A clinical pilot trial of metoclopramide therapy for gastric residuals in preterm infants

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Feeding intolerance characterized by significant gastric residuals is common in preterm infants. This usually prompts caregivers to ‘hold’ or decrease feeds, thereby postponing the establishment of full enteral feeding. The cause of gastric residuals in preterm infants is probably multifactorial. At times, gastric residuals represent the earliest sign of serious pathology such as intestinal obstruction, sepsis, paralytic ileus, lactobezoar (1) or necrotizing enterocolitis (NEC) (2). Most often gastric residuals are attributed to gut immaturity. Gastric emptying is greatly delayed in preterm infants (3); thus, drugs that may enhance gastric emptying, such as metoclopramide, have been tried in a series of cases of infants with gastric residuals, with various degrees of success (4–7). Moreover, metoclopramide is not without side effects, which include irritability, vomiting, dystonic reactions and extrapyramidal symptoms (8). A major practical textbook of neonatal pharmacology (9) states that metoclopramide ‘facilitates gastric emptying and GI motility’ and ‘may improve feeding intolerance’. At this point in time, whether metoclopramide is effective and safe in preterm infants with gastric residuals is unknown.

We therefore designed the following pilot study to determine the feasibility of a prospective, double-blinded, placebo-controlled clinical trial of metoclopramide therapy for feeding intolerance in preterm infants. We hypothesized that this pilot study would enable us to determine the sample size necessary to demonstrate the superiority of metoclopramide over placebo.

One investigator (DH) enrolled 20 preterm, gavage-fed, very low birth weight infants (500–1500 g birth weight) hospitalized at the neonatal intensive care unit of the Lis Maternity Hospital, Tel Aviv Medical Center between February 2004 and May 2005. At their first episode of significant gastric residuals, which we defined as gastric residuals greater than 20% volume of the previous feeding, infants were randomized to receive metoclopramide therapy (n = 9) or placebo (n = 9). Metoclopramide and placebo were prepared by a pharmacist blinded to patient allocation. The drug was distributed in similar vials marked only A and B, so all personnel treating the study infants were blinded to group assignment. Metoclopramide or a similar volume of placebo was given intravenously at a dose of 0.05 mg/kg body weight every 8 h (9), until the patients received a total feeding volume of >100 mL/kg body weight/day, and thereafter, the medication (or placebo) was administered enterally. It was then continued for 7 days after the infant had tolerated full feeds (160 mL/kg body weight/day). At entry to the study all infants had no electrolyte imbalance and they were free of congenital anomalies or dysmorphism. The major outcome variables of the study were time to reach full enteral feeds (10, 11), the daily number of significant gastric residuals and the incidence of NEC.

A feeding protocol was approved by all attending physicians in our institution, and strictly adhered to. The schedule clearly indicated when feeds should be started, the rate of daily increments, feeding composition (pumped human milk whenever available, diluted or non-diluted preterm infant formula), and time to reach full feeds. Bolus feeds were given every 3 h by gravity drainage using a nasogastric tube after priming of the tubing as described by us elsewhere (11). Gastric residuals were assessed every 5 h, prior to each meal. For clinical and research purposes, significant gastric residuals were defined as gastric residuals >20% of the volume of the previous feed with an absolute minimum volume of at least 2 mL.

Feeds were initiated at 20 mL/kg/day, with small equal daily increments such that full volume feeds (160 mL/kg/day) were reached within 8–14 days, depending upon the birth weight of the infant (the lower the birth weight, the lower the incremental progression of feeds). Feeds were started on day 2 at the earliest or 24 h following stabilization of an unstable blood pressure (using normal values of Versmold et al. (12)).

Expressed human milk was the nutrition of choice, and was used undiluted. When unavailable, it was replaced by Similac Special Care ready-to-feed formula (Ross...
Laboratories, Columbus, OH), which was used (by decreasing birth weight group: 1001–1250 g, 751–1000 g, 501–750 g) initially diluted to 40 cal/100 mL till days 3, 5 or 6 of feeds (depending upon birth weight), then replaced by 60 cal/100 mL till days 4, 6 or 8, by 67 cal/100 mL by days 6, 8 or 11, then by 81 cal/100 mL by days 8, 10 or 14, respectively. Supplemental fluids were given as a glucose solution on day 1, then as a standardized parenteral nutrition, and volumes were adjusted to allow a weight loss of no more than 10–15% of birth weight.

