"Synthetic Colloids in the 21st Century"

Dr. Frank Bepperling
Director, Chief Clinical Officer Volume Therapy
Kabi Innovation Centre / Business Unit Volume Therapy

Colloid solutions are indicated to treat hypovolaemia or to maintain an adequate circulating blood volume in surgical, trauma or intensive care patients (Boldt et al., 1997). This is achieved by replacing plasma losses with colloid solutions which increase the colloid-osmotic pressure of the plasma. These colloid solutions do not carry oxygen or replace coagulation factors.

An ideal (synthetic) colloid was defined with the following characteristics by the National Institute of Health:

- Long duration of volume effect / efficacy
- Minimal coagulation disturbance / safety
- Improved blood flow to tissues / safety
- No adverse organ effects / safety
- Minimal persistence in the body / safety

Besides the use of the natural colloid human albumin, intravenous solutions of synthetic colloids like gelatins, dextrans, or hydroxyethyl starches (HES) are in clinical use. Replacement of blood losses with crystalloid solutions requires huge amounts of fluid infusion. Thus, the use of colloid solutions helps to reduce these volumes by maintaining the effective colloid-osmotic pressure.

The first synthetic colloid in clinical use was gelatine solution during World War I. Gelatine solutions possess a short volume effect, a low effect on coagulation but a high risk of allergic reactions.

Dextran solutions were introduced after World War II with good volume and rheological effects. However, dextran solutions impair coagulation significantly and comprise a high risk of anaphylactic reactions.

Finally, hydroxyethyl starches (HES) were launched in 1974. HES has a good volume effect but depending on the HES specification, HES impairs coagulation.

The recent worldwide use of synthetic colloids is about 52 Mio. units/year with a market share of 52% of HES, 26% of gelatin solutions, and 22% of dextran solutions. This demonstrates the long life-cycle of this type of medicinal product. International guidelines do not give a preference to a specific synthetic colloid (GIFTASUP, 2008).

As described above, the latest and most extensively investigated synthetic colloid is hydroxyethyl starch. HES consists of

dispersed polymers with very different physicochemical characteristics like molecular weight (Mw), molecular weight distribution, and molar substitution (MS). HES is metabolised by serum amylase in the plasma and HES molecules below the renal threshold are excreted immediately. Plasma half-life and tissue persistence are positively correlated to the molar substitution, i.e. the higher the MS the longer is half-life and tissue persistence (Jungheinrich and Neff, 2005).

During the last thirty years three generations of HES preparations were developed: 1) hetastarch (HES 450/0.7), 2) pentastarch (HES 200/0.5 and 70/0.55), and 3) tetrastarch (HES 130/.4).
High doses of first- and second-generation HES solutions were associated with adverse effects on renal function, coagulation and tissue storage (Westphal et al, 2009). Therefore, the aim of the third-generation HES preparation (tetrastarch, HES 130/.4) was to keep the duration of the volume effect of older HES generations and to improve safety substantially.

The effects of tetrastarch on macro- and microcirculation was investigated in several animal models, e.g. after haemorrhage, during surgery, in sepsis or after ischemia/reperfusion, and compared with other available colloid solutions or crystalloids. The results clearly demonstrate that macrocirculatory variables (Ferreira et al, 2005; Su et al, 2007) and microcirculation, in particular functional capillary density, leukocyte adherence, vascular leakage, and tissue oxygenation were significantly improved as compared to the other solutions (Varga et al, 2008; Hoffmann et al, 2002; Kimberger et al, 2009). The mechanism of action is related to the attenuation of hypoxia-induced increases in vascular leakage and acute inflammation by improved flow and reduced leukocyte sticking.

Although the half-life of tetrastarch is the shortest of all HES preparations the duration of the volume effect is kept by maintaining a sufficiently effective colloid-osmotic pressure. This is achieved by the optimal "in vivo" molecular weight, which is a result of renal elimination of small molecules and the continuous break down of larger molecules by amylase (Ickx et al., 2003; Jungheinrich et al., 2004). Clinical trials confirmed the clinical efficacy of the third-generation HES solution compared with first- and second-generation HES solutions during surgery (Gandhi et al., 2007; Langeron et al., 2001).

During surgery there is concern that artificial colloids interfere negatively with coagulation. In a recent publication based on pooled individual patient data of 449 patients Kozek-Langenecker et al. (2008) could show that drainage loss and transfused red blood cell volume were significantly lower after infusion of 6% HES 130/0.4 as compared to 6% HES 200/0.5.

The SAFE trial demonstrated that the mortality rates after 28 days or 24 months were significantly higher in patients with traumatic brain injury after infusion of human albumin as compared to a crystalloid infusion (SAFE, 2004). Dieterich et al (2003) could demonstrate that HES was not detectable in cerebrospinal fluid after infusion of HES 200/0.5 in patients with head injury and an impaired blood-brain barrier function. This finding may explain why patients with head trauma had less peaks in intracranial pressure after infusion

of a pure HES based infusion regimen as compared to a combined infusion regimen of HES and human albumin (Neff et al, 2003).

