The Effect of an Osmotic Contrast Agent on Complete Meconium Evacuation in Preterm Infants

WHAT’S KNOWN ON THIS SUBJECT: Delayed meconium passage impairs gastrointestinal function in premature infants. No intervention has been identified that accelerates meconium passage sufficiently. Gastrografin is an osmotic contrast agent used for radiologic examination of the bowel or for conservative treatment of uncomplicated meconium ileus.

WHAT THIS STUDY ADDS: Gastrografin did not accelerate complete meconium evacuation but stimulated gastrointestinal motility in a randomized, placebo-controlled trial in premature infants. Application shortened the time to full enteral feedings and hospital stay but was associated with necrotizing enterocolitis as a possible adverse event.

abstract

OBJECTIVE: To determine whether enteral application of the osmotic contrast agent Gastrografin accelerates complete meconium excretion and improves feeding tolerance in very low birth weight infants.

METHODS: This study was a stratified, randomized, placebo-controlled trial in premature infants with a birth weight <1500 g and a gestational age <32 weeks who received 3 mL/kg Gastrografin diluted 1:3 with water within their first 24 hours of life, or placebo.

RESULTS: Passage of last meconium occurred after a median of 7 days (95% confidence interval: 6–9 days, n = 39) in the intervention group and after 8 days (95% confidence interval: 7–10 days, n = 39) in the control group (P = .61); however, Gastrografin application was associated with a 7.5-day shorter time to full enteral feedings, a 24-day shorter stay in the NICU, and a 17-day reduction in the overall hospital stay in the intervention group compared with the control group. A numerically higher incidence of necrotizing enterocolitis (21%) was observed in the intervention group, however.

CONCLUSIONS: Gastrografin application did not accelerate meconium evacuation, but the higher stool frequency during the first week of life had a beneficial effect on the time to full enteral feedings and later hospital stay; however, it may increase the necrotizing enterocolitis risk. Further investigations are needed with modified protocols, and the prophylactic use of Gastrografin cannot currently be recommended without further clinical trials. Pediatrics 2012;130:e1600–e1606
In premature infants the establishment of proper gastrointestinal function is challenging and often associated with delayed meconium passage. Meconium evacuation depends on gestational age (GA) and birth weight: the more immature an infant is, the later meconium passage starts, and the longer meconium passage lasts. The mean duration of meconium evacuation in premature infants with a GA <30 weeks is 8 days, whereas mature infants excrete their meconium in 2 days. The obstruction of deep intestinal segments by tenacious, sticky meconium frequently leads to gastric residuals, a distended abdomen, and delayed food passage, which extends the time to reach full enteral feedings. As a consequence, it prolongs the probability of acquiring infections due to intravenous access for parenteral nutrition and increases the duration of the hospital stay of the infant. The relation between meconium passage and feeding tolerance remains controversial, however. Although 1 study revealed that there is little concordance between first meconium passage and feeding tolerance, Mihatsch et al showed that rapid and complete excretion of meconium is crucial for oral feeding tolerance and has a positive effect on it. Recently, we performed a prospective randomized trial to determine whether repeated prophylactic applications of small-volume glycerin enemas accelerate passage of meconium in very low birth weight (VLBW) infants. Disappointingly, application of enemas did not accelerate meconium evacuation. A possible reason for the ineffectiveness of glycerin enemas is that the volume used was too small to mobilize tenacious meconium sufficiently from the colon and small bowel.

Gastrografin is a radiopaque contrast agent for the gastrointestinal tract that can be administered orally or rectally. In neonatal intensive care, Gastrografin is used for the treatment of meconium ileus. Gastrografin has a strong osmotic effect and leads to water influx into the intestinal lumen. It may be hypothesized that the peristaltic movement is accelerated, and the premature infant excretes stool during the hours after application. Gastrografin might be more effective in mobilizing meconium from the small bowel and deep parts of the colon. We hypothesized that enteral application of Gastrografin accelerates meconium evacuation in premature infants and thereby enhances feeding tolerance in this population.

