Glycerin laxatives for prevention or treatment of feeding intolerance in very low birth weight infants (Review)

Anabrees J, Shah VS, AlOsaimi A, AlFaleh K

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[Intervention Review]

Glycerin laxatives for prevention or treatment of feeding intolerance in very low birth weight infants

Jasim Anabrees[1], Vibhuti S Shah[2], Ahlam AlOsaimi[3], Khalid AlFaleh[4]

[1]Neonatal Care, Sulaiman Al Habib Medical Group, Riyadh, Saudi Arabia. [2]Department of Paediatrics and Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada. [3]College of Medicine, King Saud University, Riyadh, Saudi Arabia. [4]Department of Pediatrics (Division of Neonatology), King Saud University, Riyadh, Saudi Arabia

Contact address: Jasim Anabrees, Neonatal Care, Sulaiman Al Habib Medical Group, Arrayan Hospital, P.O. Box 272069, Riyadh, 11352, Saudi Arabia. jasim1800@yahoo.com.

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ABSTRACT

Background

Feeding intolerance is a common clinical problem in preterm infants. It may be an early sign of necrotizing enterocolitis, sepsis or other serious conditions, or may result from gut immaturity with delayed passage of meconium. Glycerin laxatives stimulate the passage of meconium by acting as an osmotic dehydrating agent and increasing the osmotic pressure in the gut and stimulate rectal contraction. This in turn may reduce the incidence of feeding intolerance.

Objectives

To assess the effectiveness and safety of glycerin laxatives (enemas/suppositories) for prevention or treatment of feeding intolerance in very low birth weight (VLBW) infants.

Search methods

We searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library issue 3, 2013*), MEDLINE, EMBASE, and CINAHL. We restricted our search to all randomised controlled trials and no language restriction. We searched references of identified studies and reviews on this topic by hand-searching for additional articles. We searched the database maintained by the United States National Institutes of Health (www.clinicaltrials.gov) and European trial registries to identify ongoing trials.

Selection criteria

Only randomised or quasi-randomised controlled trials that enrolled preterm infants < 32 weeks gestational age (GA) and/or < 1500 g birth weight were considered. Trials were included if they involved glycerin laxatives administration and measured at least one pre-specified clinical outcome.

Data collection and analysis

Standard methods of the Cochrane Collaboration and its Neonatal Group were used to assess the methodologic quality of the trials, data collection and analysis.

Main results

We identified only two trials that evaluated the use of prophylactic glycerin laxatives. No eligible trials that evaluated the therapeutic use of glycerin laxatives for feeding intolerance were identified. Our review showed that prophylactic glycerin laxatives administration did not reduces the time to achieve full enteral feeds and other secondary outcomes including duration of hospital stay, mortality, and weight at discharge. The administration of prophylactic glycerin laxatives resulted in less number of infants who fail to pass stool in first the 48 hours. No adverse events were reported in included trials.

Authors' conclusions

Our review of available evidence for glycerin laxatives does not support the routine use of prophylactic glycerin laxatives in clinical practice. Further studies are needed to confirm or refute the effectiveness and safety of glycerin laxatives for prevention and treatment of feeding intolerance in VLBW infants.

PLAIN LANGUAGE SUMMARY

Glycerin laxatives for prevention or treatment of feeding intolerance in very low birth weight infants

Preterm babies are at increased risk of feeding intolerance. