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Short Communication

Small Volume Enemas Do Not Accelerate Meconium Evacuation in Very Low Birth Weight Infants

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ABSTRACT

We hypothesized that small volume enemas accelerate meconium evacuation in very low birth weight (VLBW) infants. In a randomized controlled trial, VLBW infants (n = 81) received either repeated daily small volume enemas if complete spontaneous meconium passage failed within 24 h or no intervention. Small volume enemas did not accelerate complete meconium evacuation, which occurred after 6.0 to 9.6 (95% CI) d in the intervention group and after 7.7 to 11.0 (95% CI) d in the control group. No adverse events were observed. Daily administration of small volume enemas had no effect on total meconium evacuation defined by the time of last meconium passage. ***JPGN 44:270–273, 2007.*** **Key Words:** Meconium passage—Enema—Very low birth weight infants—Randomized controlled trial. © 2007 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

INTRODUCTION

The immaturity of the intestinal motor mechanisms and associated feeding problems are challenges in the treatment of very low birth weight (VLBW) infants (1). Timing of the first and last meconium stool is critical for oral feeding tolerance and proper gastrointestinal function (2). Almost all term infants pass their first meconium within 48 h of life (3,4). In contrast, many premature infants pass their first meconium only after considerable delay up to 27 d (median, 43 h) (2,5). Obstruction of the gastrointestinal tract by tenacious meconium frequently leads to gastric residuals, a distended abdomen, and delayed food passage. Recent data support the concept that rapid evacuation of meconium plays a key role in feeding tolerance (6). To prevent meconium obstruction (7) and improve feeding tolerance, premature infants may benefit from prophylactic administration of enemas. Thus, we aimed to determine whether repeated applications of small-volume glycerine enemas accelerate passage of meconium in VLBW infants.

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PATIENTS AND METHODS

Study Design

The study design was a randomized controlled trial. Premature infants with a birth weight ≤1500 g and a gestational age (GA) ≤32 weeks were eligible for inclusion in the study. Exclusion criteria were major congenital malformations and known gastrointestinal abnormalities. Infants were stratified according to their GA (< or ≥28 weeks) and block randomized to the intervention or control group. The study was approved by the Ethics Committee of the Medical University of Vienna. Written informed consent was obtained from the parents after full explanation of the procedure.

Study Groups

The intervention group was treated as follows: If the infant did not spontaneously pass meconium during the first 12 h of life, then defecation was stimulated by administration of an enema (10 mL/kg saline containing 0.8 g/10 mL glycerine). The enema was placed in a syringe and applied via a single-use urinary catheter (CH 8) into the rectum. The catheter was coated with petrolatum as a lubricant before being inserted into the rectum (2 cm in infants <1000 g and 3 cm in infants weighing

1000–2000 g). The nursing staff assessed the quality of stools as meconium (black, thick, sticky) or no meconium by appearance. If the infant had not passed meconium during the 24 h following the enema, then another enema was applied. This procedure was repeated until complete evacuation of meconium was achieved. The protocol was terminated after 2 stools without macroscopic commingling with meconium had been passed within 24 h. If no stools were passed within 24 h after the first meconium-free stool, then another enema was applied. If meconium appeared after termination of the protocol, then the infant was excluded from the study. The time to complete evacuation of meconium was defined as time when the first meconium-free stool was passed. The end of the infants' stay in the neonatal intensive care unit was also the end of the observation period. In the control group, no intervention was performed.

Feeding Schedule

Oral feeding was started in both groups, the earliest after the first 12 h of life and after the first meconium passage (8). Infants were fed every 3 h by nasogastric tube or bottle, according to the infant's ability. If the mother decided to breast-feed, then oral feedings were started with breast milk or with a 5% hydrolysate of ultrafiltrated whey-dominated milk protein (Alfare; Nestlé) until breast milk was available. At a daily oral intake of 120 mL/kg, intravenous supplementation with nutrients was stopped and breast milk was fortified with breast milk fortifier (FM85; Nestlé). The concentration of the fortifier was increased every other day by 1% until the maximum concentration of 5% was reached. Concentration and volume of formula were increased alternatively every other day. Full enteral feedings were defined as an oral intake of 150 mL/kg (8). If the mother decided not to breast-feed or if breast milk was not available in sufficient amounts, then the infants received hydrolyzed protein formula (Alfare; Nestlé) starting at a concentration of 5%. Formula concentration was increased every other day by 2% until the maximum concentration of 13% was reached. If the infant's body weighed >1000 g, a formula designed for premature infants was used (Beba F, Nestlé).

