Meconium Evacuation for Facilitating Feed Tolerance in Preterm Neonates: A Systematic Review and Meta-Analysis

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Key Words

Preterm infant · Meconium · Suppositories · Enema · Feed intolerance

Abstract

Background: A delayed passage of meconium is considered as a risk factor for feed intolerance in preterm neonates. **Objectives:** The aim of this study was to review the effects of different therapeutic agents for meconium evacuation on feed tolerance in preterm neonates. **Methods:** A systematic review of randomised controlled trials (RCTs) of different therapeutic agents for meconium evacuation in preterm neonates (gestation <32 weeks and/or birth weight <1,500 g) using the Cochrane systematic review methodology was undertaken. Databases including Google Scholar were searched in January 2016. The primary outcome was the time to reach full feeds (TFF; ≥ 120 ml/kg feeds with stoppage of parenteral nutrition >24 h). Secondary outcomes included necrotising enterocolitis (NEC), weight at discharge and adverse effects. The results were summarised as per the GRADE guidelines. **Results:** Six RCTs (2 each of glycerine suppository and enema, 1 normal saline enema and 1 oral osmotic contrast agent; $n = 442$) with a low or unclear risk of bias were included. The pooled estimate (random effects model) showed no reduction in TFF [mean difference (MD) -0.03 ,

95% CI $-2.47, 2.41$, $p = 0.98$; level of evidence: low]. No differences in NEC [risk ratio (RR) 1.71, 95% CI 0.63, 4.65, $p = 0.30$; level of evidence: low] and weight at discharge (MD -0.08 , 95% CI $-0.30, 0.15$, $p = 0.50$; level of evidence: low) were found. The trial assessing oral osmotic contrast agents reported a trend towards a higher incidence of NEC $\geq$ stage II. There were no other adverse effects. **Conclusion:** Limited low-quality evidence indicates that prophylactic glycerine suppository, small volume glycerine/normal saline enema or oral osmotic contrast agents to evacuate meconium did not reduce TFF in preterm neonates. Large, well-designed trials are essential to study this clinically significant issue.

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Introduction

Recent advances in neonatal care have improved the survival of preterm very low birth weight (VLBW) neonates. Suboptimal nutrition is linked with adverse developmental outcomes in this population of high-risk neonates [1]. Optimising enteral nutrition is challenging in preterm VLBW neonates due to feed intolerance that relates to the immaturity of gastrointestinal motility and poor coordinated peristalsis [2–5]. Feed intolerance is associated with prolonged dependence on parenteral nutri-

tion and its complications (e.g. sepsis, cholestasis) and delayed maturation of gut function [6–9]. The use of medications such as prokinetics (e.g. erythromycin, cisapride) to improve gut motility has failed to show significant benefits in VLBW neonates and is associated with adverse effects [10, 11].

A delayed passage of meconium is identified as one of the risk factors for feed intolerance in preterm VLBW neonates [12]. Mihatsch et al. [12] evaluated the correlation between the timing of the first and last meconium passage and feeding tolerance in VLBW neonates, and demonstrated that rapid evacuation of meconium was associated with improved feed tolerance during first 14 days of life. Glycerine suppositories are often used to facilitate meconium evacuation in many neonatal units [13]. Glycerine acts as a lubricant and a rectal stimulant due to the mildly irritant action of glycerol [14]. A survey of enteral feeding practises among Australian neonatologists showed that the use of glycerine suppositories (sometimes 30.9%, often 9.1%, always 3.6%) and prokinetics (sometimes 25.9%, often 5.6%, always 0%) was not uncommon to improve feed tolerance [13]. An observational study by Shim et al. [5] reported benefits of meconium evacuation by glycerine enema in achieving earlier full enteral feeds (hazard ratio 2.9, 95% CI 1.8, 4.8) and reducing the incidence of line sepsis in VLBW neonates. So far all reviews on the topic of meconium evacuation in preterm neonates are limited to the use of either a glycerine suppository or enema [15–17]. Considering these data and the significance of optimising enteral nutrition in preterm VLBW neonates, we aimed to conduct a systematic review of studies reporting the effects of different therapeutic agents for meconium evacuation on feed tolerance in this population.

