Introduction

Appropriate fluid replacement is essential for safety and the reduction of morbidity and mortality in the perioperative period. Hypovolemia is the most common cause of circulatory failure in children and can lead to critical tissue perfusion. Unlike crystalloids, colloids may be used to rapidly treat or prevent hypovolemia with the advantage of markedly reducing the total volume of the administered infusion. Optimizing the circulating volume by targeting the use of colloids to maximize stroke volume with avoidance of crystalloid overload has evolved in adults and led to a new interest in colloids [1]. Prolonged intravascular half-life and the preservation or enhancement of colloid osmotic pressure (COP) are among the reasons why colloids are now widely used in adults and children [2]. However, in contrast to crystalloids, colloids have been reported to induce adverse effects that are specific for each compound. These include anaphylactoid reactions, coagulation disorders, acute renal failure, liver failure, and pruritus [2,3**].

In children, albumin has been regarded as the gold standard for maintaining adequate COP and thereby minimizing edema formation [4,5,6*], but its use has been limited by increasing costs. For this reason, synthetic colloids are now more frequently used with each presenting unique physicochemical characteristics that determine their likely efficacy and adverse effect profile [7]. The development of third-generation hydroxyethyl starch (HES) preparations with a lower incidence of adverse reactions has added to the debate regarding the selection of the optimal colloid for use in children. This review aims to address recent findings related to intravenous fluid management in children with a particular focus on their safety profile.

Purpose of review

Albumin has been regarded as the gold standard for maintaining adequate colloid osmotic pressure in children, but increased cost, the lack of clear-cut benefits for survival, and fear of transmission of unknown viruses have contributed to its replacement by hydroxyethyl starch and gelatin preparations. Each of the synthetic colloids has unique physicochemical characteristics that determine their likely efficacy and adverse effect profile. This review will examine the advantages and disadvantages of the use of different colloid solutions in children with a particular focus on their safety profile.

Recent findings

Dextrans are rarely used because of their negative effects on coagulation and potential for anaphylactic reactions. Gelatin and albumin have little effect on hemostasis, but the disadvantages of gelatin include its high anaphylactoid potential and limited beneficial volume effect. Tetra starches have significantly fewer adverse effects on coagulation and renal function than the older hydroxyethyl starches and are now approved for children. Dissolving tetra starches in a plasma-adapted, balanced solution rather than in saline further improves safety with regard to coagulation and acid–base balance.

Summary

Tetra starches offer the best currently available compromise between cost-effectiveness and safety profile in children with preexisting normal renal function and coagulation.

Keywords

children, coagulation, colloid, gelatin, human albumin, hydroxyethyl starch, renal function
excessive physiological effects of albumin have been described, including ligand binding and an antioxidant and anti-inflammatory action [8]. For many years, albumin 5% was considered the gold standard for plasma volume replacement in infants and children due to their physiological hypoproteinemia [4]. As an example, an improvement in the outcome of children with meningococcal sepsis was described with aggressive albumin-based fluid regimes [9]. However, in the adult literature, major controversy followed the publication of a systematic review suggesting that albumin decreased survival [10]. The Saline versus Albumin Fluid Evaluation (SAFE) study [11], a large randomized trial, was unable to show a difference between the use of crystalloid and albumin as a resuscitation fluid in critically ill patients, although albumin was shown to be well tolerated. Children were excluded from the SAFE trial and extrapolation of these results to the pediatric population remains, therefore, speculative. A meta-analysis focusing on the influence of albumin on mortality reported that the relative risk of death with albumin was 1.11 in all patient populations and 1.19 in a subgroup of neonates [12], thus suggesting no relevant difference between neonates and adults.

Concern has been expressed recently regarding the use of albumin, a plasma-derived product, and the potential risk of prior infection. However, studies addressing this issue are reassuring [13].

Albumin has been frequently used in pediatric cardiac surgery as a priming solution for cardiopulmonary bypass. Albumin is believed to help precoat the circuit, thereby delaying the absorption of circulating fibrinogen and reducing surface activation and adhesion of platelets. However, a recent study comparing the novel HES 6% 130/0.4 with 4% albumin in 119 children undergoing cardiac surgery with cardiopulmonary bypass reported a similar amount of blood loss with both priming solutions, but an increased need for allogenic blood transfusion in the albumin group [14*].