METHODS

Study Design
The study design was a randomized, double-blind, placebo-controlled trial performed at the NICU of the Department of Pediatrics, Medical University of Vienna/Austria from October 2007 to February 2011. Premature infants with a birth weight \(\leq 1500\) g and a GA \(\leq 32\) weeks were eligible for inclusion in the study. Randomization lists were generated by using a Web-based program by a clinical pharmacologist (B.J.) not otherwise involved in the conduct of the trial. Randomization assignment was performed by using sealed opaque envelopes. Block sizes of 10 contained 5 subjects of each group. Infants were stratified according to their GA (<28 vs \(\geq 28\) weeks) and assigned randomly to the intervention or control group. The study was approved by the ethics committee of the Medical University of Vienna. After full explanation of the procedure, written informed consent was obtained from the parents.

Exclusion Criteria
Exclusion criteria were defined as major congenital disorders, chromosomal aberrations, systemic metabolic disease, and preexisting gastrointestinal abnormalities (ie, Morbus Hirschsprung). Because Gastrografin is an osmotic contrast agent, it is possible that Gastrografin can aggravate preexisting conditions of severe hypotension. Severe hypotension was defined as persisting hypotension even under catecholamine (eg, adrenaline, epinephrine) support for >3 hours.

Study Medication
Gastrografin (Bayer, Leverkusen, Germany) is an osmotic, ionic contrast agent with an osmolarity of 2150 mOsmol/L. One hundred milliliters of gastroenteral solution contain 10 g of sodium amidotrizoate and 66 g of meglumine amidotrizoate. The iodine concentration is 370 mg/mL. The contrast-enhancing substance of Gastrografin is a salt of the amido (dia-) trizoic acid in which the radiograph-absorbing iodine is present in a stable chemical bond. Absorption of amidotrizoic acid, the radiopaque agent of Gastrografin, after oral administration is only 3%. In newborn infants, the manufacturer recommends diluting Gastrografin 1:3, with water for injection resulting in a final osmolarity of 717 mOsmol/L. Thyrotropin levels were measured on the fourth, 14th, and 28th days of life to monitor possible systemic adverse effects of the study medication on thyroid function.

Study Groups
Infants in the intervention group were administered 3 mL/kg of Gastrografin orally via gastric tube, diluted 1:3 with water (total 9 mL/kg) within the first 6 to 24 hours of life. As the primary end point was time to complete meconium evacuation, starting as early as possible was assumed to increase assay sensitivity. The control group received the equivalent amount of water (8 mL/kg). Based on the order in which infants entered the study, infants were assigned a randomization number (whereby stratification was applied for GA at randomization). The details of the randomization were unknown to the investigator and the site staff except for the study nurse, who
prepared and applied all the study medication and was not otherwise involved in the conduct of the trial.

After admission of the patient to the NICU, the infant received primary care according to standard principles of neonatal intensive care (monitoring of oxygen saturation, heart rate, blood pressure, temperature, fluid intake, and urine rate, and intravenous access by peripheral or central venous line).

To exclude an already existing perforation or a gastrointestinal abnormality, a plain abdominal radiograph was performed before the beginning of the study. During the study, unblinding was avoided by covering the abdomen of the infants with a small lead gown used for premature infants when they received chest radiographs. The nursing staff assessed the quality of stools as “meconium” (black, thick, sticky) or “nonmeconium” by appearance and documented data into the patient documentation system. The time to complete meconium evacuation was defined as the day of life on which the last meconium was passed. Documentation of stool consistency, color, and amount was continued until the end of each infant’s stay at the NICU. The observation period ended when the infant was transferred or discharged.11

Feeding Schedules

Standardized Feeding Regimen

All preterm infants routinely received a gastric tube during the first hour of life. Within the first 12 hours of life, minimal enteral nutrition was started, defined as 1 mL of nutrition (preterm formula or breast milk) every 3 hours. The introduction of enteral feedings was achieved by using colostrum of the premature infant’s mother.12 If no breast milk was available, undiluted hydrolyzed preterm formula (Prematil HA; Milupa, Puch bei Hallein, Austria) or Beba F (Nestle, Vevey, Switzerland) was used.13 As soon as breast milk was available, nutrition was changed to breast milk. The daily amount of nutrition was increased by 20 mL/kg/d.14,15 Full enteral feedings were defined as 140 mL/kg.16 At an enteral intake of 100 mL/kg, breast milk was supplemented with breast milk fortifier, such as Aptamil FMS (Milupa), FM 85 (Nestle). If the concentration of the fortifier was increased, the volume of feedings remained the same for 2 days.16

