Early volume expansion for prevention of morbidity and mortality in very preterm infants

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An updated version of this systematic review has been published and can be found online at [www.cochrane.org](http://www.cochrane.org). We will soon update the below RHL summary to reflect the updated findings of the systematic review.

Early volume expansion in preterm very-low-birth-weight does not appear to have any clinically significant benefit. The role of early volume expansion in such infants is therefore questionable because of the complex pathophysiological mechanisms leading to cardiovascular compromise in these infants.

**RHL Commentary Deorari A and Sasi A**

**1. INTRODUCTION**

With the emergence of specialized intensive care and technology, there has been an increase in the survival of preterm very-low-birth-weight (VLBW) infants even in under-resourced settings (1, 2). As per a prospective multicenter hospital-based report from India, VLBW infants account for nearly 3.5% of all live births (1). Cardiovascular maladaptation due to myocardial immaturity is an important morbidity in these neonates. Nearly one third have hypotension or low systemic blood flow. About 16%–52% of VLBW infants receive fluid therapy and up to 40% require vasopressor support in the first 72 hours of life (3). The problem is compounded by postnatal factors like asphyxia, ventilation and difficulty in assessment of adequacy of tissue perfusion. Early circulatory compromise in these infants is associated with cerebral injury and adverse long-term neurological outcome.

Hence, various strategies, such as volume expansion, use of inotropes and corticosteroids, to support the perfusion in the immediate postnatal period are in practice. However, evidence regarding the most appropriate therapeutic measure is conflicting. This Cochrane review examines the role of early volume expansion within first 72 hours of life, for prevention of morbidity and mortality in preterm infants ≤ 32 weeks or ≤ 1500 g (4). The sub-group analysis based on postnatal age of treatment, type of fluid used and method of diagnosis of hypoperfusion was also done as a part of this review.

**2. METHODS OF THE REVIEW**
The eligible randomized controlled trials were identified by a comprehensive search of the Cochrane trial register, MEDLINE, EMBASE databases as well as conference abstracts and cross-references with no language restriction. Methodological quality of each study was assessed independently by the reviewers as per the standard Cochrane guidelines, though the latest GRADE format was not used. The majority of studies were of good quality with adequate randomization and allocation concealment procedure, although blinding of intervention was done in only one study. Even though no significant heterogeneity was observed between the trials, two thirds of infants were enrolled in a single trial conducted more than a decade ago. The intervention reviewed was volume expansion defined as at least 10 ml/kg additional volume above maintenance requirements given over less than 6 hours. This included normal saline, fresh frozen plasma, albumin, plasma substitute or blood, within the first 72 hours of life. The primary outcomes included neonatal mortality and mortality to discharge, peri/intraventricular hemorrhage (P/IVH), periventricular leukomalacia (PVL) or neurodevelopmental disability (cerebral palsy, developmental delay or neurosensory impairment). The secondary outcomes measured were use of inotropes in the first 72 hours, failure to correct low systemic blood flow, failure to correct hypotension, patent ductus arteriosus (PDA), renal impairment, chronic lung disease (CLD), definite necrotizing enterocolitis (NEC) or retinopathy of prematurity (ROP). The reviewers have clearly represented the data of the main as well as sub-group analysis in text as well as tables and forest plots.

3. RESULTS OF THE REVIEW

A total of eight trials involving 1223 infants were included in the review. Meta-analysis of four trials comparing volume expansion versus no treatment (940 infants) showed no difference in mortality. Few studies had reported on P/IVH or PVL, and none of them showed any significant clinical benefit of early volume expansion. Only one study had reported on long-term neurodevelopment outcome, which again showed no statistically significant difference in terms of severe disability, cerebral palsy and death, and severe disability. There was also no significant difference with regard to other reported outcomes such as hypotension, renal dysfunction, PDA, NEC or CLD. None of the trials had estimates of ROP or low blood flow states.

The subgroup analysis comparing the effect of different types of fluids used in volume expansion mainly albumin, normal saline, fresh frozen plasma or gelatin based plasma substitutes also failed to show any significant difference in outcomes. Meta-analysis of two trials compared 5% albumin versus normal saline showed no difference in mortality or any grades of P/IVH. The higher mean blood pressure and greater reduction in the need for inotropes for persistent hypotension in the albumin group reported in one of the latest studies did not result in improved urine output or reduction in any morbidity (5). Neither the timing of the treatment (within first 12 versus 24 hours) nor the infant type (hemodynamically stable versus unstable) changed the results of the review.

4. DISCUSSION

4.1 Applicability of the results

Early volume expansion in preterm VLBW infants failed to show any clinically significant benefit. The role of early volume expansion in preterm VLBW infants is therefore questionable because of the complex pathophysiological mechanisms leading to cardiovascular compromise in these infants. Hypovolemia is rarely encountered in the first 72 hours in VLBW infants, unless there is a setting of perinatal blood loss or early sepsis (6). There is also very poor correlation between blood volume and blood pressure in preterm VLBW neonates. Hence there is lot of skepticism about the utility of volume expansion in these situations and it may even be detrimental.

Based on the existing evidence routine preemptive use of early volume expansion in preterm VLBW infants
cannot be recommended. This review failed to show any improvement in mortality, short-term morbidities or long-term neurodevelopmental outcome with volume expansion. However, in another Cochrane review (7), restricted (60–150 ml/kg of body weight/day) compared to liberal fluids intake (140–200 ml/kg of body weight/day) had significantly lower NEC and PDA, with trend towards reduction in mortality and CLD.

Even though all the trials included in this review are from the developed world, the similarity in mechanisms of early cardiovascular compromise in VLBW infants makes it equally applicable to under-resourced settings. However, it’s likely that there is increased incidence of peripartum blood loss or infection in under-resourced settings, making it important to identify the aeti-poathogenesis of shock (especially in neonates with cardiovascular compromise) and to use fluids judiciously in these subgroups of neonates.

4.2 Implementation of the intervention

In our opinion there is no role for prophylactic volume expansion in the very preterm infants. In those with signs of poor perfusion like metabolic acidosis or prolonged capillary refill time and hypotension, treatment has to be tailor-made according to the cause of cardiovascular compromise. The threshold for starting inotropic support in these babies has to be kept low, with limitation of fluid boluses to 10-20 ml/kg of body weight, unless there is a setting of blood loss or septic shock.

4.3 Implications for research

Most trials included in the above meta-analysis had enrolled infants based on gestational age or birth weight, without attention to cardiovascular instability. More trials comparing volume expansion with no treatment as well as different inotropes need to be conducted exclusively in the subgroup of VLBW infants with hemodynamic compromise. There is also need to develop and validate sensitive clinical tools for the detection of shock in these neonates as hypotension is not synonymous with hypoperfusion and often blood pressure cannot be reliably recorded in these infants, especially in primary and secondary health-care settings. Even though bedside echocardiography is emerging as reliable tool in neonatal intensive care units for the assessment of myocardial functions and systemic blood flow, it has limited utility in under-resourced settings.

References