Methods

The Cochrane methodology and PRISMA guidelines (online suppl. material; see www.karger.com/doi/10.1159/000444075 for all online suppl. material) were used for conducting and reporting this systematic review, respectively [18, 19]. Ethics approval was not required.

Eligibility Criteria

Randomised controlled trials (RCTs) and quasi-RCTs were eligible for inclusion. Non-RCTs, reviews and commentaries were excluded, but read to identify other potential studies.

Participants and Types of Intervention

Inclusion criteria were neonates born ≤ 32 weeks of gestation and/or with a birth weight $< 1,500$ g. The exclusion criteria were based on major chromosomal and congenital anomalies. Within

the studies, meconium evacuation with any therapeutic agent (e.g. rectal suppository or small volume enema) versus control represented the types of intervention of interest.

Types of Outcome

The primary outcome was the time to reach full feeds (TFF), defined as enteral feeds ≥ 120 ml/kg or full feeds with stoppage of parenteral nutrition > 24 h. Secondary outcomes included the following: (1) necrotising enterocolitis (NEC; $\geq$ stage II) [20], (2) mortality, (3) duration of hospital stay, (4) weight at discharge, (5) rectal bleeding, (6) perforation and (7) other adverse effects, e.g. vomiting, dehydration.

Search Strategy

We searched MEDLINE (from 1966), EMBASE (from 1980), CINAHL and the Cochrane Central Register of Controlled Trials in December 2014 for published studies, and updated the searches in January 2016. We used the following search terms in various combinations: (a) population: neonate(s), newborn(s), infant*, premature, very low birth weight(s); (b) intervention: meconium (subject heading) OR meconium*, enema*, glycerol, suppositories*, laxative; (c) outcome-feed*, feed intolerance, nutritional intolerance, enteric feeding, enteral nutrition. We restricted our search to publication type ‘randomized controlled trial’, ‘controlled trial’ or ‘clinical trial’. Online abstracts of Pediatric Academic Society (PAS) meetings were reviewed from 2002. Abstracts of conference proceedings including the Perinatal Society of Australia and New Zealand (PSANZ), European Academy of Paediatric Societies, and the British Maternal and Fetal Medicine Society were searched in EMBASE. Google Scholar was searched for articles that might not have been cited in the standard medical databases. The reference lists of identified studies and review articles were searched to identify additional eligible studies. We also searched www.clinicaltrials.gov and the Australian New Zealand trial registry (www.anzctr.org.au) for ongoing studies. No language restriction was applied. Reviewers M.D. and H.B. conducted the literature search independently.

Study Selection

The abstracts of the citations obtained from the initial broad search were read independently by reviewers M.D. and H.B. to identify potentially eligible studies. Full-text articles of these studies were obtained and assessed independently by reviewers M.D. and H.B. for eligibility using the predefined eligibility criteria. Differences in opinion were resolved by group discussion among all reviewers to reach a consensus. Multiple publications of the same study were identified and excluded to avoid duplication of the data.

Data Extraction

Reviewers M.D. and H.B. extracted the data independently using a data collection form designed for this review. For dichotomous outcomes, the number of patients with the event and the number of patients analysed in each treatment group of each trial were entered into the form. For continuous outcomes we planned to enter the mean and standard deviations. Information about study design and outcomes were verified by all reviewers. Discrepancies during the data extraction process were resolved by discussion and consensus among all reviewers. We contacted authors for additional information/clarifications when details were not available in the published manuscripts.

Fig. 1. Flow chart of the study selection process after screening of the electronic search.