Gastric Residuals and Feeding Intolerance

Detailed information concerning gastric residuals and feeding intolerance is given in the Supplemental Information.

Data Collection

Demographic data were recorded for all infants. Infants were monitored, with documentation of clinical condition of the abdomen (size, tension, peristalsis, apparent standing intestinal loops), stools pattern, ventilation, and ventilator support (positive end-expiratory pressure) every hour during the first 48 hours after Gastrografin administration. Blood pressure was monitored continuously by an arterial line during the first 3 days of life. Electrolytes and urinary output in milliliter per kilogram per hour were monitored every 12 hours. During the further study period, the following parameters were recorded daily: body weight, volume of enteral and parenteral fluids, volume and color of gastric residuals before every meal, abdominal girth, presence of gross abdominal distension, presence of persistent visible loops without peristalsis, presence of abdominal tenderness, stool pattern, and respiratory support. Concomitant application of suppositories and enemas were recorded as well as laboratory parameters of infection (complete blood cell count, C-reactive protein, interleukin-8, blood culture), and antibiotic therapy. Necrotizing enterocolitis (NEC) was defined according to the stages by Bell as proven NEC grade 2a.17 The physician assessing the NEC radiographs was blinded to the treatment assignment.

Sample Size Calculation and Statistical Analysis

We hypothesized that the enteral application of Gastrografin during the first 24 hours of life can accelerate meconium evacuation, defined as the time until the last meconium was passed in days (primary outcome).

Chart reviews of previous patients at our department indicated that the mean time to meconium evacuation was 9.32 days (SD ± 5.1). We performed an open pilot study in 20 subjects: in the intervention group, we observed 7.38 days to meconium evacuation (SD ± 1.8); in the control group, we observed 8.91 days to meconium evacuation (SD ± 1.2). The pilot study suggested a 17% difference between groups, so we calculated to have a power of 95%, if we are able to include 37 subjects in each group of the per protocol (PP) analysis.

Secondary outcome variables were feeding tolerance as evidenced by “start of enteral feeding,” “amount of nutrition on the 14th day of life,” and “day of full enteral feedings” (defined as 140 mL/kg of supplemented breast milk or formula). To evaluate the efficacy of Gastrografin, the stooling frequency during the first 2 weeks of life was calculated.

Results of primary and secondary outcome variables are expressed as the median and the range in tables and as median and 95% confidence intervals (CIs) in the text. Given non-normal distribution of the data, all comparisons were performed by using nonparametric tests. The \( \chi^2 \) test was used for dichotomous (demographic) variables. The Mann–Whitney \( U \) test was used to evaluate differences in the primary and secondary outcome. Multivariate logistic regression models (including these variables: birth weight, group, NEC, and persistent ductus arteriosus) were used.
to identify the possible influence of predictors. For all tests, a $P$ value < .05 was considered as statistically significant. SPSS statistical software system (version 16.0; SPSS Inc, Chicago, IL) was used for all calculations.

**RESULTS**

**Study Population**

During a 3-year study period, 789 infants were eligible for enrollment in the study. Six hundred ninety-three infants were excluded for the following reasons: informed consent was not obtained in time ($n = 660$), parental refusal ($n = 21$), and 12 infants died before randomization. The final cohort included 98 infants. Owing to protocol violations for 18 infants (study medication was not administered or the infant vomited, $n = 5$; transfer before the 14th day of life/primary outcome could not be evaluated, $n = 13$), recruitment in excess of the calculated sample size was necessary. Because of the protocol violations, both the PP and intention-to-treat (ITT) population were analyzed. The PP population included 78 infants. Both analyses led to comparable results, suggesting that the protocol violations did not introduce any bias.