Another point of concern is the effect of HES solutions on renal function. Boldt et al. (2007) compared the effects of 6% HES 130/0.4 with human albumin on renal function in patients with an impaired renal function undergoing cardiac surgery. They demonstrated similar hemodynamic effects and transfusion requirements, while the increase of NGAL, a sensitive enzyme of the renal tubular function, was even higher after infusion of human albumin. In a recent review article Boldt (2010) concluded that tetrastarch solution is an alternative to human albumin.

New artificial colloids can be divided into two groups, either with or without oxygen carrying properties. As examples given, two molecules of each group are described below.

Carboxymethyl starch (CMS) is a polyanionic starch which resembles human albumin with respect to its water binding capacities and is more hydrophilic than HES. It may exert a higher colloid-osmotic pressure (COP) and thus a higher volume effect than HES and is expected to be eliminated at a higher rate (Madjdpour et al., 2007). Thirty pigs received infusions of 20ml/kg of either CMS, HES or CM-HES (a combination of both) as a top-load infusion within 30 minutes. Besides other parameters, plasma concentrations, plasma molecular weight, haemoglobin, COP, and coagulation variables were measured for up to 20 hours. Plasma concentrations, molecular weight and COP were higher after infusion of CMS and CM-HES and the decrease of haemoglobin was more pronounced compared to HES. Factor VIII activity decreases were least after infusion of HES. The authors concluded that coagulation was more impaired after infusion of CMS and CM-HES than HES, and therefore it seems that the development of CMS will not be further pursued.

PEG-conjugated human albumin (PEG-HA) is a human albumin, which is surface decorated with PEG chains (Mw 5000 Da) through extension arm facilitated PEGylation. It yields similar oncotic properties as human albumin, but at much lower concentrations. Therefore, it is expected to act as a plasma expander at lower plasma concentrations than human albumin. It has a lower glomerular filtration rate and a diminished proteolysis than human albumin.

Martini et al. (2008) et al compared PEG-HA (with 6 PEG chains) with tetrastarch in a severe haemorrhagic shock model in rats. After an initial haemodilution of 50 % exchange of blood volume with PEG-HA or HES, animals were subject of a 60 % haemorrhage and observed for another hour in shock. The results are quite impressing as all animals of the PEG-HA group survived the full procedure, while all animals in the tetrastarch group already died during the haemorrhage phase.

PEG-conjugated recombinant human albumin incorporating heme (PEG (HSA-FeP)) exhibits similar oxygen binding affinity as red blood cells. PEGylation significantly improves circulating half-life and also the stability of the oxygenated complex.

Huang et al. (2006) carried out an extreme haemodilution (65% of blood volume) with

human albumin in rats, followed by a 30 % haemorrhage which was replaced by PEG (HSA-FeP), washed red blood cells or human albumin. Animals were observed for additional 120 minutes post haemorrhage. All animals receiving PEG (HSA-FeP) or red blood cells survived the procedures but all animals of the human albumin group died during the observation period. These results clearly demonstrates the potential role of PEG (HSA-FeP) as an oxygen carrying plasma expander.

During the last 20 years there were a lot of additional efforts to develop synthetic colloids with oxygen carrying properties as an alternative to human red blood cells. Based on haemoglobin derived from human, bovine or recombinant sources, these colloid solutions (haemoglobin-based oxygen carriers, HBOCs) were extensively investigated in preclinical and clinical trials with the aim to replace blood loss. A tabular overview about all relevant projects is presented by Silverman and Weiskopf (2009).

Moore et al. (2009) investigated the clinical efficacy of a haemoglobin solution in trauma patients, the ultimate clinical scenario. At the scene patients received either Polyheme or a crystalloid solution. In the shock room additional Polyheme of up to 6 units was infused to the study group followed by blood, while patients of the control group received blood once available. The primary endpoint in this trial was the 30 days mortality rate. While the mortality rate in patients with blunt trauma was similar in both groups, patients with penetrating trauma had even a higher 30 days mortality rate in the Polyheme group. FDA eventually rejected the NDA-file of Polyheme. Therefore, benefits and risks of haemoglobin-based oxygen carriers are still under extensive discussion and most projects were recently terminated (Silverman and Weiskopf, 2009).

Summary and conclusion

Basic research of new synthetic colloids shows promising results, which need further confirmation in clinical trials. Colloid solutions based on haemoglobin are still associated with safety concerns in clinical trials and commercial availability is not to be expected in the next years.

For the time being, the third-generation HES solution (Voluven® 6% HES 130/0.4) is available in most parts of the world. As compared to other HES solutions, the key advantage of 6% HES 130/0.4 is an improved safety profile. This is reflected by a higher recommended maximum dose of 50 mL/kg/day, which offers a higher flexibility to the clinician in perioperative fluid management and provides an alternative to human albumin.

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