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REVIEW ARTICLE

Albumins in critically ill pediatric patients: a literature review

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Abstract

Introduction and Objectives: This review aims to evaluate the effectiveness of the use of human albumin in critically ill pediatric patients admitted to intensive care units. **Methods:** The research covered the following databases: Cochrane Library, LILACS, Medline (PubMed) and Uptodate, to May 2014. The publications were selected and submitted to critical reading by two independents researchers. The main outcomes were death and organ dysfunction. **Results and Conclusion:** The use of human albumin in critically ill children showed no benefit in reducing mortality and organ dysfunction compared to use of others volumetric expanders. For another outcomes, as time of permanence in intensive care unit and endotracheal intubation time, the albumin employment also was not superior.

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INTRODUCTION

Circulatory failure, especially due to hypovolemia, is an important cause of morbidity and mortality in children seeking emergency services. Children with more severe systemic infections may progress to circulatory failure (septic shock); patients with autoimmune disorders, pancreatitis, vasculitis, thromboembolism, burns, and surgery may also present systemic inflammatory response syndrome (SIRS), followed by shock and organ failure[1,2].

Early diagnosis of circulatory failure is essential to the initiation of early treatment with fluid administration[2-4]. While rapid actions for volume replacement are essential for the survival of pediatric patients, there is still discussion regarding the composition of the fluid to be administered: crystalloid solutions (e.g., saline solution) or colloid solutions (e.g., albumin). The results of controlled trials and systematic reviews do not indicate a reduction in important outcomes, such as mortality and organ dysfunction, with the use of colloids in these patients[5,6].

Children generally react to severe disease with decreased cardiac output and increased peripheral resistance ("cold shock"); in adults, there is a decrease in peripheral resistance ("hot shock"). As children have a larger body surface, they present a more significant net loss than adults. Observations like these contribute to the direct extrapolation of findings from clinical studies in adults to pediatric patients[7].

It is therefore necessary to review the scientific literature in order to find consistent evidence that better clarifies the therapeutic role of human albumin in hemodynamically unstable patients.

This review aimed to assess the effectiveness of the introduction of human albumin in pediatric critically ill patients admitted to intensive care units with shock, sepsis, or hypovolemia, pre- or postoperatively.

METHODS

The following databases were searched: Cochrane Library, LILACS, Medline (via PubMed). The search used the following descriptors (MeSH terms): *albumins, critically illness, mortality, child.* For PubMed, the following search strategy was adopted: *(("Critical Illness"[Mesh]) AND "Albumins"[Mesh]) AND "Mortality"[Mesh]* e *("Albumins"[Mesh]) AND "Child"[Mesh] Filters: Randomized Controlled Trial, Guideline, Systematic Reviews, Meta-Analysis*. The www.uptodate.com database was also accessed, to search for references to primary articles that could not be found in the aforementioned databases.

The publications were selected according to the following criteria: systematic reviews of randomized controlled trials and cohort studies; or randomized clinical trials and cohorts as primary studies that evaluated the use of human albumin intravenously in critically ill hemodynamically unstable children, compared with the use of other colloid or crystalloid solutions, supportive treatment, and standard treatment for the clinical condition in question. Articles published in English, French, Spanish, and Portuguese were selected.

The main outcomes studied were death and organ dysfunction. The following secondary outcomes were also assessed: length of stay in the intensive care unit; total volume of infusion or replacement of colloid and crystalloid solutions and transfused blood; time of tracheal intubation; weight gain; and results of additional tests. The titles and abstracts of all the retrieved studies were reviewed by two independent reviewers. Disagreements were resolved by a third reviewer. The search included all articles published up to May 2015.

The internal validity, i.e., the presence of biases in each publication, was evaluated with the use of scores validated for this purpose[8-10].

RESULTS

Seventeen studies that met the inclusion criteria were initially retrieved, of which six were selected. The criteria for the selection of the studies included in the review are described in Figure 1.