Risk of Bias Assessment

The risk of bias was assessed using the Cochrane ‘Risk of Bias Assessment Tool’ [21]. Two authors (M.D. and H.B.) independently assessed the risk of bias in the domains of random number generation, allocation concealment, blinding of participants and outcome assessors, completeness of follow-up, selective reporting and other biases. The studies were assigned as of high, low or unclear risk of bias. Difference of opinion was resolved by group discussion to reach a consensus.

Data Synthesis

A meta-analysis was conducted using Review Manager 5.3 (Cochrane Collaboration, Nordic Cochrane Centre), with ‘intention to treat analysis’ of the data. We used a random-effects model assuming wide heterogeneity. The categorical measure of effect size was expressed as the risk ratio (RR; Mantel-Haenszel method), and the mean difference (MD; inverse variance method) was used for continuous measures. Statistical heterogeneity was assessed using the χ^2 test, I^2 statistic, and by visual inspection of the forest plot (overlap of confidence intervals). The risk of publication bias was intended to be assessed by a funnel plot [22].

Summary of Findings

Data concerning the quality of evidence, the magnitude of effect of the intervention, and the sum of available data on the main outcomes were presented in the ‘summary of findings table’ as per the GRADE (the grading of recommendations assessment, devel-

opment and evaluation) guidelines [23]. The domains of risk of bias, inconsistency or heterogeneity of evidence, indirectness of evidence, imprecision of results and publication bias were included.

Results

The databases and Google Scholar search retrieved 188 potentially relevant citations (fig. 1). A total of 16 studies were read in detail. We identified 7 studies that assessed interventions to evacuate meconium. The observational study by Shim et al. [5] ($n = 83$) was excluded from the final analysis. Thus, a total of 6 studies ($n = 442$) assessing different interventions (glycerine suppository/enema, saline enema, oral osmotic contrast agent) for meconium evacuation were eligible for inclusion in the analysis [24–29]. The characteristics of these studies are shown in table 1. The risk of bias in these studies was low or unclear (fig. 2). Four of the 6 studies had TFF as the primary outcome [24, 26, 27, 29], and those by Haiden et al. [25] and Saenz de Pipaón Marcos et al. [28] had TFF as the secondary outcome. We used the method of Hozo et al. [30] to

