Are colloid solutions essential for the treatment of pediatric trauma or burn patients?

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Summary

Colloid solutions are widely used for fluid resuscitation including children, although there is an ongoing controversy concerning their actual use in children. To support the Expert Committee on the Selection and Use of Essential Medicines in their decision whether to include a colloid solution in the Essential Medicines List for Children this review of the literature was conducted. No high-level evidence studies could be identified to answer the question. From the available evidence it appears that colloid solutions do not have a proven benefit compared to crystalloid solutions. Because colloids are more expensive and more likely to cause adverse effects an inclusion may not be recommended.
Objective

The objective of this review is to examine the available scientific evidence for use of Colloids in children to enable informed decision whether colloids should be included in the Essential Medicine List for Children (EMLc) and if yes, which one should be. The review will focus primarily on trauma and burns as indications for the use of colloids in children.

Currently only Dextran 70 is listed on the adult list.

Background

Injury and violence are major killers of children throughout the world, responsible for over 900,000 deaths in children and young people under the age of 18 years each year (1). In 2004, 38,8 per 100,000 children worldwide died from unintentional injuries and nearly 96,000 children globally died from burns (2). Road traffic injury is the second leading cause of death in children between 1 and 14 years and the leading cause of death in the age group between 15 and 18 (2). Non-fatal falls are the most common reason for children to be taken to an emergency room (1).

Approximately 30-40% of trauma mortality can be attributed to hemorrhage (3). Even if most of the deaths due to hemorrhage occur in the pre-hospital phase, the main reasons for early deaths in hospital yet are continued hemorrhage, coagulopathy and incomplete resuscitation (3). So it is obvious that fluid therapy plays an important role in the treatment of trauma patients with substantial blood loss as well as in patients with burn injuries and remains the cornerstone in resuscitation. But there is an ongoing controversy concerning the kind of fluid to be used in treatment of hypovolemic patients.

Main available options for fluid resuscitation are either crystalloid or colloid solutions. If more than 40% of blood volume is lost blood transfusion is recommended additionally because these fluids are helpful to maintain tissue oxygenation (4).

In contrast to commonly used crystalloid solutions like Normal Saline or Ringer-Lactate, colloid solutions contain molecules which cannot penetrate the intact cell wall and therefore cause an oncotic gradient that attracts additional interstitial fluid into the vessels. The type of molecule is different for the different colloid solutions but is always of biological origin.
The most commonly used colloids are albumin, which is the only natural one, others include nonprotein colloids like hydroxyethyl starches (HES), dextrans and gelatins.

Albumin is a naturally occurring protein in the human organism with a molecular weight of 69 kDa. There is no limitation to the maximum daily dose for albumin. It may cause hypersensitivity and allergic reactions and the transfer of infection by administration of albumin is not totally excluded (5).

Hydroxyethyl starches (HES) are high polymeric glucose compounds. They are available in different concentrations with molecular weights from 70 kDa to 670 kDa. There are other determinants for their physicochemical characteristics like concentration, degree of substitution and C2/C6 ratio. The maximum dose that can be administered per day depends on the type of HES (5).

Dextran is a glucose polymer which is available either as a 6% iso-oncotic solution or as a 10% hyper-oncotic solution with a molecular weight of 70 kDa respectively 40 kDa. The maximum recommended dosage of dextran is 1,5 g/kg/day, it has dose-dependent negative effects on hemostasis and may cause anaphylactic reactions (5).

Gelatin is made of bovine collagen and has a molecular weight of 30-35 kDa. There is no maximum limit of dose, anaphylactic reactions may occur following its administration (5).

A recent Cochrane review did not find evidence to prove superiority of any one colloid solution over others in terms of effectiveness and safety (6).

**Search methods**

An online database search in the Cochrane library and Pubmed for articles published from 1950 to present was conducted using the search terms colloids, pediatric and trauma (see appendix 1 for detailed search strategy). The search was complemented with the use of other resources, such as trauma care protocols, Google scholar and various national guidelines available on the web.

The identified abstracts were screened and full text versions of possibly relevant articles were obtained. Reference lists of articles were screened to identify additional sources.

Criteria for final inclusion of an article for this review were:
• English or German language article
• Human subjects
• Study referring to children with traumatic or burn injuries
• The treatment group received a colloid solution of any volume for any duration at any time

Accordingly criteria for exclusion were:

• Non English or German language article
• Animal study
• Study targeting pediatric population with conditions other than traumatic or burn injury
• Study including pediatric populations, but pediatric specific data not reported separately
• Individual case report

Results
The search identified 457 articles of which 20 were thought to be relevant after abstract review. After review of the full text versions the following 14 articles qualified to be included in the review. They consist of reviews, guidelines and expert opinion based on evidence. No randomized controlled trial to answer the question was identified.

See tables 1 and 2 for included and excluded studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication type</th>
<th>Population</th>
<th>Colloid</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocks A et al.</td>
<td>Retrospective review</td>
<td>Pediatric burn patients (burned BSA &gt;5%) admitted to ICU between 01/90 and 12/96</td>
<td>Albumin</td>
<td>Very low</td>
</tr>
<tr>
<td>Faraklas I et al.</td>
<td>Retrospective review</td>
<td>Pediatric patients admitted to a burn center because of acute burns &gt;15% BSA and survived at least 72 h between 01/04 and 05/09</td>
<td>Albumin</td>
<td>Very low</td>
</tr>
<tr>
<td>Author</td>
<td>Reason for exclusion</td>
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<tr>
<td>Spelten O et al. (20)</td>
<td>Does not compare treatment options for children</td>
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<tr>
<td>James MFM (21)</td>
<td>Does not refer to children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wade CE et al. (22)</td>
<td>Does not refer to children</td>
<td></td>
<td></td>
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<tr>
<td>Akech S et al. (23)</td>
<td>Does not refer to trauma or burns</td>
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<tr>
<td>Endorf FW et al. (24)</td>
<td>Does not refer to children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bailey AG et al. (25)</td>
<td>Does not refer to trauma or burns</td>
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</tbody>
</table>

Table 2: Excluded Studies
Efficacy

No high-level evidence studies could be identified for the use of colloids in children with traumatic injuries or burns.

All articles reviewed indicated that there is very little evidence available currently for or against the use of colloids in children. Especially randomized controlled trails are not available to support any evidence for use of colloids in children. Some authors therefore additionally referred to the available evidence for adults stating that this is scarce too.

Overall only three of the fourteen included articles recommended the use of a colloid solution.

Faraklas et al. showed that through administration of albumin in pediatric burn patients the Input/Output ratio could be normalized quickly which they thought may have the potential of overcoming the problem of “fluid creep”. In their study they analyzed 53 patients resuscitated either with crystalloids alone or with additional use of albumin. Certainly they qualify that results should be looked upon critically because the patients who received albumin were in general more severely injured and the decision to use colloids additionally was not made purely objectively (7).

Walker GM on behalf of the Care of Burns in Scotland network (COBIS) recommended in their guideline for treatment of children with burn injuries to use crystalloid solutions for the first 8 hours and albumin for the following 16 hours. To formulate their recommendations a group of experts representing the Scottish centers that are involved in treatment of children with burn injuries assessed existing guidelines and reviewed the available evidence. Despite they stated that the evidence in general is scarce they agreed on the inclusion of a colloid in their treatment recommendations (8).

Hennenberger et al. described a formula they had developed which combines Ringer-Lactate and Dextran for the resuscitation of children with burns and allows the additional use of albumin. Evidence for the usefulness of their formula was not presented (9).

Several other authors stated that colloids should not be used as general baseline therapy but could be considered for some special indications.

Schellinger et al. representing the German Society for Pediatric Surgery as leading editor on behalf of several professional German medical societies issued a consensus-based guideline on the treatment of
children with burn injuries. In these guidelines the use of crystalloid solutions was recommended for the first 24 hours, colloids should be used in prolonged shock and under strict indications only (10).

Because of the small number of pediatric publications the evidence-based guideline of the Dutch Pediatric Society by Boluyt et al. considered adult studies as well and concluded that the first choice fluid for initial resuscitation should be isotonic saline. They added that it is possible to use a synthetic colloid when large amounts of fluids are needed (11).

Schulman et al. stated that no clear evidence for the use of colloids is available and that in their opinion it should be an expert clinical judgment if colloids are needed in individual cases. The article did not present any clear evidence (12).

In a recent review of the literature Pietrini et al. had a closer look on pharmacodynamics of colloids, especially Hydroxyethyl starch (HES) solutions, and due to limited data they concluded that HES may indeed be considered for plasma volume restoration in children but further clinical trials were needed to assess if it is actually beneficial in the treatment of hypovolemic children (13).

Likewise there were recommendations by some authors which did not include the use of colloids.

Turner et al. recommended the administration of a bolus of 20 ml/kg normal saline which may be repeated once. In case of persistent signs of shock administration of 10 ml/kg packed red blood cells was recommended (14). This recommendation was in line with the recommendations of the Advanced Trauma Life Support (ATLS) protocol of the American College of Surgeons (4) and the Pediatric Trauma Care Guidelines of the University of Kentucky (15) however no evidence was named in all of these publications.

Dehmer et al. proposed principles for a pediatric massive transfusion protocol. In their review of the literature no specific data supporting the use of colloids were identified, they stressed that mechanisms causing adverse effects have to be considered (16).

Finally there are authors who were not making a recommendation at all.

Cocks et al. tested their colloid-based fluid formula for resuscitation in children with burns by analyzing 85 pediatric patients (with >5% BSA burned) who were admitted to their ICU. Patients were divided into two groups. Group one was resuscitated according to the colloid-based formula used in their hospital whereas the second group included patients who were initially resuscitated in other hospitals with
mixed crystalloids and colloids formulas before they were transferred to their hospital. They found that patients resuscitated with their formula were consistently underestimated concerning fluid requirements and no significant difference in adverse effects could be seen between the two groups. Overall they were not able to recommend a definite approach to the fluid resuscitation in pediatric burn patients (17).

Kallen et al. merely stated that it is imperative to substitute lost volume however recommendations as to which solution should be used were not made (18).

In their review Kissoon et al. were not able to identify a clear benefit of one fluid over the other. The review referred to critically ill patients with all kinds of etiology and the studied patient population included patients other than children. It was concluded that the choice of fluid depended upon personal preference, purported physiologic benefits and practical considerations (19).

**Safety**

For crystalloids like Ringer-lactate and Normal saline 0,9% no side effects are described when used in accordance with regulations.

Possible side effects of all colloids are hypersensitivity and anaphylactic reactions up to anaphylactic shock and affection of coagulation. This applies especially to HES and dextran. HES may also cause pruritus which is often refractory to treatment (5,26,27).

**Costs**

Colloid solutions are much more expensive than crystalloid fluids. The prices of common colloid and crystalloid solutions according to WHO International Drug Price Indicator Guide, 2010 Edition can be found in table 3.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Median price/ml buyer in USD</th>
<th>Median price/ml supplier in USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>0,5980</td>
<td>0,7500</td>
</tr>
<tr>
<td>Dextran 70</td>
<td>Not stated</td>
<td>0,0105</td>
</tr>
<tr>
<td>Polygeline 3,5%</td>
<td>0,0272</td>
<td>0,0098</td>
</tr>
<tr>
<td>Normal saline 0,9%</td>
<td>0,0009</td>
<td>0,0009</td>
</tr>
<tr>
<td>Ringer’s lactate</td>
<td>0,0009</td>
<td>0,0009</td>
</tr>
</tbody>
</table>

Table 3: Prices of solutions according to WHO

Conclusion

There is very little evidence to support the use of colloids in children with traumatic injury or burns. Much of the available evidence is not specifically for children and not derived from randomized, placebo-controlled trials.

From the evidence identified, however, it appears that colloids do not have a proven benefit compared to crystalloids. This view is also supported by a recent Cochrane review addressing the question, for all indications and all types of colloids in adults (28). Colloids are more expensive and are more likely to cause adverse effects. Therefore they may not be considered essential for the treatment of children with traumatic injury or burns.

There may be other legitimate indications that may justify inclusion of colloids on the essential medicine list for children but considering the indications of trauma and burns we conclude that there is not sufficient evidence to recommend the inclusion of any colloid in the Essential Medicines List for Children.

Other Indications

Other possible indications for colloids that were not further considered in this review may be Sepsis/septic shock, Malaria and Dengue, Dialysis, Chronic liver disease and Heart surgery.
References

(4) American College of Surgeons Committee on Trauma “Advanced Trauma Life Support for Doctors” 8th Edition 2008
(6) Bunn F et al. “Colloid solutions for fluid resuscitation” Cochrane Database of Systematic Reviews 2012, Issue 7
(7) Faraklas I et al. “Colloid normalizes resuscitation ratio in pediatric burns” J Burn Care Res. 2011 Jan-Feb;32(1):91-7
(14) Turner CLS et al. “Fluid therapy in paediatric trauma” Trauma 2002; 4: 169-175
(15) Section of Pediatric Surgery, University of Kentucky “Pediatric Trauma Care Guidelines 2011” http://www.mc.uky.edu/traumaservices/PediatricTraumaCareGuidelines2011.pdf


(22) Wade CE et al. “Efficacy of hypertonic 7.5% saline and 6% dextran-70 in treating trauma: A meta-analysis of controlled clinical studies” Surgery 1997 Sep; 122(3):609-616


Appendix 1 (search terms)

Cochrane

Colloid* AND pediatr*

Colloid* AND children

“Dextran 70” AND pediatr*

“Dextran 70” AND children

Albumin AND children

Albumin AND pediatr*

HES AND children

HES AND pediatr*

Medline

Colloid* AND pediatr* AND trauma; limits: human, Language English or German

Colloid* AND children AND trauma; limits: human, Language English or German

Colloid* AND pediatr* AND resuscitation; limits: human, Language English or German

Colloid* AND children AND resuscitation; limits: human, Language English or German

“Dextran 70” AND pediatr* AND trauma; limits: human, Language English or German

“Dextran 70” AND children AND trauma; limits: human, Language English or German

Albumin AND pediatr* AND trauma; limits: human, Language English or German

Albumin AND children AND trauma; limits: human, Language English or German

HES AND pediatr* AND trauma; limits: human, Language English or German

HES AND children AND trauma; limits: human, Language English or German