Trophic feeding of the preterm infant

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Trophic feeding is the practice of feeding minute volumes of enteral feeds in order to stimulate the development of the immature gastrointestinal tract of the preterm infant This paper reviews the randomized controlled studies that have examined the physiological and clinical responses to trophic feeding of the preterm infant. Trophic feeding alters gastrointestinal disaccharidase activity, hormone release, blood flow, motility and microbial flora. Clinical benefits appear to include improved milk tolerance, greater postnatal growth, reduced systemic sepsis and shorter hospital stay. There is currently no evidence of any adverse effects following trophic feeding.

Key words: *Enteral nutrition, feeding methods, infant, parenteral nutrition, premature, trophic feeding*

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In circumstances of profound immaturity, malformation or disease in an infant total parenteral nutrition (TPN) is often required. Whilst beneficial overall, TPN has many drawbacks and complications. Not least of these is the likelihood from animal studies of gastrointestinal (GI) atrophy developing within 2–3 d of commencement of TPN even in infants kept in a positive nitrogen balance (1, 2). This is because enterocytes rely on GI luminal contents for nutrition.

The practice of trophic feeding was introduced in the late 1980s in an attempt to overcome the lack of GI stimulation during TPN, whilst minimizing stress to the ill infant. Alternative names include gut priming, minimal enteral nutrition and early hypocaloric feeding. Trophic feeding can be defined as the practice of feeding nutritionally insignificant volumes of enteral substrate to the compromised newborn infant in order to stimulate and supply nutrients to the developing GI system. Typically, only tiny volumes of 0.5 or 1 ml kg^{-1} h^{-1} are fed to preterm infants. Randomized controlled trials (RCTs) have examined the effects of trophic feeding in the preterm infant.

Physiological effects of trophic feeding

Intestinal disaccharidase activity

Only one RCT (3) has examined this response to trophic feeding. Eighty preterm infants requiring TPN were randomized to either receive trophic feeding of 1 ml kg^{-1} h^{-1}, or not, until clinically stable. Trophically fed infants had a significantly higher lactase to sucrase activity ratio in their proximal intestinal fluid both at the end of the period of trophic feeding and 14 d after the introduction of substantive enteral feeds: mean difference (95% confidence interval) 1.8 (0.03, 3.57) and 0.78 (0.2, 1.35) units l^{-1}, respectively.

Endocrine effects

In the preterm infant trophic feeding results in a similar elevation of the fasting and postprandial plasma concentrations of several enteric hormones, e.g. gastrin, enteroglucagon and motilin to that seen in healthy, milk-fed, term infants (4–6). Infants maintained on exclusive TPN from birth show no such rise. These hormones are known to stimulate GI growth, function and motility.

Metabolic effects

Dunn et al. (7) suggested that trophic feeding resulted in lower and more quickly resolving peak bilirubin plasma levels and lower levels of alkaline phosphatase (implying a reduction in metabolic bone disease). Unfortunately, three other RCTs were unable to duplicate these findings (5, 8, 9).

Enteric blood flow

Both the median peak systolic velocity and time average mean velocity in the superior mesenteric and coeliac arteries increase significantly following the first 1 ml milk feed in preterm infants (10). Whether a difference in enteric haemodynamics is sustained during trophic feeding is not known.

Gastrointestinal motility

Berseth (6) used intraluminal manometry to demonstrate that development of proximal intestinal motor activity is enhanced by trophic feeding. This was evident as greater migrating motor activity, longer motor quiescence periods and a greater postprandial change in motor activity following substantive feeding. Gastric emptying, as measured by serial abdominal ultrasound scanning, appears to be unaltered by previous trophic feeding (11). Two RCTs have shown that the whole gut transit time (WGTT) is reduced up to 6 wk after birth by trophic feeding (11, 12).

Exocrine pancreatic function

Only one RCT has examined pancreatic exocrine function following trophic feeding. In this study (3) of 80 infants (birthweight < 1750 g) there was no evidence that faecal chymotrypsin concentrations were altered.

Gastrointestinal flora

The choice of breast or formula milk feeds profoundly affects the development of GI flora in newborn infants. Therefore, it might be expected that trophic feeding would affect flora development, but to date no published RCT has examined this. In an unpublished RCT the present author examined the prevalence of coagulase-negative staphylococci (CONS) in serial faecal samples from 56 infants of birthweight < 1750 g. CONS prevalence was significantly reduced in infants receiving trophic feeding throughout the period from 2 wk of age (68% vs 84%) to 2 wk following the introduction of substantive feeding (44% vs 65%).

Clinical studies of trophic feeding

There have been 10 published RCTs (5–9, 12–16; Ref. 16 is in abstract form only) comparing the clinical outcome of the addition of trophic feeding or not to TPN in preterm infants. Entry criteria in all trials were based on either gestation (< 32 wk of gestation) (6, 14, 15) or birthweight (generally < 1500 g) (5, 7–9, 12, 16). A total of 831 infants was studied with trial sizes ranging from 27 (6) to 313 (16). Daily milk volume ranged from 12 (8) to 25 ml kg^{-1} (16), but in the majority 24 ml kg^{-1} was given (5, 6, 9, 13–15). Mean duration of trophic feeding or enteric starvation in controls varied between 7 and 18 d. In two, substantive milk feeds were introduced upon recovery from the acute phase of their illness (9, 15). A meta-analysis of the earliest eight RCTs was performed in 1998 (17). For the purposes of this review their published data (17) and those of the two later studies (9, 12) have been combined to evaluate the effect of trophic feeding on the following clinical outcomes.