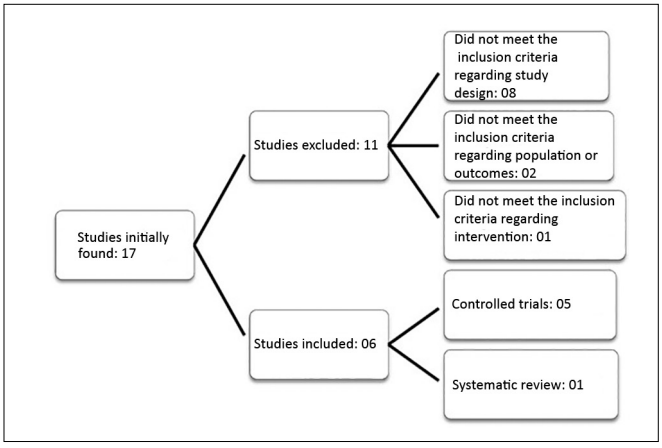

Figure 1. Selection of the studies included in the review.

The internal validity of the selected items is summarized in Table 1.

Table 2 summarizes the included studies, highlighting the designs and the numerical results of each study. Table 3 lists the studies excluded from the review, as well as the reasons for the non-inclusion.

Due to the large number of outcomes studied in the works selected, the authors chose to analyze and synthesize the most relevant information from a clinical standpoint, i.e., mortality, organ dysfunction, length of stay in the ICU, and intubation time.[11-14]

Mortality

A randomized clinical trial[11] that evaluated the mortality rate in children with and without severe hypotension,

Table 1. Internal validity of the included studies

Reference	Internal Validity
15	Adequate protection against biases.
16	The studies were selected and assessed by two independent researchers. Two studies did not have blinded allocation and were quasi-randomized; the other two studies were not double-blinded. The studies were heterogeneous, with methodological limitations and considerable risk of biases.
17	Adequate protection against biases.
18	Adequate protection against biases.
19	The study was not designed to assess safety. Adequate protection against biases.
20	There were no differences regarding the demographic characteristics of each group, but there were protocol breaches; in one case, the colloid "rescue therapy was administered prior to the study drug; and in two patients from the colloid "rescue therapy group, human albumin serum was administered before the maximum dose of the study drug had been reached.

Table 2. Characteristics and results of the included studies.

Ref. no.	Study Design	Population	Results
15	Controlled, multicenter randomized clinical trial.	Age: 2 months to 12 years; febrile disease complicate by alterations in consciousness and/or respiratory difficulties (A) without severe hypotension and (B) with severe hypotension.	Morte em 48h: (A): RR 1.44 saline solution in bolus *vs*. control (95% CI 1.09-1.90); RR 1.01 albumin bolus *vs*. saline bolus (95% CI 0.78-1.29); RR 1.45 for any bolus *vs*. control (IC95% 1.13-1.86). (B): RR 1.23 01 albumin bolus *vs*. saline bolus (95% CI 0.70-2.16); Neurological sequelae: 2.2% albumin bolus; 1.9% saline bolus, and 2% control group ($p = 0.92$).
16	Systematic review of controlled, randomized clinical trials	Age: 1 month to 12 years with severe infection.	Death in cases of malaria: (1) SSaline solution *vs*. albumin solution: lower mortality in the albumin group ($p = 0.013$) and in the group with severe malaria complicated with coma ($p = 0.002$); no difference in the cases without coma ($p = 0.7$). (2) Albumin *vs*. gelofusine: no difference in mortality in the albumin group ($p = 0.06$), only in comatose patients ($p = 0.04$). (3) 2% albumin *vs*. 16% gelofusine; OR 0.2 (95% CI, 0.05 to 0.83). Neurological sequelae: 7% albumin solution *vs*. 2% saline and 3% Gelofusine - absence of statistical significance reported, but *p* value or 95% CI not reported.
17	Controlled, double-blinded randomized clinical trial (the perfusionist was not blinded)	Infants and children up to 10 kg who underwent open heart surgery	Total volume infused (L) 8 ± 4.2 (range 3-17) Fresh frozen plasma *vs*. 6.1 ± 4.1 (range 2-16) Albumin ($p = 0.035$) Time to extubation: $p > 0.10$. Intensive Care Unit length of stay: $p > 0.10$. Same perioperative mortality in both groups.
18	Controlled, double-blinded randomized clinical trial.	Age three days to four years with less than 14kg submitted to heart surgery with cardiopulmonary bypass.	Time to extubation: $p = 0.463$ Intensive care unit length of stay: $p = 0.596$. Hospitalization time: $p = 0.698$. Mortality: 6.8% albumin group *vs*. 4.8% crystalloid group ($p > 0.05$).
19	Controlled, double-blinded randomized clinical trial	Age: 2 to 12 years submitted to elective surgery for congenital heart disease with cardiopulmonary bypass.	No significant differences found for the outcomes: mechanical ventilation, length of the time in the ICU, severe adverse effects with multiple organ failure - *p* value and CI not reported.
20	Controlled, double-blinded randomized clinical trial	Age one to 15.5 years, with moderate hypothermia, submitted to surgery for correction of congenital heart disease.	Volume of infusion: $p > 0.05$. Colloid infusion 24h after surgery: $p > 0.05$. Crystalloid infusion 24h after surgery: $p > 0.05$.

