Eur J Pediatr (1998) 157: 699–702

REVIEW

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Use and misuse of albumin infusions in neonatal care

Received and accepted: 30 April 1998

Abstract During the neonatal period, albumin infusions are administered in response to a variety of clinical scenarios. Review of currently available literature, however, demonstrates that crystalloid rather than colloid infusions should be used both to treat hypovolaemic hypotension and as the replacement fluid in a dilutional exchange. The role of an albumin infusion in ''treating'' metabolic acidosis needs further evaluation, but the practice of giving albumin to correct ''asymptomatic'' hypoalbuminaemia or at resuscitation should be discouraged.

Conclusion The neonatologist would be well advised, when reaching for an albumin infusion, to reflect that there may be a safer, certainly cheaper and equally effective alternative.

Key words Neonate · Albumin · Plasma protein · Hypotension

Abbreviations *BP* blood pressure · *RDS* respiratory distress syndrome · *VLBW* very low birth weight

Introduction

Albumin infusions are frequently administered in the neonatal period. Although there is dispute as to what constitutes a low albumin level [29], albumin has been given to infants perceived to be hypoalbuminaemic in the hope of improving fluid balance and, as a consequence, respiratory status [13]. Administration of colloid solutions has been recommended to try and reduce the haematocrit and blood viscosity of polycythaemic infants and improve the blood pressure of hypotensive infants. It seems clear that albumin infusions are now widely used to ''treat'' metabolic acidosis and as part of the resuscitation of a depressed infant in the labour ward [27]. The purpose of this review is to determine whether such strategies are safe, effective and appropriate.

Hypoalbuminaemia

A child or an adult with a serum albumin level below 30 g/l is classified hypoalbuminaemic. Yet, many infants born prior to 36 weeks of gestation have albumin concentrations below such a level [6]. In addition, in such a population, a poor correlation was found between the serum albumin level and amount of oedema or respiratory distress severity [6]. The patients were, however, suffering from a variety of disorders and had a range of postnatal ages and thus there could have been several explanations for their oedema. Nevertheless, it might be considered that hypoalbuminaemia is ''normal'' for the preterm infant [29]. Yet, low albumin levels were found in infants who developed necrotizing enterocolitis, but not in a control group matched for mode of delivery, gestational age, birth weight, sex, race and type of feed [1]. Infants with respiratory distress have high histamine

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concentrations which affect capillary permeability [7] and thus might be predicted "pathologically" to have low albumin levels due to loss from the circulation into, for example, the lungs [17].

Albumin is an important component of the circulating osmotic pressure and thus increasing the concentration from a perceived low level might be expected, by elevating the colloid osmotic pressure, to increase the plasma volume, glomerular filtrate rate and hence urine output. Indeed, in premature infants with respiratory distress syndrome (RDS), an albumin infusion increased the colloid osmotic pressure and the creatinine clearance rate [19]. In a study [13] of ten babies, who had albumin levels less than or equal to 30 g/l but were normotensive, administration of 5 ml/kg of 20% salt-poor albumin as part of the maintenance fluids was associated with a significant increase in albumin level from a mean of 27 g/l to 32 g/l and a doubling of urine output; the babies lost approximately 40 g in weight over the study period. The lack of a control group requires that other explanations for those changes should be considered, for example increasing postnatal age rather than the albumin perfusion per se. Interestingly, however, similar findings were demonstrated in a subsequent randomized controlled trial [14].

Respiratory status

During the perinatal period, there is a spontaneous diuresis [22]. Several studies have demonstrated a temporal relationship between the onset of the diuresis and lung function improvement seen in infants with RDS [9, 16, 18]. Consequently, it has been postulated that the diuresis represents removal of excess lung liquid, which is necessary for the lung function improvement [16]. Whether administration of albumin, by promoting a diuresis, might influence respiratory status has been examined in a randomized controlled trial [14]. "Hypoalbuminaemic", normotensive ventilator dependent infants received 5 ml/kg of 20% salt-poor albumin or as a placebo, 5 ml/kg of the infant's maintenance fluids [14]. The volume of each trial infusion was subtracted from the total daily fluid requirement and given at the maintenance rate. Infants who received albumin, but not the placebo, had a significant increase in albumin level and reduction in weight, but there were no significant changes in the peak inspiratory pressure in response to either infusion. Over the course of the study, there was a modest ($<15\%$) reduction in the inspired oxygen concentration, but this occurred in both groups. Those data suggest that administration of albumin to "hypoalbuminaemic", sick preterm infants is unlikely to influence their respiratory status, which was predictable from the failure of other diuresis promoting agents in such circumstances to lessen ventilatory requirements. For example, frusemide administration, which promoted diuresis and weight loss, has not been shown to alter the course of RDS [21, 30, 35].