Table 1. Characteristics of the included studies

Study	Characteristics	
Haiden [25], 2007	Population	GA $\leq$ 32 weeks, BW $\leq$ 1,500 g, n = 81 (intervention 42 vs. control 39)
	Intervention	Enema: 10 ml/kg NS containing 0.8 g/10 ml glycerine; repeated if failed to pass meconium in the 24 h following the first enema until complete evacuation of meconium
	Comparison	No intervention
	Primary outcomes	Meconium evacuation
	Secondary outcomes	TFF (150 ml/kg), duration of hospital stay and weight at discharge
Khadr [24], 2011	Type of milk	EBM, formula feed or a mixture depending on the availability of breast milk
	Population	GA $\leq$ 32 weeks, n = 54 (intervention 29 vs. control 25)
	Intervention	Glycerine suppository daily for 10 days
	Comparison	No intervention
	Primary outcomes	TFF (discontinuation of parenteral nutrition for $\geq$ 48 h without feeds being withheld or reduced)
Saenz de Pipaón Marcos [28], 2013	Secondary outcomes	NEC, episodes of blood culture-positive sepsis, feed intolerance, growth and nutrition
	Type of milk	EBM, formula feed or a mixture depending on the availability of breast milk
	Population	GA $\leq$ 28 weeks, n = 60 (intervention 30 vs. control 30)
	Intervention	Twice daily enema (10 ml/kg saline) until complete evacuation of meconium and rectal stimulation thereafter until two stools were passed daily without intervention for 3 days
	Comparison	Enema/rectal stimulation only in the presence of abdominal distension without the passage of stools for the previous 24 h
Mena [26], 2014	Primary outcomes	Normalisation of stooling pattern
	Secondary outcomes	TFF (120 ml/kg)
	Type of milk	EBM, formula feed or a mixture depending on the availability of breast milk
	Population	Preterm, BW = 500–1,250 g, n = 101 (intervention 50 vs. control 51)
	Intervention	Enemas with glycerol (0.8 ml glycerol + 3 ml saline or 1 ml glycerol + 5 ml saline depending on BW under or over 800 g, respectively); the enemas were initiated between 12–96 h and repeated every 12 or 24 h, respectively, depending on whether meconium was passed or not, and continued until transition stools appeared
Shinde [27], 2014	Comparison	Rectal stimulation starting within the first 4 days
	Primary outcomes	Meconium evacuation and TFF (discontinuation of parenteral fluids)
	Secondary outcomes	Sepsis, hyperbilirubinaemia and NEC
	Type of milk	EBM, formula feed or a mixture depending on the availability of breast milk
	Population	GA 28–32 weeks, BW = 1,000–1,500 g, n = 50 (intervention 25 vs. control 25)
Haiden [29], 2012	Intervention	Glycerin suppository (1 g) once a day from day 2 to day 14 of life
	Comparison	No intervention
	Primary outcomes	TFF (180 ml/kg/day of feed for at least 24 h)
	Secondary outcomes	Time to regain BW and NEC
	Type of milk	EBM, formula feed or a mixture depending on the availability of breast milk
Haiden [29], 2012	Population	GA $\leq$ 32 weeks, BW $\leq$ 1,500 g, n = 96 (intervention 47 vs. control 49)
	Intervention	Oral Gastrografin 3 ml/kg diluted 1:3 with water during the first 6–24 h of life
	Comparison	Oral water 9 ml/kg within the first 6–24 h of life
	Primary outcomes	Meconium evacuation and TFF (140 ml/kg)
	Secondary outcomes	Duration of hospital stay, weight at discharge home and adverse effects of intervention
	Type of milk	EBM, formula feed or mixed feeds depending on the availability of breast milk
GA = Gestational age; BW = birth weight; NS = normal saline.		

derive the mean and standard deviation from the median and range reported in the original article. For the purpose of the meta-analysis we divided the studies according to mode of intervention (rectal or oral).

Details of the Included Studies

In a double-blind RCT by Shinde et al. [27], preterm neonates (gestation 28–32 weeks, birth weight 1,000–1,500 g) were randomised to receive glycerine supposi-

tory (1 g/day) or a sham procedure from day 2 to 14. All received either expressed breast milk (EBM) or formula feeds. The primary outcome was TFF (tolerating 180 ml/kg/day of feed for at least 24 h). Secondary outcomes included the time to regain birth weight and NEC.

Khadr et al. [24] performed a non-blinded trial where preterm neonates (<32 weeks) were randomised to a glycerine suppository (250–500 mg/day) or no intervention from 24 h of age until day 10. All neonates received either EBM, formula or a mixture depending on breast milk availability. A standardised feeding protocol was used. The primary outcome was TFF defined as the tolerance of full enteral feeds and discontinuation of parenteral nutrition for ≥48 h without feeds being withheld or reduced. Secondary outcomes included NEC, episodes of blood culture-positive sepsis, feed intolerance, growth and nutrition.

In a study by Haiden et al. [25], preterm neonates (≤32 weeks, birth weight ≤1,500 g) who did not pass meconium during the first 12 h of life were randomised to receive repeated glycerine enema (10 ml/kg normal saline containing 0.8 g/10 ml) or no intervention. Repeat enema was administered if the neonate failed to pass meconium in the 24 h following the first enema, which was subsequently continued until the complete evacuation of meconium. All neonates received either EBM, formula or mix feeds depending on breast milk availability. A standardised feeding protocol was used. The primary outcome was the time when the last meconium was passed. Secondary outcomes were TFF (150 ml/kg), the duration of hospital stay and weight at discharge.

Mena et al. [26] reported a 3-centre trial carried out in South America. Neonates (birth weight 500–1,250 g) were randomised to enemas with glycerol (0.8 ml glycerol + 3 ml saline or 1 ml glycerol + 5 ml saline depending on birth weight being under or over 800 g, respectively) versus rectal stimulation starting within the first 4 days. The enemas were initiated between 12 and 96 h and repeated every 12 or 24 h, respectively, depending on whether meconium was passed or not, and continued until transition stools appeared. A standardised feeding protocol was used. The primary outcome was meconium evacuation and TFF (discontinuation of parenteral fluids). The secondary outcomes included sepsis, hyperbilirubinaemia and NEC.

In a second study by Haiden et al. [29], preterm neonates (<32 weeks, <1,500 g) were randomised to oral Gastrografin (3 ml/kg, diluted 1:3 with water, total 9 ml/kg) or an equal volume of water via the gastric tube within the first 6–24 h of life. All subjects received either EBM, for-

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Haiden [25], 2007	+	?	?	?	+	+	+
Haiden [29], 2012	+	+	+	+	+	+	+
Khadr [24], 2011	-	+	-	-	-	+	+
Saenz de Pipaón Marcos [28], 2013	-	-	-	-	+	+	+
Mena [26], 2014	+	+	+	?	+	+	-
Shinde [27], 2014	+	+	+	+	+	+	-

Fig. 2. Summary of the risk of bias for included studies.

mula feeds or mixed feeds depending on the availability of breast milk. A standardised feeding protocol was used. The primary outcomes were the time when the last meconium was passed and TFF (140 ml/kg). Secondary outcomes included the duration of hospital stay, weight at discharge home and adverse effects of the intervention.

Saenz de Pipaón Marcos et al. [28] considered neonates born at ≤28 weeks of gestation that were randomised to either the intervention or control group. Intervention consisted of the following: twice daily enema (10 ml/kg saline) until the complete evacuation of meconium and rectal stimulation thereafter until two stools were passed daily without intervention for 3 days. Control group neonates received enema/rectal stimulation only in cases of abdominal distension without the passage of stools for the previous 24 h. All neonates received either EBM, formula feeds or a mixture depending on the

Fig. 3. Effect of meconium evacuation on TFF.

availability of breast milk. A standardised feeding protocol was used. The primary outcome was the time to a normal stooling pattern. The secondary outcome was TFF (120 ml/kg).

Primary Outcome

All six studies reported TFF as the primary outcome ($n = 442$). None of the individual studies demonstrated a statistically significant reduction in TFF. Haiden et al. [29] noted a trend towards reduced TFF in the oral Gastrografin group [median (range) 26 (9–109) vs. 19 (10–115) days, $p = 0.15$]. Saenz de Pipaón Marcos et al. [28] found significantly increased TFF in the intervention versus control group [26 (21) vs. 15 (8) days, $p = 0.005$], but the regression analysis showed that patent ductus arteriosus rather than enema and rectal stimulation was significantly associated with an increased TFF. Results from the other studies [Haiden et al. [25]: 26 (8–83) vs. 27 (5–75) days, $p = 0.91$; Mena et al. [26]: 19.3 (8.2) vs. 20 (10.3) days; Khadr et al. [24]: 7.4 (4.6–30.9) vs. 9 (4.4–13.3) days, $p = 0.78$, and Shinde et al. [27]: 11.9 (3.1) vs. 11.3 (3.6)

days] did not show any difference in TFF in the intervention versus control groups [24–27].

The overall pooled estimate suggested that various strategies used for meconium evacuation did not reduce TFF (MD -0.03, 95% CI -2.47, 2.41, $p = 0.98$; heterogeneity: $\chi^2 = 10.37$, $I^2 = 52\%$; fig. 3). The subgroup analysis showed no difference in TFF irrespective of an oral or rectal mode of intervention.

