学術講演

New trends in plasma volume substitution

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Haemorrhage and other kind of hypovolaemia are frequent pathologies in emergency praehospital care, operating theatre and critical care medicine. In contrast to acute anaemia a lack of circulating blood volume is an emergency which must be treated immediately within short time. It causes tissue malperfusion – e.g. in the splanchnic region – which may lead to increased morbidity and mortality by triggering systemic inflammatory response syndrome (SIRS) and multi-organ dysfunction syndrome (MODS). A MODS finally determines the outcome of the patient.

The old controversy crystalloids only or combined with colloids for volume resuscitation is still going on: Several meta-analyses have not been able to reveal an advantage of either regimen [3)7)8)] But, the underlying studies included different types of colloids and the primary outcome measures did not comply with the objectives of the meta-analyses. So the meta-analyses` result is of quite questionable value. As with crystalloids five fold the volume demand has to be infused within short (extravasation!), this regimen has its clear practical limits in acute situations. Aside it leads to significant tissue oedema and increase in diffusion distances. Recent controlled prospective studies have proven modern colloids offering clear benefit to patients with hypovolaemia under the premise of correct application (combined with crystalloids 1:1 to 1:4). This acknowledges numerous experimental data from animal trials.

Small volume resuscitation (SVR) – i.e. the infusion of a small amount of a hyperosmotic-hyperoncotic colloid solution - in acute trauma with hypovolaemic shock is a safe mode of the immediate approach to correct an acutely reduced circulating blood volume[16)] Quick recovery and improvement can be reached not only for macrocirculation but especially for microcirculation even at a "point of no return" in shock. Already malfunctioning cells (endothelium, blood cells etc.) may become re-established. SVR may also prevent damage from ischemia-reperfusion-injury reducing capillary leakage and fluid sequestration into "third space". Aside of all SVR is capable to diminish the increase in intracranial pressure after e.g. trauma without significant rebound.[10)20)]

SVR always should be followed by a "conventional" infusion therapy to maintain a stable circulation. In other words, dehydration and the maintenance of fluid homoeostasis need crystalloid solutions; a lack of circulating blood volume needs additionally colloid infusion. The combined application of polysaccharidic colloids with crystalloids to maintain diuresis shall not be underestimated.

The choice of colloid depends firstly on the reliability of the volume effect, thereafter on welcome side effects and undesired actions of the substance considered.

Only polysaccharides preparations (Dextran, hydroxyethylated starch) offer reliable volume effectiveness. That of albumin is less and that of gelatine preparations is disappointing. Gelatine

preparations must be applied in multiple amounts of polysaccharide preparations to achieve the same volume effect, because they exert a high transcapillary escape rate and a quick elimination via the kidneys.

In central Europe hydroxyethylated starch preparations (HES) dominate the clinical practise today. Unlike other colloids the pharmacological properties of HES are less defined by the primary average molecular mass (Mw in the bottle) but predominantly by the *degree of substitution* (DS; % of glucose monomers bearing OH-groups;[1]) and the *pattern of substitution* (C2, C3 or C6 position of the glucose-monomers; PS). Both (DS >> PS) control the effect of degrading enzymes and the resulting in vivo molecular mass which plays the deciding role in therapeutic and side effects. In contrast to older HES types (with DS 0.5 and higher) the most recent HES130/0.4 has a low degree of substitution (0.4) but a high C_2C_6-pattern (9:1)[2]. HES130/0.4 results in a lower mean in-vivo-mass of HES- molecules but has the same reliable volume effect as HES200/0.5 (100% up to 4 hrs). Due to the improved degradability HES130/0.4 achieves enough smaller volume active molecules out of the bigger ones in vivo. Also the clearance from the body is superior to HES with DS of 0,5 and higher.

HES enhance remarkably microcirculation and supply of oxygen and substrate to the tissues. A diminution of whole blood viscosity by haemodilution due to reduction of haematocrit as well as a reduction of increased plasma viscosity is important. While all dextran preparations increase plasma viscosity, which has been appreciated by certain authors in the past (Messmer, Krieter, Intaglietta), all HES preparations decrease it depending on the DS (0.4>0.5>0.62>0.7-0.9) being considered to be useful by others (Ehrly, Kiesewetter, Pilgramm, Landgraf). The latter could be proven in patients when the blood driving forced are reduced, e.g. in occlusive arterial disease [9)2)] Actual studies demonstrate e.g. a significant and prolonged increase of microcirculation and tissue pO_2 in humans after HES in general. The effect of HES130/0.4 was superior to all other types of HES (200/0.5, 70/0.5) and more sustained. [13)23)]

Over-activation of mediator cascades and leukocyte sticking leading to microcirculatory breakdown are key attitudes of SIRS, sepsis or ischemia-reperfusion-injury. Numerous publications revealed that (only) polysaccharidic colloids give a certain protection against these pathophysiologies. While gelatines even worsen the situation [1], dextrans and HES hinder overactive mediators e.g. IL-6[21], IL-8, IL-10, p-Selectin, e-Selectin, s-ICAM-1and s-VCAM-1[4)6)14)21)] A reduction of tissue damage, of half-viable cells surrounding infarctions and of fluid extravasation can be observed in the presence of all kind of HES in various organs [19;26;27]. Less inflammation, less fluid sequestration into interstitium, better haemodynamics and better pulmonary gas exchange are factors which may improve patient outcome[1)5)17)18)]