Polycythaemia

Polycythaemia occurs commonly in neonates, perhaps affecting as many as 5% [33]. The resulting hyperviscosity leads to impaired tissue perfusion and hypoxia with organ compromise. Neurological damage can even occur in polycythaemic infants who are asymptomatic during the neonatal period [15]. Treatment of polycythaemia is aimed at reducing the haematocrit and blood viscosity and a dilutional exchange (or partial exchange transfusion) is usually performed [34], although the exact packed cell volume at which such a manoeuvre is undertaken is controversial. During a dilutional exchange, the circulating volume is maintained using a replacement fluid. Traditionally colloid infusions have been used, as they are expected to have a greater and more sustained haemodilutional effect than a crystalloid solution, because they remain longer in the intravascular space. No such advantage, however, may be seen in a sick infant who has increased capillary permeability and protein leak into the extravascular space. The efficacy of colloid and crystalloid solutions as replacement fluid in the treatment of polycythaemia has been compared in two studies [28, 34]. In the first [28], Ringer solution (a crystalloid) was equally as effective as a serum preparation (a colloid) in reducing the haematocrit. The study design, however, had limitations: no long-term outcome measures were used and the effect on the haematocrit was measured at a maximum of 4 h after the exchange. In addition, the small sample size of 20 individuals meant only a large difference between the groups could have been detected with confidence. In the second study [34], the effects of isotonic saline and 5% albumin as replacement fluids were compared in 103 infants with a packed cell volume of at least 65%. The haematocrit both 4 and 24 h after the dilutional exchange did not differ significantly between the two groups, suggesting the crystalloid solution, at least in the short-term, was of similar efficacy.

Hypotension

Colloid infusions are often given as the first-line treatment for neonatal hypotension, blood pressure (BP) could be improved in such circumstances either due to the addition of a protein load, the volume infused or both. Two studies [8, 32] have demonstrated that it is the additional volume which is most influential regarding BP improvement and those data [8, 32], therefore, question the appropriateness of administering a colloid solution in such a clinical situation. In a randomized trial 5 ml/kg of 20% albumin (1 g/kg of albumin), 15 ml/kg of 4.5% albumin (0.675 g/kg albumin) and 15 ml/kg of fresh frozen plasma (2 g/kg protein) were administered to hypotensive (systolic BP <40 mmHg) preterm infants. Although the infants received different volumes of protein, care was taken to standardize the

infusion rate. One hour after completing the infusions, the BP was significantly higher in the groups receiving the higher volume, but lower protein load [8]. In the second study [32], infants (birth weight < 2000 g), hypotensive within the first 2 h of life, were randomized to receive 10 ml/kg of either 5% albumin or isotonic saline. Infants were subsequently given inotropic support if they remained hypotensive after a total of three such infusions. No difference was noted regarding the number of infants who went on to require inotrope support, suggesting the crystalloid infusion was as effective as a similar volume of colloid. Those data are consistent with findings in adults [26] where colloid and crystalloid volume expanders were shown to be equally effective in treating hypotension due to capillary leak syndrome. It may be that a crystalloid, rather than a colloid, infusion is not only equally effective, but more appropriate to treat hypovolaemic hypotension. Infants given an albumin infusion had a significantly higher weight gain in the first 48 h than those who received saline [32], which suggests the former group suffered fluid retention.