The study was approved by the local Institutional Review Board and written informed consent was obtained from both parents of each infant.

The sample size was empirically determined as this study was a pilot one, aiming to determine the feasibility of a definitive study. The randomization schedule used computer-generated random numbers and was blocked according to three birth weight groups in order to decrease the risk of chance differences in terms of baseline characteristics (in particular, birth weight and gestational age) comparability of the two groups. The randomization sequence was kept at the central pharmacy of the hospital.

Statistical analysis was performed using the Minitab version 13 (State College, PA, USA) and included the Kruskal–Wallis tests for continuous variables and Fisher exact tests for categorical variables. Results are expressed as median, range and mean ± SD or median (range) or n. A p-value of <0.05 was considered significant. Sample size calculations used the assumption of a p-value of <0.05, and a power of 80%. A flow chart showing the progress of participants through the trial is included in Figure S1.

Clinical characteristics of the study infants are presented in Table 1. Twenty infants were enrolled in the study, but only 18 infants were retained in the final analysis, after the exclusion of 2 infants (one in each group) because of sepsis (n = 1) or intestinal anatomical obstruction (n = 1). No infant developed NEC during the study period. The groups did not differ in baseline characteristics such as gender, birth weight, gestational age, Apgar scores, age at which feeds were started, age at which the first episode of gastric residuals occurred, age at which infants were randomized and metoclopramide started, a history of respiratory distress syndrome, patent ductus arteriosus, intraventricular haemorrhage of grade >2, apneas, assisted ventilation, indomethacin therapy or xanthine therapy.

There were no significant differences between the groups in the major outcome variables of the study, that is, time to reach full enteral feeds, the daily number of significant gastric residuals and NEC (Table 1). Assuming that the very small difference in time to reach full feeds was a true one, we calculated that a sample size of 1250 infants in each group would be necessary to reach statistical significance (p < 0.05), assuming a power of 80% and equal variances.

We found only three studies that examined the effect of metoclopramide upon feeding tolerance in small preterm infants. None of them used a control group that received placebo. The study by Blumenthal and Costalos included 15 infants using the serial meal technique and reported that ‘…the results indicate that metoclopramide does not promote gastric emptying in the newborn period’ (4). Another study, by Meadow et al., included 14 infants with feeding intolerance, which ‘improved steadily after metoclopramide was administered’, and which did not show any harmful side effect such as extrapyramidal symptoms, worsening of hepatic function or NEC (6). A smaller study by Sankaran et al. found that metoclopramide administered to six preterm infants led to an ‘excellent response’ and withdrawal of the drug led to ‘prompt recurrence of all symptoms and signs which again disappeared on reinstitution of the medication’ (5). The non-randomized, non-controlled, non-blinded nature of these three reports, as well as their very small sample size, limits greatly their conclusions.

In contrast, the current pilot study was randomized, controlled and double-blinded. We showed in a group of 18 preterm infants with gastric residuals that metoclopramide does not improve feeding tolerance. Moreover, 2500 infants would be necessary to demonstrate that the very small difference (0.2 days out of 13 days, or 1.5%) between the two groups is real, assuming equal variance, a p-value of <0.05 and a power of 80%.

The findings of this study may be limited by the possibility that infants on different advancement schedules may indeed benefit from metoclopramide therapy. Although no significant side effects of metoclopramide were identified in this study, the sample size precludes any conclusions regarding the safety of metoclopramide in preterm infants with gastric residuals.

Thus, we conclude that a large study of metoclopramide therapy for feeding intolerance in small preterm infants is not feasible as no conceivable benefit is to be expected from this intervention.

References


**Supplementary material**

The following supplementary material is available for this article:

**Figure S1** Progress of participants through the trial.

This material is available as part of the online article from: http://www.blackwell-synergy.com/doi/abs/10.1111/j.1651-2227.2007.00373.x

(This link will take you to the article abstract).

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