Milk tolerance

Eight RCTs examined the number of days to reach full enteral feeding (6–9, 12, 14–16). Six showed a reduction in those receiving milk (6–8, 12, 14, 15). The weighted mean difference (WMD) (95% confidence interval) was −3.6 (−4.9, −2.4) d. Four studies also measured the number of days on which feeds were withheld (6–8, 14). All found a reduction in favour of infants receiving trophic feeding, WMD −3.1 (−4.6, −1.6).

Postnatal growth

Five studies examined the number of days that infants took to regain their birthweight (7, 8, 14–16). Although slightly reduced in those given trophic feeding, the WMD was not significant, −0.3 (−0.8, 0.2). McClure and Newell (9) also examined growth velocity over the first 6 postnatal weeks. There was a significantly greater mean weight, 130 (1, 250) g and head circumference, 0.7 (0.1, 1.3) cm gain in the fed infants. Therefore, it is possible that trophic feeding does have some beneficial effect on postnatal growth.

Phototherapy duration

Only one study (7) out of three (5, 7, 9) showed a significant reduction in the duration of phototherapy. Combined there was an insignificant increase in the WMD of 0.14 (−0.18, 0.47) d in infants receiving trophic feeding.

Sepsis

Only one study has examined whether the incidence of sepsis was altered (9). In this RCT of 100 infants the total number of episodes of culture positive sepsis was significantly reduced by more than half, 24 compared with 63 ($p = 0.04$) in the trophic feeding group. The number of days when the C-reactive protein was greater than 10 was also more than halved, 106 compared with 222 ($p = 0.02$).

Necrotizing enterocolitis

In eight studies the number of infants suffering from this disease was stated (5, 7–9, 12, 13, 15, 16). In none was there a significant difference. Overall, there was a slight, but non-significant increase in the odds ratio in infants receiving trophic feeding, of 1.2 (0.72, 1.95). As over 300 infants were recruited to each treatment group in these studies it is probable that if any true increase does exist it is marginal.

Hospital stay

In four out of five studies there was a reduction in the number of days of hospital stay in milk-fed infants, three of which were significant (5, 6, 9, 12, 14). The WMD was 7.8 (5.6, 101) d less in those exposed to trophic feeding.

Discussion

The exact mechanism of action for trophic feeding is unknown. It is possible that the volumes of milk used are enough to provide direct nutrition to enterocytes. Several vitamins and minerals are known to be growth factors; for example, folate and vitamin B_{12} are essential for DNA synthesis. Glutamine is the prime respiratory fuel for enterocytes. Nutrients requiring digestion may be capable of directly inducing a mucosal response, e.g. disaccharides inducing disaccharidase production. The small amounts of milk supplied are, however, unlikely to provide direct nutrition distal to the proximal intestine.

More likely is that both direct and indirect trophic effects are exerted on the GI tract. Many peptides and hormones found in expressed breast milk, including epidermal growth factor, insulin-like growth factors and bombesin, are known to be directly trophic (18). Several of these, such as bombesin, are also present in formula milk. Indirect trophic effects are likely to follow the surge of enteric hormones after trophic feeding. Secretions stimulated by the release of enteric hormones may also be important. For example, increased biliary secretion caused by motilin release may result in altered intestinal lipid handling and, thereby, enteric flora.

As GI motility patterns are altered it is likely that trophic feeding influences the enteric nervous system, either directly via GI neuroreceptors or indirectly via hormone release. At least some direct stimulation is likely as the motility response to trophic feeding has been shown to be independent of enteric hormonal increases (19). Lastly, alteration of the intestinal flora may exert important effects on GI development.

Despite considerable research, there are several outstanding questions regarding the use of trophic feeding. Which babies should be treated? When is the best time to start? What is the optimum duration? What is the correct volume? What is the best substrate? Nevertheless, the following recommendations can be made on the basis of the published studies. Almost all very low birthweight infants unable to tolerate substantial milk feeds should be considered for trophic feeding Obvious exclusions are infants with necrotizing enterocolitis or congenital GI abnormalities, such as gastroschisis. As delaying feeds appears to confer no obvious advantage it is reasonable to start trophic feeding on day 1 or 2, providing the infant is stable. It appears that $1\ \mathrm{ml\ kg^{-1}\ h^{-1}}$ is a safe and effective volume. The optimum duration of trophic feeding is difficult to recommend, as it is so dependent on clinical status and the facilities available on each neonatal unit. Rather than specify a set time, regardless of clinical status, it is probably more sensible to suggest that trophic feeding be continued until the infant is stable enough to tolerate substantial volumes of milk safely. Breast milk, if available, should be preferred to formula.

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