It is important, however, to remember that low BP is not necessarily due to hypovolaemia [25], but could be due to a number of aetiologies, which include myocardial dysfunction [11], a haemodynamically significant patent ductus arteriosus (particularly in those of birth weight < 1000 g [10]) and vascular tone deficiency. Indeed, systolic BP is of limited value in detecting hypovolaemia in very low birth weight (VLBW) infants [3]. It is, therefore, not surprising that in one series [12], only 45% of hypotensive VLBW infants responded to a plasma protein fraction infusion, whereas 89% responded to dopamine. As a consequence, an ''initial filling test'' has been recommended [25] that is to administer between 5 and 12.5 ml/kg of fluid to a presumed hypovolaemic infant, half given rapidly within 10 to 15 min. If the blood pressure fails to respond or the infant requires a volume greater than 12.5 ml/kg this should prompt a Doppler echocardiography evaluation to exclude other causes of hypotension and thus avoid provoking an important increase in pulmonary arterial pressure, particularly if the ductus arteriosus is open.

Metabolic acidosis

Metabolic acidosis is common on the neonatal intensive care unit and, if severe, can be associated with adverse outcome [20]. Specific treatment is directed at the underlying aetiology and additional therapy is frequently given to rapidly improve the pH. Additional therapy may be an infusion of tris(hydroxymethyl) aminomethane or sodium bicarbonate, but both inflict a hyperosmolar load and the latter may result in hypernatraemia. An alternative practice is to given an albumin infusion, the presumed rationale is not only to correct the metabolic acidosis associated with hypotension, but also in normotensive infants to increase the buffering capacity of the plasma and so influence the pH. A retrospective case note review [4] demonstrated that administration of 10 ml/kg of 4.5% albumin in response to metabolic acidosis (pH < 7.25) in ventilated, normotensive VLBW infants (median gestational age 26 weeks) resulted in an immediate significant improvement in the base deficit and an increase in the pH from a median of 7.23 prior to, to 7.28 6 h post infusion. No significant change was noted in BP or peripheral core temperature gap, thus an improvement in perfusion seems unlikely to be the mechanism of the response. In the absence of a control group, one cannot be confident that the effects noted were due to the albumin infusion, but all the infants had a ''stable'' metabolic acidosis for at least 6 h prior to the infusion. A randomized trial is warranted to further assess the efficacy of albumin infusion in ''treating'' a metabolic acidosis.

Initial resuscitation

Recent experience suggests, at least in severely asphyxiated term infants, albumin infusions are frequently given as part of the initial resuscitation process [27]. Such a practice appears ill-judged as low Apgar scores are not necessarily indicative of hypotension [23] and may be associated with asphyxial myocardial depression, in which case volume load is contra-indicated [25]. In addition, asphyxia will lead to increased capillary permeability and an albumin infusion could impair resuscitation by increasing protein leak into the lung [17]. At best, a modest improvement in pH might be achieved [4]. There are no randomized studies assessing the efficacy of an albumin infusion at initial resuscitation, but comparison of the efficacy of 8 ml/kg of 25% salt-poor albumin, 4.2% sodium bicarbonate, both or glucose in water in 53 premature babies of less than 2 h of age failed to detect any statistically significant difference in the RDS, intraventricular haemorrhage or mortality rate.

Side-effects

Any possible benefit of giving an albumin infusion must of course outweigh any associated adverse effects. All colloid solutions consist of biological products and carry, therefore, the potential risk of infection. In addition, there is the risk of provoking an anaphylactic reaction with such an infusion. Albumin infusions potentially could aggravate the protein leak seen in sick infants [17] and this may be the mechanism of pulmonary oedema following this treatment [2]. Extravasation of plasma proteins into the alveolar space may also lead to inactivation of surfactant [31] and deterioration in lung mechanics [24]. There is dispute as to the rate of albumin loss from the circulation in neonates. In two studies [13, 14] the albumin level was higher than that seen pre-infusion at 6 h [14] and 24 h [13] respectively post-transfusion. The speed of loss, however, may be

faster in sick infants, as in those in whom hypovolaemia was suspected because of a metabolic acidosis, a toe-abdominal skin temperature difference of greater than 2.5°C, hypotension, tachycardia or cyanosis, there was only a small and poorly sustained increase in the albumin level [5]. It should be noted, however, that only a relatively low amount of albumin was infused in that study [5].

In conclusion, albumin infusions can improve BP, promote diuresis and may help to correct a metabolic acidosis. Equally effective alternatives are available, however, and they may be safer.

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