**Baseline Characteristics and Outcome Data**

Baseline characteristics and outcome data between study groups were balanced and are summarized in Table 1. No differences between the groups or between the ITT and PP population were observed; however, in the PP population, 8 treated infants (21%) and 3 control infants (8%) developed NEC. In the intervention group, the mortality related to NEC was 13% ($n = 5$) vs 0% in the control group. Onset of NEC was between the 12th and 27th days of life and not confounded by type of enteral feedings (breast milk or formula).

**Primary and Secondary Outcome**

Clinical characteristics, including feeding and stooling variables of study patients, are given in Table 2. In the PP group, the primary end point meconium evacuation lasted a median of 7 days (95% CI: 6–9 days) in the intervention group and 8 days (95% CI: 7–10 days; not significant) in the control group. A post-hoc subgroup analysis showed no difference in meconium evacuation between infants with a birth weight <1000 g and those with birth weights of 1001 to 1500 g. Time to full enteral feedings was 7.5 days shorter in the intervention group (median, 19 days; 95% CI: 12–33 days; not significant) than in the control group (median, 26.5 days; 95% CI: 26–42 days; $P = .05$). This reduction was associated with a 24-day shorter stay in the NICU and a 17-day reduction in the overall hospital stay in the intervention group compared with the control group (Table 2). A detailed analysis of the stool pattern showed that infants in the intervention group produced significantly more stools during the first week of life than infants in the control group (controls: 7.5 stools versus intervention: 10.5 stools, $P = .013$; Table 3). The mean daily stool frequency also was higher in the intervention group.

In a multivariate analysis (logistic regression model), treatment group remained a significant independent predictor of the duration of hospitalization at our tertiary care center, when days to total enteral nutrition were entered in the model ($P < .05, \beta = .31$).

**Side Effects After Administration of Study Medication**

No pathologic results were observed in baseline radiograph films obtained before Gastrografin use. Gastric residuals were analyzed separately during the first 24 hours after administration of the study medication, and data are given in Table 4. Infants in the control group had significantly more frequent bloody gastric residuals (18%) than in the intervention group (3%; $P = .03$). These data indicate that the application of Gastrografin caused no local mucous irritations in the stomach. None of the infants developed hypotension with Gastrografin use or within 24 hours after Gastrografin administration. Furthermore, no infant in either group developed pathologic thyrotropin values.

**TABLE 1** Demographic Characteristics and Outcome Data Concerning the Study Population, Divided Into ITT and PP Populations

<table>
<thead>
<tr>
<th></th>
<th>ITT Control Group, $N = 49$</th>
<th>ITT Intervention Group, $N = 47$</th>
<th>PP Control Group, $N = 39$</th>
<th>PP Intervention Group, $N = 39$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, g; median (range)</td>
<td>900 (480 to 1414)</td>
<td>870 (480 to 1440)</td>
<td>795 (480 to 1414)</td>
<td>870 (480 to 1440)</td>
</tr>
<tr>
<td>GA, wk; median (range)</td>
<td>27 + 3 (23 + 4 to 31 + 2)</td>
<td>26 + 6 (24 + 1 to 30 + 5)</td>
<td>26 + 6 (23 + 4 to 31 + 2)</td>
<td>26 + 6 (24 + 1 to 30 + 5)</td>
</tr>
<tr>
<td>GA, d; median (range)</td>
<td>192 (165 to 219)</td>
<td>188 (169 to 215)</td>
<td>188 (165 to 219)</td>
<td>188 (169 to 215)</td>
</tr>
<tr>
<td>Male gender, N (%)</td>
<td>20 (59)</td>
<td>20 (42)</td>
<td>22 (56)</td>
<td>14 (26)</td>
</tr>
<tr>
<td>Deceased, N (%)</td>
<td>7 (14)</td>
<td>8 (17)</td>
<td>6 (15)</td>
<td>7 (18)</td>
</tr>
<tr>
<td>NEC, N (%)</td>
<td>4 (8)</td>
<td>10 (21)</td>
<td>3 (6)</td>
<td>8 (21)</td>
</tr>
<tr>
<td>NEC surgery, N (%)</td>
<td>1 (2)</td>
<td>6 (13)</td>
<td>1 (3)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Intraventricular hemorrhage I + II, N (%)</td>
<td>13 (27)</td>
<td>9 (19)</td>
<td>9 (23)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Intraventricular hemorrhage III + IV, N (%)</td>
<td>3 (6)</td>
<td>3 (6)</td>
<td>3 (8)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Persistent ductus arteriosus, N (%)</td>
<td>28 (57)</td>
<td>22 (46)</td>
<td>24 (61)</td>
<td>18 (46)</td>
</tr>
</tbody>
</table>