comparing volume replacement with saline solution, albumin, or without bolus (control), observed that 48-h mortality was higher for any type of bolus. Death within four weeks was also significantly higher in the group with bolus, regardless of the type of infusion used.

The systematic review[16] that evaluated children with severe infection did not have mortality as the primary outcome. However, in one study, the mortality rate was lower among the cases with coma in the group that received albumin than in the group that received saline solution; in cases

Table 3. Characteristics of the excluded studies.

Bibliographical reference	Reasons for non-inclusion
Roberts I, Blackhall K, Alderson P, Bunn F, Schierhout G. Human albumin solution for resuscitation and volume expansion in critically ill patients. Cochrane Database Syst Rev. 2011 Nov 9;(11):CD001208. doi: 10.1002/14651858.CD001208.pub4. Review. PubMed PMID: 22071799.	Study included in another selected review
Delaney AP, Dan A, McCaffrey J, Finfer S. The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta-analysis. Crit Care Med. 2011 Feb;39(2):386-91. doi: 10.1097/CCM.0b013e3181ffe217. Review. PubMed PMID: 21248514.	Study included in another selected review
Akech S, Gwer S, Idro R, Fegan G, Eziefula AC, Newton CR, et al. Volume expansion with albumin compared to gelofusine in children with severe malaria: results of a controlled trial. PLoS Clin Trials 2006;1:e21.	Study included in another selected review
Maitland K, Pamba A, English M, Peshu N, Marsh K, Newton C, Levin M. Randomized trial of volume expansion with albumin or saline in children with severe malaria: preliminary evidence of albumin benefit. Clin Infect Dis. 2005 Feb 15;40(4):538-45. Epub 2005 Jan 25. PubMed PMID: 15712076.	Study included in another selected review
Vincent JL, Navickis RJ, Wilkes MM. Morbidity in hospitalized patients receiving human albumin: a meta-analysis of randomized, controlled trials. Crit Care Med. 2004 Oct;32(10):2029-38. PubMed PMID: 15483411.	Study included in another selected review
Grundmann R, von Lehndorff C. [Indications for postoperative human albumin therapy in the intensive care unit-a prospective randomized study]. Langenbecks Arch Chir. 1986;367(4):235-46. German. PubMed PMID: 3528718.	Study in German
Offringa M, Gemke RJ, Henny CP. [Excess mortality in critically ill patients after treatment with human albumin]. Ned Tijdschr Geneeskd. 1998 Aug 15;142(33):1855-8. Dutch. PubMed PMID: 9856165.	Study in German
Hanart C, Khalife M, De Villé A, Otte F, De Hert S, Van der Linden P. Perioperative volume replacement in children undergoing cardiac surgery: albumin *versus* hydroxyethyl starch 130/0.4. Crit Care Med. 2009 Feb;37(2):696-701. doi: 10.1097/CCM.0b013e3181958c81. PubMed PMID: 19114887.	Study included in another selected review
Yu K, Liu Y, Hei F, Li J, Long C. Effect of different albumin concentrations in extracorporeal circuit prime on perioperative fluid status in young children. ASAIO J. 2008 Sep-Oct;54(5):463-6. doi: 10.1097/MAT.0b013e3181878631. PubMed PMID: 18812733.	Study assessed outcomes with different albumin doses, but did not compare with other kinds of fluid replacement.
Yap FH, Joynt GM, Buckley TA, Wong EL. Association of serum albumin concentration and mortality risk in critically ill patients. Anaesth Intensive Care. 2002 Apr;30(2):202-7. PubMed PMID: 12002929.	Study excluded individuals younger than 18 years
Russell JA, Navickis RJ, Wilkes MM. Albumin *versus* crystalloid for pump priming in cardiac surgery: meta-analysis of controlled trials. J Cardiothorac Vasc Anesth. 2004 Aug;18(4):429-37. PubMed PMID: 15365922.	Study included only one pediatric patient; the remaining patients were adults.