Feeding was usually started at a volume of 8 mL/kg. Gastric residuals were assessed by aspiration via nasogastric tube before each feeding. If feeding was tolerated, then the amount was increased daily by a maximum of 16 mL/kg (8). Feeding intolerance was defined as previously described (2). All of the stools were tested for the presence of haemoglobin (Haemoccult; Beckman-Coulter, Krefeld-Fischlen, Germany). In case of feeding intolerance, feeding was withheld according to the clinical condition of the infant. Feeding was withheld for 6 h after extubation and during indomethacin therapy.

Statistical Analysis

The primary study outcome was defined as the time when the last meconium was passed. Based on studies investigating meconium passage in VLBW infants (6), a sample size estimation indicated that a total of 52 infants would suffice to detect a 30% difference in the outcome between the groups (α and β errors of 0.8 and 0.05, respectively). Secondary outcome of the study was defined as feeding tolerance represented by the variables "introduction of oral feedings," "feeding amount on 14th day of life," and "full enteral feedings." Results are expressed as median and range in the tables and as median and 95% confidence interval (CI) in the text. Given the non-normal distribution of the data, all comparisons were performed using nonparametric tests. The Mann-Whitney U test was used to compare groups. The χ^2 test was used to compare proportions. Times to complete meconium evacuation were compared by the log rank test. Multiple Cox regression models included the covariates birth weight, GA, and Clinical Risk Index for Babies score (9). A P value <0.05 was considered significant. SPSS software (SPSS Inc, Chicago, IL, version 10.0) was used for all calculations.

RESULTS

Study Population

Of 92 eligible infants, 9 were not included because of parental refusal, and 2 infants died before randomization. Due to protocol violations in 23 infants (no enema in the intervention group, n = 15; enemas in control group, n = 8 infants) recruitment in excess of the calculated sample size was necessary. Subjects were excluded from the per-protocol (PP) analysis if a protocol violation occurred 1 time during the study period. The PP population included 58 infants.

Baseline characteristics between study groups concerning GA, birth weight, sex, death, necrotizing enterocolitis (NEC), intraventricular haemorrhage, persistent ductus arteriosus, and Clinical Risk Index for Babies score were balanced (data not shown). Clinical characteristics, including feeding and stooling variables of study patients, are given in Table 1.

Intention-to-Treat (ITT) Population

The primary endpoint of the study was reached after median 9 d (95% CI, 7.7–11.0) in the control group and after 6.5 d (95% CI, 6.0–9.6) in the intervention group.

PP Population

The control group passed the last meconium after 10 d (95% CI, 7.2–11.3) and the intervention group after 5 d (95% CI, 4.9–10.0). The ITT and PP analyses showed only insignificant trends ($P = 0.11$ in both cases). Log rank tests were also insignificant ($P > 0.05$). Merely GA was a significant predictor for last meconium passage (ITT: $P = 0.01$, 95% CI, 1.01–1.05; PP: $P = 0.02$, 95% CI, 1.01–1.06). Furthermore, there were no differences in the secondary outcome variables between the groups (Table 1).

In the ITT population 1 infant in the control group and 3 infants in the intervention group developed NEC. None of these infants was treated according to study protocol, which led to termination and exclusion from the PP analysis. Of these 4 infants, 1 infant in each group

TABLE 1. *Demographic data and clinical characteristics of the study population, including feeding and stooling pattern*