The $\chi^2$ test was used for dichotomous (demographic) variables. The Mann–Whitney U test was used to evaluate differences in the primary and secondary outcome. There were no significant differences in baseline characteristics or outcome data between groups ($P > .05$).
Periods of Feeding Intolerance and Use of Suppositories and Enemas
No differences were observed between groups in periods of mild or severe feeding tolerance until full enteral feedings (Table 5); however, infants in the control group received significantly more glycerin suppositories until complete meconium excretion was achieved \( (P = .008) \).

DISCUSSION
This double-blind, randomized, placebo-controlled trial examined the effect of enterally applied Gastrografin on meconium evacuation in VLBW infants. The results indicate that the osmotic contrast agent Gastrografin did not accelerate complete meconium excretion; however, the stool frequency was significantly higher during the first week of life, indicating that gastrointestinal mobility was enhanced. Time to full enteral feedings and hospital stay in the NICU were significantly shorter in the Gastrografin group as compared with the group receiving placebo.

Gastrointestinal Function
In the literature, the relationship between meconium evacuation and feeding tolerance in premature infants is controversial. Although some authors showed a link between feeding tolerance and meconium passage, others could not prove a causality. The establishment of proper gastrointestinal function is characterized by feeding tolerance and a normal, regular stool pattern, however. The so-called “meconium obstruction of prematurity” is a distinct clinical condition in VLBW infants with obstructive symptoms such as abdominal distension occurring several days after having passed some initial meconium. This meconium obstruction should be avoided by all means, but so far it remains unclear if meconium passage can be influenced prophylactically (eg, by enemas). For therapeutic purposes, agents such as N-acetylcysteine and Gastrografin (an osmotic contrast agent) are proven to be effective in solving gastrointestinal obstructions caused by meconium. Gastrografin can be administered orally or as an enema and is used as a contrast medium for the radiologic examination of the gastrointestinal tract. Gastrografin can be given by enema for conservative treatment of an uncomplicated meconium ileus. There is an advantage to the high osmotic pressure of the contrast medium; the surrounding tissue is forced to release considerable amounts of fluid, which then flows into the gut and dissolves the inspissated (thickened or hardened) meconium. The intention of this trial was to investigate if Gastrografin also can be used prophylactically to accelerate complete meconium excretion. Although Gastrografin did not accelerate meconium evacuation, the
stool frequency was significantly higher in the intervention group compared with placebo during the first week of life. These data indicate that gastrointestinal mobility was enhanced by Gastrografin, which could have accelerated the time to enteral feedings. Full enteral feedings were achieved 7.5 days earlier in the Gastrografin group compared with the placebo group, and consequently parenteral feedings and intravenous catheter days were reduced by the same amount of time. This reduction also was associated with a shortened hospital stay. In the Gastrografin group, infants were discharged from the hospital 17 days earlier than in the placebo group.