without coma, there was no significant difference between the albumin and saline groups. The same was observed in the albumin group compared with the Gelofusine group in two studies. Other articles that evaluated mortality showed no significant difference in the use of albumin compared to other volumetric expanders.

Another randomized clinical trial[17] that evaluated children undergoing cardiopulmonary bypass compared fluid resuscitation with albumin 5% or with one unit fresh frozen plasma (FFP) in the bypass prime. Perioperative mortality was described as similar between the groups, although the authors did not report p-values or 95% CI.

A different randomized clinical trial[18] that compared crystalloid and albumin in children undergoing heart surgery requiring cardiopulmonary bypass found no statistically significant differences in mortality between these groups.

Organ dysfunction

There was no significant difference in the appearance of neurological sequelae[15,16] or in the reduction of adverse effects, such as suspected pulmonary edema or increased intracranial pressure[15].

In the article[19] that compared the use of albumin with hydroxyethyl starch (6%) in children undergoing elective cardiac surgery, only the mean volume of colloidal solution and the supply of total protein were significantly higher in the latter group. Furthermore, a higher number of renal replacements and serious adverse effects with multiple organ failure were reported in the albumin group. Nonetheless, the study did not report values that would demonstrate that these results are statistically significant.

Length of stay in the ICU and duration of endotracheal intubation

Three studies[17-19] assessed length of stay in the ICU and duration of intubation as outcomes. None of these studies observed statistically significant differences in the groups receiving albumin or another volume expander.

DISCUSSION

Studies in adults have found no solid evidence to recommend the use of albumin in critically ill patients who need volume replacement, including patients with sepsis.

The lack of summarized data in pediatrics motivated the present systematic review, which included six articles from an initial selection of 17. Each article was critically read, to search for biases that would hinder their internal validity (Table 2). It was not possible to pool the results of the primary studies in a meta-analysis due to the heterogeneity observed among them-regarding the mode of administration of the solutions, patient age, or underlying clinical condition that led to the treatment.

CONCLUSIONS

From the summary of information collected, it can be concluded that there is an absence of solid evidence to indicate that the infusion of albumin (compared with crystalloid or other plasma expanders) can reduce the risk of mortality and organ dysfunction when used in the resuscitation of critically ill pediatric patients who are hemodynamically unstable[5,6,11-14].

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