Secondary Outcomes

All 6 studies reported the outcome of NEC $\geq$ stage II ($n = 442$). Overall, 12% of neonates in the intervention group and 7% in the control group developed NEC. None of the individual studies showed any statistically significant increase in the risk of NEC in the intervention versus control arm, even though Haiden et al. [29] and Saenz de Pipaón Marcos et al. [28] noted an increased trend towards NEC in the intervention group. The former showed a statistically non-significant increase in NEC (21 vs. 8%) in the Gastrografin group, the latter showed a similar statistically non-significant increase in NEC (23 vs. 3%) in

Fig. 4. Effect of meconium evacuation on NEC.

the intervention group. Haiden et al. [25] noted more cases of NEC in the glycerine enema versus the control group (7 vs. 2.5%). Khadr et al. [24] reported more cases of NEC in the glycerine suppository versus the control group (14 vs. 4%). Mena et al. [26] noted less number of cases of NEC in the glycerol enema versus the control group (6 vs. 15%), and Shinde et al. [27] found no NEC cases out of 25 neonates in the glycerine suppository arm as opposed to 1 out of 25 (0 vs. 4%) in the control arm. The overall pooled estimate showed no significant increase in risk of NEC in the intervention versus control groups (RR 1.71, 95% CI 0.63, 4.65, $p = 0.30$; $\chi^2 = 9.39$; $I^2 = 47\%$; fig. 4). The 95% CI reflects the uncertainty of these results, possibly because of the small sample size. The subgroup analysis showed no difference in the incidence of NEC irrespective of the mode of intervention (oral or rectal).

Five out of the 6 studies reported mortality as an outcome ($n = 361$). Overall mortality was 13% in the intervention group and 12% in the control group. None of the

individual studies showed a statistically significant increase in mortality in either group. Haiden et al. [29] found no significant difference between the intervention and control groups (17 vs. 14%). Saenz de Pipaón Marcos et al. [28] also noted no significant difference between the two groups (17 vs. 10%). Khadr et al. [24] reported slightly more deaths in the intervention versus control group (17 vs. 16%). Mena et al. [26] reported mortality rates of 10 versus 14% in the glycerine enema versus control group, and Shinde et al. [27] found 4% mortality in each group. The overall pooled estimate showed no difference between the intervention and control groups (RR 1.08, 95% CI 0.63, 1.85, $p = 0.78$; $\chi^2 = 0.96$; $I^2 = 0\%$). The subgroup analysis showed no difference in TFF irrespective of an oral or rectal mode of intervention.

A total of 4 of the 6 studies reported the length of hospital stay as a secondary outcome ($n = 281$). None of the individual studies showed a significant difference in the duration of hospital stay between the intervention and

Table 2. Summary of findings for pooled data as per the GRADE guidelines [23]

Outcome	Absolute risk		Relative effect (95% CI)	Partici- pants, n	Quality of evidence grade	Comment
	estimated risk in control group	corresponding risk in intervention group				
TFF	Mean 8–27 days	Mean 0.03 days lower (–2.47 to 2.41)	MD –0.03 (–2.47, 2.41)	442	Low	Small sample size
NEC	16/219 (7.3%)	27/223 (12.1%)	RR 1.71 (0.63, 4.65)	442	Low	Small sample size and het- erogeneity
Mortality	22/180 (12.2%)	24/181 (13.2%)	RR 1.08 (0.63, 1.85)	361	Low	Small sample size and het- erogeneity
Hospital stay	Mean 48–85 days	Mean 0.91 days lower (–10.28 to 8.47)	MD –0.91 (–10.28, 8.47)	281	Low	Small sample size and het- erogeneity
Weight at discharge	Mean 2.075–2.38 kg	Mean 0.08 kg lower (–0.30 to 0.15)	MD –0.08 (–0.30, 0.15)	177	Low	Small sample size

control groups. Haiden et al. [29] noted no difference between the intervention and control group [median (range) 61 (4–209) vs. 70 (4–179) days, $p = 0.35$]. In their earlier study, Haiden et al. [25] also noted no difference between the intervention and control groups [90 (65–140) vs. 85 (55–168) days, $p = 0.66$]. Similarly, Khadr et al. [24] [60.5 (26–222) vs. 80 (29–143) days, $p = 0.275$] and Shinde et al. [27] [mean (SD) 53.7 (14.4) vs. 48.9 (14.8)] showed no difference between the intervention and control groups. The pooled results suggested no effect of intervention on the duration of hospital stay (MD –0.91, 95% CI –10.28, 8.47, $p = 0.85$; heterogeneity: $\chi^2 = 6.05$; $I^2 = 50\%$).