Among adverse reactions of colloids the rate of anaphylactoid reactions is crucial, as they may be life threatening or fatal. Gelatines and dextrans (even under protection with hapten dextran) elicit anaphylactoid reactions in a very high rate (all degrees of severity: 0,35 rsp. 0,27%; severe degrees 0,06 rsp 0,05%). This is nowadays not acceptable anymore. Modern hydroxyethylated starch solutions in contrast (Pentastarch HES200/0.5 and Tetrastarch HES130/0.4) are well tolerated (0,06%; severe 0,02%) - even better than albumin preparations (0,1%; severe 0,03%) [15)]

Haemostasis is influenced by colloids in several ways. Haemodilution already at minor degrees leads to improved microcirculatory perfusion

[1] The higher DS or PS the slower and more incomplete the enzymatic degradation

[2] DS overweighs PS on the sum effect

resulting in visible "oozing" at the operation site often misinterpreted by surgeons as "coagulation failure". At higher degrees all colloids lead to unspecific dilution of all coagulation factors and cells but. Aside colloids may specifically affect haemostasis by influences on factor VIII qualities, Glycoprotein receptor functionality (GP IIb/III3a), fibronectin, adhesion molecules and receptors as well as platelet function. Generally all these effects parallel quantity and in vivo molecular mass[25] of the colloid aside from the type. Dextran preparations inhibit very strongly haemostasis followed by older HES types with high DS in quite a distance. This brought daily maximum dosage limits by the drug supervising authorities. Due to the optimised *intravital* molecular mass Tetrastarch keeps the primary and the secondary haemostasis - aside from dilutional effects - nearly "untouched". The effects of Tetrastarch parallel those of gelatines being measurable[24] but mostly judged as non important. Therefore the daily dosage limit of HES130/0.4 is considerably higher (3g /kg⁻/BW/day⁻) than that of other types HES or dextrans (1.5-2.0g rsp. 1.2g). Only HES130/0.4 is suitable to be used alone for volume substitution until reaching the individual transfusion trigger. In praehospital emergency setting and dramatic loss of intravasal volume such dosage limitations need not to be obeyed. Recent research focussed the composition of the HES solute (mostly NaCl 0.9%). Because of the lack of calcium normal saline was accused amongst others to be inferior to a balanced electrolyte solution regarding coagulation.[11]

Impairment of organ function after application of various colloids must be concerned. Renal failure has been described after all colloids inclusive albumin. Most cases developed after colloid infusion in dehydrated individuals without concomitant hydration by crystalloid solutions. For polysaccharides it has been clarified that there is no real nephro-toxic effect but in such cases an increase in viscosity of plasma and consequently of primary urine. Additionally - driven by the dehydration - water resorption in renal tubuli creates a lack of solute and makes the urine sludgy and worse flowing. A natural reuptake of the oncotic active molecules through the tubular cells – normally focussed to endogenous proteins - make them ballooning by lysosomal vacuoles containing colloid and narrowing the renal canals. Histologically this has been described as "osmotic nephrosis like lesions" found after dextran and HES preparations but also after gelatine and albumin. This all together may lead to a functional oligo-/anuria. but not to a real toxic damage. After rehydration and in less frequent cases after intermediate removal of the colloid by haemofiltration urinary output restarts. As tubular cells´ lysosomes own a low content of glycosidases polysaccharides are digested only slowly. Obviously the degradability of a colloid is crucial and explains why dextrans and old HES types with higher DS are less suitable in this context.

The uptake into and residence in mononuclear phagocytising cells (MPS) is a feature of all hydrocolloids. MPS consist e.g. from macrophages, cells of the skin, glious cells, von Kupffer´s cells etc. While dextrans and gelatines are only shortly residing, HES may persist there for longer times although in small quantities. The higher the DS the longer the persistence of HES in the body. This parallels the plasmatic accumulation of each preparation after repeated infusion. After usual clinical dosages our working group could detect Hetastarch HES 450/0.7 up to 54 months and Pentastarch HES 200/0.5 up to 35 month after infusion e.g. in cells of the skin. This may explain why pruritus after HES – which dosage dependent has been associated with the tissue uptake of HES - may endure so long after application[22] Due to the facilitated elimination the uptake of HES130/0.4 into tissues is much shorter than after Pentastarch or Hetastarch. After 12.6 g/kg over 18 days at day 52 after last infusion radioactive labelled HES 130/0.4 was detectable in amounts of only 25% compared to HES

200/0.5. [2] This may be a real advantage especially in critical care and chronic hemodilution therapy, where sometimes patients need quite high total dosages.

In summary the ideal plasma substitute has not been found to date, but HES130/0.4 actually exhibits to be the best compromise. Therefore it can be considered the colloid of choice in many medical disciplines at present.

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