Protein supplementation of human milk for promoting growth in preterm infants

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In preterm infants, human milk supplemented with protein leads to short-term increases in weight and linear and head growth. However, preterm infants fed only breast milk suffer not only from protein deficit but also deficits in energy, calcium, phosphate, trace minerals and vitamins. Hence, in current practice the focus has shifted from protein supplementation alone to multi-component breast milk fortifiers.

RHL Commentary by Kumar P and Sundaram V

1. INTRODUCTION

Growth failure is a significant problem in hospitalized preterm infants in both developed and developing countries (1). This is due to preterm infants' high protein requirements (3–4 g/kg/day), increased incidence of illnesses (and resultant excessive catabolism), and a delay in the initiation of early and aggressive enteral as well as parenteral nutrition (2). Moreover, the nutrient content of human milk provides insufficient quantities of protein, electrolytes and minerals to sustain adequate growth in preterm infants beyond the initial couple of weeks (3). Consequently, preterm infants fed human milk alone show slower growth in comparison to those who are fed preterm formula milk with a higher protein content (4). Hence, supplementation of the human milk with protein can potentially help in promoting growth in these infants. The Cochrane review on protein supplementation for promoting growth in preterm infants had the objective of determining whether in preterm infants the addition of protein to human milk leads to improved growth and neuro-developmental outcomes without significant adverse effects (5).

2. METHODS OF THE REVIEW

The review authors sought to include randomized and quasi-randomized controlled trials that had evaluated supplementation of human milk with protein in preterm infants (<37 weeks gestation) receiving care in hospital, in comparison to infants not receiving protein supplements. A subgroup analysis was planned to evaluate differences in outcomes between supplementation with bovine and human milk protein. Apart from short- and long-term growth parameters, the authors intended to analyse neuro-developmental outcome at 12–18 months of age as a primary outcome. Various secondary outcomes such as nitrogen retention, serum albumin concentration and adverse effects, such as feed intolerance, diarrhoea, necrotizing enterocolitis, metabolic acidosis and blood urea, were studied. Standard search methods of the Cochrane Neonatal Group prevalent in the late nineties were used to identify the studies. Searches for trials were made in the Oxford Database of Perinatal Trials, MEDLINE, previous reviews including cross-references, abstracts, and conferences and symposia proceedings. The authors also used expert informants and hand searched journals.
mainly in the English language. The methodological quality of the included trials was adequately assessed for type of randomization, method of random allocation, concealment of allocation, blinding (of intervention and outcome), and quality of follow-up. Although the authors have not reported methodological quality assessment according to the GRADEprofiler tabular format, it has been presented in a simple fashion, making it easy for the reader to understand the data.

3. RESULTS OF THE REVIEW

The review includes four single-centre trials conducted between 1982 and 1989, which included a total of 90 very-low-birth-weight (VLBW) infants. Three of the four trials excluded infants with major illnesses and malformations. Lyophilized human milk protein was used as the protein source in varying concentrations in three trials, whereas casein hydrolysate was used in the fourth. Enteral feeds were initiated within the first two days of life in all infants and the maximum feed volume was targeted at between 164–200 ml/kg/day. The duration of the intervention was unclear in three trials, whereas in the fourth supplementation continued until the weight of the infant reached 2200 grams. All trials evaluated short-term growth (weight gain and linear and head growth) and biochemical changes (blood urea level) as primary outcomes. One trial also assessed serum albumin level and feed intolerance. None of the studies had assessed long-term growth and neuro-developmental outcomes.

Supplementation with protein resulted in an average increase in weight gain of 3.6 g/kg/day, with the 95% confidence interval (CI) being 2.4–4.8. In infants receiving protein supplementation, there was significant increase in linear growth [weighted mean difference (WMD) 0.28 cm/week, 95% CI 0.18–0.38] as well as head growth (WMD 0.15 cm/week, 95% CI 0.06–0.23). The data were inadequate to compare the two types of protein used in the trials (bovine versus human milk protein). One study that had evaluated serum albumin concentration did not find any difference between the two groups. The same study had also assessed the risk of necrotizing enterocolitis (NEC) and found that no infant developed NEC. One study found that blood pH was significantly lower in infants receiving supplemental protein at 2 weeks of age (7.32 versus 7.37, p<0.05; standard deviation data not provided), but there were no differences at subsequent intervals. Another study did not find any significant difference in bicarbonate levels between the groups (23.2 versus 21.1 mmol/L). Three studies showed increased urea levels in supplemented infants (WMD 1.0 mmol/L, 95% CI 0.8–1.2), suggesting adequacy of protein intake.

4. DISCUSSION

4.1 APPLICABILITY OF THE RESULTS
In preterm infants, protein supplementation of human milk leads to short-term increases in weight gain and linear and head growth. Although the differences between the intervention and control groups for short-term growth outcomes are small, the effect is cumulative. For preterm infants who have prolonged hospital stays, even a small advantage in weight gain or linear or head growth can potentially have a significant impact on growth parameters at discharge from hospital and duration of hospital stay. Although these and long-term growth and neuro-developmental outcomes were not reported in any of the included studies, there are some data to suggest that neuro-developmental outcomes at 9 months and 18 months of age are similar in those who received multi-component fortification versus those who did not (6). In developing countries, the growth deficits in preterm hospitalized infants are even more significant than in developed countries (1). Hence, even though none of the included trials was conducted in a developing country, these results have considerable relevance to under-resourced settings. Preterm infants fed only breast milk suffer not only from protein deficit but also receive inadequate amounts of energy, calcium, phosphate, trace minerals and vitamins. Hence, appropriately, the focus in current practice has shifted to multi-component breast milk fortifiers rather than protein supplements alone (6).

### 4.2. IMPLEMENTATION OF THE INTERVENTION

The studies included in the review seem to have a ‘high risk of bias’ on a Risk Of Bias (ROB) 6-point assessment scale. Moreover, the sample size for the whole review is not large enough, with only 90 subjects being available for weight gain as an outcome. Hence, a recommendation of routine protein supplementation of the human milk in preterm infants cannot be made with the currently available evidence. In any case, multi-component rather than isolated protein supplementation is now being practiced (6).

The use of multi-component fortifiers in developing countries is, however, difficult because of their high cost, limited availability and risk of contamination during mixing. Before embarking on protein or multi-component supplementation of human milk, efforts should be directed towards starting enteral nutrition in preterm infants as soon as their gut is ready, minimizing the catabolic processes and avoiding certain potentiation factors such as sepsis and hypothermia that can predispose a baby to poor weight gain in the initial few days of life.

### 4.3. IMPLICATIONS FOR RESEARCH

Further research should be directed towards modification and refinement of available and new multi-component preparations in terms of their effects on short- and long-term growth and neuro-developmental outcomes. Another question that remains to be addressed is how long should a preterm infant receive fortified human milk. The safety, feasibility and cost–effectiveness of human milk fortification in developing countries also needs to be demonstrated. Compared with the practice in developed countries, in developing countries, VLBW infants are discharged home much earlier (and at lower weights). Hence, fortification needs to be continued at home. Further studies are needed on the safe use of ready-to-use fortification formulations at home.

### References

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