Only 3 out of the 6 studies reported weight at discharge as an outcome. Haiden et al. [25, 29] failed to show any statistically significant difference in weight at discharge [median (range) 2.013 (1.64–3.6) vs. 2.075 (1.43–4.13) kg, $p = 0.54$, and 2.27 (1.65–6.72) vs. 2.38 (1.61–4.65) kg, $p = 0.64$, respectively]. Saenz de Pipaón Marcos et al. [28] reported statistically significant lower weight z scores at 36 weeks corrected gestational age in the intervention versus control groups [mean (SD): –2.2 (0.7) vs. –1.4 (0.7), $p < 0.05$]. However no suitable data was available for the meta-analysis. The pooled estimate based on the studies by Haiden et al. [25, 29] suggested no difference in weight at discharge between the intervention and control groups ($n = 177$; MD –0.08, 95% CI –0.30, 0.15, $p = 0.50$; heterogeneity: $\chi^2 = 0.04$; $I^2 = 0\%$).

Considering other secondary outcomes, Haiden et al. [25, 29], Khadr et al. [24] and Shinde et al. [27; pers. commun.] reported no rectal perforation and no rectal bleeding secondary to the intervention. For other adverse effects, Haiden et al. [29] reported a high proportion of NEC $\geq$ stage II (21 vs. 8%), vomiting, nausea and bradycardia in neonates in the Gastrografin group [29]. None of the studies reported dehydration or any further adverse effects.

Grading of Evidence and Summary of Findings

The overall evidence was deemed to be of low quality considering the small sample sizes and heterogeneity in the included studies, as per GRADE guidelines [23] (table 2). We did not assess publication bias as the number of studies was too small [31].

Discussion

The results of our systematic review suggest that the use of a glycerine suppository, small-volume enema with glycerine or normal saline, or the administration of an oral osmotic agent, such as Gastrografin, to evacuate the meconium did not reduce the time to reach full enteral feeds in preterm VLBW neonates. These findings are not unexpected as normal function of the upper as well as lower gastrointestinal tract is essential for the complete

Table 3. Ongoing studies evaluating the effects of meconium evacuation on feed tolerance

Study	Inclusion criteria	Sample size, n	Intervention	Primary outcome	Status
Glycerine suppositories used prophylactically in premature infants (SUPP): a pilot randomised placebo-controlled trial (NCT02153606)	GA 24–32 weeks BW 500–1,500 g	30	Glycerine suppository vs. sham suppository	Time to reach 150 ml/kg feeds	Start: January 2015 Estimated completion date: June 2015, results are expected to be available in 2016
Efficacy of prophylactic glycerine suppositories for feeding intolerance in VLBW preterm infants: a randomised trial (NCT01799629)	BW <1,250 g	220	Glycerine suppository vs. no intervention	Time to reach 140 ml/kg feeds	Start: March 2013 Estimated completion date: August 2016
The effect of early aggressive meconium evacuation on duration to reach full oral feeds in VLBW infants: a randomised control trial comparing regular daily saline rectal washout with conventional management using glycerine suppositories (ACTRN12614000128695)	BW 750–1,500 g	60	Rectal washout with normal saline (20 ml/kg twice a day) vs. glycerine suppository (1/4) if baby fails to pass meconium in 48 h	Time until 2 days of yellow stools or ≥ 110 ml/kg/day of feeds, whichever is earlier	Start: November, 2013 Still recruiting