**Side Effects and Adverse Events**

No severe adverse events were observed in direct context to Gastrografin application. In 5 infants, problems with the volume of study medication occurred. The quantity of Gastrografin/water mixture was 9 mL/kg, which is a large feeding volume for a premature infant on or her first day of life. Three infants reacted with emesis of study medication, and 2 infants developed bradycardia after instillation of 4 to 5 mL. Although nausea and vomiting are reported to be frequent side effects of enteral Gastrografin administration, these problems were observed only in infants with a birth weight between 500 and 650 g. These smallest premature infants seemed to be more sensitive to high feeding volumes than larger neonates. A numerically higher proportion of infants in the Gastrografin group (21%) developed NEC, as compared with the control group (8%). Although this difference is not significant, an NEC incidence of 21% in the treatment group is alarming. A detailed analysis of the NEC cases showed that all NEC infections occurred between the end of the second and the end of the fourth week of the infant's life, which is consistent with the literature. Thus, the development of NEC occurred well after the end of Gastrografin administration; however, this finding does not exclude the possibility that Gastrografin might be a risk factor for the development of later NEC. Tuladhar et al. report a case of severe Gram-negative sepsis caused by complete breakdown of mucosal integrity after enteral Gastrografin application. In this report, undiluted Gastrografin was given to a premature infant for gut stimulation for 6 consecutive days; 3 days after the last dose, the mucosal integrity of the bowel collapsed, and the infant developed Gram-negative sepsis. Irreversible damage to the mucosa of the small intestine also was reported in an animal model, in which newborn rats received undiluted Gastrografin twice a day to investigate bacterial translocation of Klebsiella bacteria; however, in neonates Gastrografin should always be diluted (according to the summary of product characteristics), otherwise severe gastrointestinal side effects may occur. If not only a chance finding, one may speculate that a baseline mucosal injury that acts as a nidus may perhaps be responsible for the Gastrografin-associated incidence of NEC occurring many days after its use. This study raises the question, “Where is the ‘safety cutoff point’ of osmolarity for the premature gut?” The American Academy of Pediatrics recommended that osmolarity of milk or formula should not exceed 400 mOsmol/L. This osmolarity is easily exceeded when therapeutic supplements, such as multivitamins, are added. The osmolarity of milk is then increased up to 700 to 1000 mOsmol/L, depending on the supplement added. Supplementation of human milk or formula is a common practice in neonatology, even in the smallest infants, but it usually starts when premature infants tolerate a minimum of half-ental feeds. In the current study, we used a drug with an osmolarity of 717 mOsmol/L, which is comparable to supplemented human milk, but we administered it during the first hours of life. It is possible that the mucosa is much more vulnerable early after birth than later in life. Factors related to premature birth, such as selective mesenteric ischemia in response to perinatal stress, may aggravate mucosal damage caused by high osmolarity.

**CONCLUSIONS**

Gastrografin did not accelerate complete meconium evacuation in premature infants but stimulated gastrointestinal motility, as evidenced by a significantly higher stool frequency during the first week of life. This finding was associated with accelerated full enteral feedings and shortened stay in the NICU in infants treated with Gastrografin. Although the results are of clinical interest, the observed numerical increase in NEC is a concern that strongly argues against prophylactic routine use of Gastrografin. Further clinical trials may be warranted to examine the safety and efficacy of Gastrografin at higher dilution.

### TABLE 5 Feeding Intolerance, Suppositories, and Enemas

<table>
<thead>
<tr>
<th></th>
<th>Control Group, Mean (SD); N = 39</th>
<th>Intervention Group, Mean (SD); N = 39</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periods of mild feeding intolerance until full enteral feedings</td>
<td>1.23 (0.94)</td>
<td>1.15 (0.89)</td>
<td>.55</td>
</tr>
<tr>
<td>Periods of severe feeding intolerance until full enteral feedings</td>
<td>0.71 (1.05)</td>
<td>0.68 (1.08)</td>
<td>.92</td>
</tr>
<tr>
<td>No. of glycerine suppositories until complete meconium evacuation</td>
<td>0.67 (0.77)</td>
<td>0.26 (0.55)</td>
<td>.008*</td>
</tr>
<tr>
<td>No. of enemas until complete meconium evacuation</td>
<td>1.38 (0.78)</td>
<td>1.15 (0.87)</td>
<td>.25</td>
</tr>
</tbody>
</table>

* = P < .05.

The Mann–Whitney U test was used to evaluate differences in the primary and secondary outcome.
REFERENCES

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