloid Therapy

- “We are just giving colloid to the patient!
- What should happen?”

Possible side effects amongst others can be:
- Influence on Renal Function
- Influence on coagulation
- Anaphylaxis reaction
- Tissue accumulation
- Acid base balance disturbances

Safety Profile Of HES 130/0.4

- Influenced on Hemostasis
  - Fast & complete elimination → minimal influence on coagulation
  - Evidence showed that after HES 130/0.4 → faster recovery of the vWF and Ristocetin co-factor compared to HES 200/0.5 (Vogt et al 1998, Bepperling et al 1999, Jungheinrich C et al 2004)
**Anaphylactoid Reactions**

- The lowest rate of allergic reaction of all colloids (0.06%)
- Major anaphylactoid reaction (gr III & IV) are seldom during HES therapy (Ring and Mezmer, 1997; Laxenaire et al, 1994)

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**No Influenced on The Normal Kidney**

- No affect on the healthy kidney, if the dosage instructions are not exceeded
- After long-term HES therapy could be caused by reduced diuresis as a result of hyperviscosity of renal tubular
- **Evidenced showed:** HES 130/0.4 safely administered to patients with severe renal impairment as long as urine flow is preserved (Jungheinrich, et al 2002)
Relevance of Mol Weight, Molar Substitution and C₂:C₆- ratio

Influence on Kidney function and coagulation depend on MS,C₂:C₆ than MW

- MS >> C₂: C₆ > MW

TETRAHES (6% HES 130/0.4)

GOOD INTRAVASCULAR VOLUME EFFECT
IMPROVEMENT OF MACRO & MICROCIRCULATION
MINIMAL SIDE EFFECT (COAGULATION, RENAL, ANAPHYLACTOID RX, TISSUE ACCUMULATION)
Thank You