Other special indications for albumin administration are neonatal resuscitation and plasma exchange transfusion for polycythemia. Recent studies suggest that isotonic crystalloid solutions, rather than albumin, may be the fluid of choice as crystalloids are equally effective, safer, and less expensive than albumin or other colloids [15–17].

In summary, increased cost, lack of evidence of a clear-cut benefit for survival, the fear of transmitting unknown viruses, and the need for production in glass bottles have all contributed to the replacement of albumin as the first-choice colloid in children [6*,14*].

**Dextran**

Dextran solutions are neutral glucopolysaccharides dissolved in 0.9% saline. After infusion, dextran molecules less than 50 000 Da are excreted rapidly via the kidneys and a small amount is stored within the reticuloendothelial system and slowly degraded to CO₂ and water. Advantages of dextrans include their relatively low production costs and their good storage capacity at room temperature. Dextran solutions have an antithromboembolic effect through the reduction of the activity of factor VIII, von Willebrand factor (vWF), and the glycoprotein IIb/IIIa receptor. However, anaphylactoid reactions are a major risk as a consequence of preexisting endogenous antipolysaccharide antibodies, which crossreact with dextran molecules [18]. In addition, osmotic kidney failure and an alteration of erythrocyte cross-matching results, due to in-vivo and in-vitro erythrocyte aggregation, have been reported in adults [3**]. Owing to these multiple drug-related adverse effects and the high anaphylactoid potential, dextrans have been withdrawn from the market in various countries and their usage is declining worldwide [19].

**Gelatin**

Gelatin products are derived from bovine collagen and prepared as polydispersive solutions through multiple chemical modifications. They have a low molecular weight and, therefore, the volume effect (70–80%) and the duration of volume expansion (2–3 h) are modest, and repeated infusions are necessary to maintain adequate blood volume. In contrast to other synthetic colloids, the daily dose of gelatin solutions is not limited and they are of relatively low cost. Gelatin has been shown to be effective for fluid resuscitation in children with septic shock [20], dengue shock syndrome [21], and malaria [22]. The impact on the coagulation system appears to be limited owing to the dilution of coagulation factors, platelets, and red blood cells. Further, gelatin is considered to be well tolerated in terms of renal function. However, the rate of anaphylactoid reactions is the highest among all synthetic colloids and severe reactions occur in 0.05–0.1% of patients [3**].

**Hydroxyethyl starch**

HES solutions are derived from amylpectin, a highly branched polymer of glucose, obtained from waxy maize or potatoes. By their molecular structure, HESs are the first synthetic colloids with a configuration similar to the natural colloid albumin. HESs are generated by nucleophilic substitution of amylpectin to ethylene oxide. Available preparations are characterized by their concentration, molar substitution, and molecular weight. A higher molecular weight and a more extensive molar substitution result in a slower elimination. After infusion of HES, there is initially a rapid amylase-dependent
breakdown and subsequently renal excretion of up to 50% of the administered dose within 24 h [23]. First-generation HES preparations were manufactured with a high average molecular weight (450–650 kDa, heta-starch), but were soon found to have significant adverse effects related to their slow rate of degradation and the persistence of large fractions within the plasma and tissues [3**,23]. This led to interference with coagulation through binding to the vWF/factor VIII complex, hyper-oncotic renal failure due to accumulation of large molecules in plasma and renal tubules, and itching related to accumulation of starch particles in the reticuloendothelial system. Consequently, development was directed toward producing HES products with lower molar substitution. The second generation of HESs with a molar substitution of around 0.5 (pentastarch) led to fewer adverse effects. Finally, the third-generation HES preparations with a molar substitution of around 0.4 (tetra starch) present even more favorable physicochemical properties and are approved for use in children with a maximal daily dose of 50 ml kg\(^{-1}\). In a safety study on children, HES 130/0.42 did not induce serious adverse effects such as anaphylactoid reactions, renal failure, or clotting disorder [24*]. A randomized trial on infants undergoing non-cardiac surgery to compare HES 130/0.4 with albumin 5% reported no difference in perioperative stabilization of hemodynamic parameters, coagulation parameters, blood gas analyses, or other laboratory values [6*]. A further study showed no difference in plasma volume expansion in 26 hypotensive neonates with low cardiac output receiving 6% HES 200/0.5, albumin 5%, or isotonic saline [25]. In addition, there were no adverse effects related to fluid resuscitation, and none of the infants in the HES group exhibited intraventricular hemorrhage [25].