Sources: www.clinicaltrials.gov; www.anzctr.org.au. GA = Gestational age; BW = birth weight.

evacuation of meconium and feed tolerance. Interventions such as a glycerine suppository or small-volume enemas do not have an effect on the right colon or the small bowel [12]. Preterm VLBW neonates have poor gastro-duodenal coordination with excessive quiescence in motor activity as well as delayed and slow colonic motility; together these may play an important role in a delayed stooling pattern and feed intolerance [32]. Gastric aspirates reflect poor gastric emptying, gastroduodenal hypomotility and duodeno-gastric reflux [32]. The gastro-anal transit time is significantly longer in preterm neonates as small bowel motility is poorly developed, especially before 28 weeks [33, 34].

Our findings are in line with previous systematic reviews on this topic which also suggested no significant advantage of glycerine suppositories or enema for meconium evacuation to reduce feed intolerance [15–17]. Our review is comprehensive in that it evaluates all therapeutic agents for meconium evacuation regardless of their route of administration. The limitations include the small sample size, inherent bias due to a lack of blinding of the intervention in some studies, and lack of a standard definition for TFF. The milk type may also have an effect on feed tolerance and TFF in preterm neonates. However, none of the studies had subgrouped the data according to milk type. The external validity of our results may be difficult to assess as the frequency of administration of suppositories/enemas, etc. to aid the passage of meconium is expected to vary significantly.

It is important to consider the adverse effects of interventions for meconium evacuation in preterm neonates. Enteral administration of hyperosmolar agents (e.g. 1:3 diluted Gastrografin = 717 mosm/l) has the potential to stimulate both the upper as well as the lower gastrointestinal tract. However, their use may not be without risk as the recommended osmotic load cut-offs for enteral feeds in preterm neonates is 450 mosm/l [35, 36]. Hyperosmolar contrast agents have been associated with an increased risk of NEC in preterm neonates [37]. Haiden et al. [29] reported that the administration of oral Gastrografin for meconium evacuation was associated with a higher frequency of NEC in preterm VLBW neonates, although it was not statistically significant. However, it is important to note that this study was not powered to detect such important adverse effects of the intervention. The role of contrast agents such as barium enema is currently limited to evacuation of the meconium plug in neonates [38–41]. Cuenca et al. [38] have reported a spontaneous resolution of 97% of cases of meconium plug with rectal stimulation or contrast barium enema treatment.

The 2 currently ongoing trials comparing glycerine suppository versus no intervention ($n = 250$) and another trial comparing glycerine suppository versus rectal washouts ($n = 60$) are expected to provide important data (table 3). Pending the results of these studies, other strategies, such as probiotic or prebiotic supplementation to stimulate gastrointestinal maturity and function in preterm VLBW neonates, could also be evaluated [42–47]. Systematic reviews of RCTs have shown that prophylactic

probiotic supplementation can significantly reduce the risk of NEC $\geq$ stage II and all-cause mortality while facilitating feed tolerance in preterm VLBW neonates [44, 48, 49]. Prebiotic oligosaccharides can modulate electrical activity and gastric emptying and may improve feed tolerance in preterm neonates [43, 46]. They can also significantly reduce the stool viscosity and accelerate gastrointestinal transport in preterm neonates [47].

In summary, the limited, low-quality evidence indicates that strategies such as prophylactic glycerine suppository, small-volume glycerine/normal saline enema or oral osmotic contrast agents do not reduce the TFF by facilitating meconium evacuation in preterm neonates. These findings will help in designing a large definitive RCT to address this important clinical issue. Such a trial

should assess the rectal mode of intervention (glycerine suppository or enema) versus no intervention, preferably in neonates <28 weeks of gestation, considering that they are at high risk of feed intolerance. A total of 480 such neonates need to be recruited in such a trial to detect a 20% reduction in the duration of TFF (mean $\pm$ SD 14 $\pm$ 10 days) from baseline, with 80% power ($\alpha < 0.05$), assuming a 20% loss to follow-up.

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