	ITT			PP		
	Control group N = 39 median (range)	Intervention group N = 42 median (range)	*P* value	Control group N = 31 median (range)	Intervention group N = 27 median (range)	*P* value
Birth weight, g	939 (568–1450)	931 (491–1523)	0.56	1006 (568–1450)	890 (491–1523)	0.12
Gestational age, wk	27 + 2 (24 + 0–31 + 5)	27 + 3 (23 + 2–30 + 6)	0.84	27 + 2 (24 + 1 – 31 + 5)	27 + 2 (23 + 6 – 30 + 2)	0.9
Gestational age, d	191 (168–222)	192 (163–216)	0.84	191 (169–222)	191 (167–212)	0.9
Duration of observation period, d	31 (2–146)	24.5 (2–139)	0.36	29 (2–146)	26 (2–104)	0.5
Duration of hospital stay, d	85 (55–168)	90 (65–140)	0.66	85 (64–146)	90 (78–140)	0.59
Weight at discharge home, g	2075 (1430–4130)	2013 (1648–3606)	0.54	2090 (1430–4130)	1926 (1648–3170)	0.06
Introduction of oral feedings, day of life	2 (0–9)	2 (0–8)	0.99	2 (0–9)	2 (0–6)	0.76
Feeding amount on 14th day of life, mL/kg	45.8 (0–109.8)	53.4 (0–105.7)	1.00	48 (13.2–109.8)	64 (0–105.7)	0.89
Full enteral feedings (day of life)	27 (5–75)	26 (8–83)	0.91	25.5 (5–54)	26 (10–75)	0.65
Passage of first meconium, day of life	1 (1–6)	1 (1–13)	0.73	1 (1–4)	1 (1–4)	0.68
Passage of last meconium, day of life	9 (2–24)	6.5 (1–26)	0.11	10 (2–24)	5 (1–26)	0.11

Data are median and range; Mann-Whitney *U* test was applied as appropriate.

required surgery for intestinal perforation. A total of 6 infants received indomethacin for closure of persistent ductus arteriosus, which was not associated with intestinal perforation or NEC in any case. No adverse events such as bowel perforation or dehydration were observed in association with the enemas.

DISCUSSION

This study investigated the effect of small-volume enemas on meconium evacuation in VLBW infants. Although meconium evacuation tended to occur earlier in the intervention group (Table 1), it did not meet the preset efficacy criteria of a 30% difference between groups.

In the present study, a relatively high number of protocol violations occurred necessitating ITT and PP analysis. However, both analyses led to comparable results. Applying enemas for prophylactic and not for therapeutic purposes seemed to be a challenge for the nursing staff. Scheduled enemas in the intervention group were not applied when the abdomen of the baby looked soft and tender without major distensions of the belly, whereas in the control group, infants received enemas when the abdominal girth increased, the baby passed only tiny dark smudges, or visible and palpable loops of bowel occurred.

In mature neonates with hyperbilirubinemia and neonatal jaundice, treatment with glycerine laxatives causes earlier passage of meconium and lowers bilirubin level by reducing enterohepatic circulation (10). Recent published data on the efficacy of glycerine enemas and suppository chips in neonates reported that glycerine laxatives may also be helpful in preterm infants with feeding intolerance who have gastric residuals, emesis, and abdominal distension from gastrointestinal hypomotility (10). Thus far, prophylactic evacuation of meconium for prevention of meconium plug formation has not been investigated. However, the present study indicates that small-volume glycerine enemas do not significantly accelerate meconium passage. One reason for the ineffectiveness of glycerine enemas may be that the volume used was too small to sufficiently mobilise meconium from colon and small bowel. Hyperosmolar fluids such as Gastrografin may be more effective in the small volume used.

In addition, the frequency of enema application every 24 h until complete meconium evacuation may be too low to be efficient. A more frequent application (eg, 12 h) may be more effective in accelerating passage of meconium. It is also possible that meconium evacuation cannot be accelerated by enemas because rapid and sufficient meconium passage indicates a correct functionality of the digestive tract. In this respect ''forcing'' the meconium passage with enemas will prove useless.

Meconium evacuation appears to be a key factor for feeding tolerance. Rapid evacuation of meconium is associated with improved early feeding tolerance (6). In the Mihatsch et al. study, enteral feeding could be advanced early in healthy VLBW infants who evacuate their meconium within a few days. Meconium evacuation also correlated with variables of feeding tolerance in our

study. However, oral feeding was introduced after the first meconium passage and this effect can be explained solely by the use of a feeding protocol depending on first meconium passage. Although the clinical relevance of accelerated meconium passage could be improved feeding tolerance, this needs to be shown in future randomized trials with more effective but still safe interventions.

All NEC cases occurred in infants who were not treated according to protocol. Therefore, it is difficult to relate occurrence of NEC to study treatment.

CONCLUSION

Repeated daily application of small-volume diluted glycerine enemas does not accelerate meconium evacuation in VLBW infants.

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