HES-induced pruritus has been reported in adults, particularly with the older HES compounds that undergo very slow degradation. Experimental and clinical studies with tetrastarch in volunteers suggested that tissue accumulation was minimal with the more recent products [2,26,27]. The currently available literature does not provide any evidence for the potential of the tetrastarches to accumulate in the tissues, but studies addressing this issue in the pediatric population are lacking.

**Coagulation**

All intravenous fluids provoke a dilution coagulopathy and colloids specifically interact with the coagulation system. The hemostatic system in infants displays some differences compared with adults. Principal age-related differences concern vitamin K-dependent coagulation factors and anticoagulatory proteins; at birth, these are present at about 50% of adult values and they gradually increase to about 80% during the first 6 months. Fibrinogen and coagulation factors V, VIII, XIII, and vWF are also decreased during the first 2 months, thus making neonates and infants particularly vulnerable to alteration of hemostasis induced by colloids.

The colloid-specific effects on coagulation are acquired von Willebrand syndrome, inhibition of platelet function, and fibrin polymerization. Dextran are potent anticoagulants and have platelet-inhibiting effects. Albumin and gelatin have little effect on hemostasis, besides their hemodilutional effect. Gelatin may disturb clot architecture and mechanics by interfering with polymerization of fibrin monomers [28,29]. HES solutions impair coagulation through a reduction in factor VIII activity, vWF antigen concentration, and factor VIII-related ristocetin co-factor, with the last leading to decreased platelet adhesion [30]. The most pronounced anticoagulant effects are found with high molecular weight starches with high molar substitution. Tetrastarches have been developed to minimize the impact on platelet function and coagulation. An extensive review of the effect of HESs on coagulation in adults concluded that the tetra starches were substantially safer than the older starches in terms of coagulation effects and their usage was associated with a significant reduction in blood loss compared with HESs with a higher molar substitution [31].

A recent study on infants and toddlers (3–15 kg) compared the impact of 15 ml kg\(^{-1}\) 6% HES 130/0.4, albumin, or gelatin on hemostasis [5]. For all tested colloids, thrombelastographic parameters and routine coagulation tests were significantly altered from baseline values. These changes were very similar for albumin and gelatin, but significantly more pronounced following HES. However, the study was not powered to detect differences in blood loss or transfusion requirements. By contrast, a more recent clinical trial reported on alterations in thrombelastographic parameters in children receiving HES 130/0.42 or gelatin [32*]. With both solutions, mean values of the different thrombelastographic parameters remained within normal ranges [32*]. Considering these possible alterations in clot formation, it is important to point out that blood loss was comparable following the administration of albumin or tetrastarch for fluid replacement in children undergoing noncardiac surgery [6*]. In children undergoing cardiac surgery, transfusion requirements were evaluated after 10 ml kg\(^{-1}\) of fresh frozen plasma or HES 130/0.4. The HES group showed a significantly prolonged international normalized ratio, but transfusion requirements and partial thromboplastin time values were comparable in the two groups [33].

Recently, tetrastarches have become available in a plasma-adapted, balanced electrolyte solution with a physiological electrolyte pattern and acetate as bicarbonate precursor. There is accumulating evidence that
balanced HES preparations may offer some advantages on hemostasis. An in-vitro study showed fewer deleterious effects on thrombelastographic data and platelet aggregation than a saline HES preparation [34]. The balanced, but not the nonbalanced, HES preparation increased the expression of activated platelet GP Ib/IIa induced by adenosine-5'-diphosphate, thus indicating improved hemostasis [23,35].

To increase our knowledge of the influence of the interaction of the tetrastarches on coagulation in children, further studies with a special focus on blood loss and transfusion requirements are necessary. It would also be of interest to investigate the impact of high amounts of fluids on the incidence of adverse effects.

Renal function
As all synthetic colloids are eliminated primarily via the kidney, impaired renal function is expected to occur as a result of colloid accumulation. The administration of hyperoncotic colloids in hypovolemic patients may induce hyperviscosity of the urine and lead to subsequent renal failure. Although older HES solutions have been consistently incriminated in the impairment of renal function, there are no reports yet on such effects with tetrastarches when administered in patients with normal renal function [3**]. However, the impact of tetrastarches on renal function in septic patients is still under debate [36]. By contrast to the adult literature, there are only a few studies assessing renal function after administration of different colloids in children. A study on 13 healthy neonates found that 10 ml kg⁻¹ HES 200/0.5 did not increase serum creatinine [27]. Serum creatinine was not altered either in recent pediatric studies using tetrastarches [6*,24**]. However, studies investigating the impact of tetrastarch in children with preexisting impaired renal function are still lacking.

Allergic reactions
All colloids have the potential to induce anaphylactic/anaphylactoid reactions. A study on adult patients reported a higher incidence of allergic reactions with gelatin (frequency, 0.345%) and dextran (frequency, 0.273%) than with albumin (0.099%) and HES (0.058%) [37]. In a large randomized trial comparing dextran 70, 6% HES, and Ringer’s lactate solution in 383 children with dengue shock syndrome, 8% of children in the dextran group presented adverse reactions such as fever, whereas only one child who received starch had an urticarial rash without fever [18].

It is important to highlight that none of the clinical trials using tetrastarches in children has reported on the occurrence of allergic reactions. Furthermore, a recent meta-analysis including 19 trials reported no allergic reactions with colloid solutions used for fluid resuscitation in adults [38].

Metabolic changes
As albumin, HES, and gelatins are dissolved in saline solutions, the use of high amounts of these colloids may lead to hyperchloremic acidosis. A recent study on children scheduled for major surgery investigated the effects of 6% HES 130/0.4 or gelatin 4% on acid–base equilibrium [39]. Both molecules were shown to induce a significant increase in plasma chloride concentration. The anion gap decreased significantly with the electroneutral HES, but remained unchanged after the negatively charged gelatin infusion. Therefore, consideration should be given to synthetic colloids as a cause of alteration of anion gap in metabolic acidosis.

Finally, the plasma-adapted, balanced tetrastarch solution with a physiological electrolyte pattern was compared with isotonic saline HES and balanced HES demonstrated beneficial effects on acid–base status in both adults and children [40,41*]. In specific settings, the use of balanced electrolyte HES may prevent an increase in chloride concentration and a decrease in bicarbonate and base excess that may occur with isotonic saline HES.

Conclusion
Whether the choice of a plasma substitute can be life-saving is still a matter of debate. For rational decision-making in fluid management, an improved understanding of the impact of the different products on hemostasis is necessary. In addition, volume-expanding efficacy, safety index, and individual adverse effect profile need to be considered. Albumin can no longer be considered as the first-choice colloid for volume replacement in children. Among the currently available synthetic colloids, dextrans appear to have the poorest risk/benefit ratio owing to their relevant anaphylactoid potential, risk of renal failure, and, perhaps most importantly, their major impact on hemostasis. Disadvantages of gelatins include a high anaphylactoid potential and a limited beneficial volume effect when compared with HES. The development of tetrastarches has led to the implementation of these solutions in many institutions. Based on the currently available evidence, tetrastarches offer the best cost-effective and safety profile in children of all ages with normal renal function and coagulation status. Modern HES preparations that are plasma-adapted, balanced solutions may further improve safety with regard to coagulation and acid–base balance.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 433–434).


An interesting review of synthetic colloids in adults with a special focus on pharmacokinetics and dynamics, as well as colloid-induced adverse effects.


This study showed that HES 130/0.4 and human albumin 5% were effective for hemodynamic stabilization in noncardiac surgery on young infants with no adverse impact on coagulation or other safety parameters.


A clinical study on 316 children demonstrated that hydroxyethyl starch appears to be well tolerated and effective even in neonates and small children.


This clinical trial demonstrates that HES 130/0.42 and gelatin had comparable effects on coagulation at a dose of 10 ml kg\(^{-1}\) monitored by thrombelastography and the values remained in the normal range. The induced alteration of coagulation is only because of hemodilution.


This study found fewer infusion-related acid-base and electrolyte alterations in a balanced HES solution than in HES in isotonic saline.


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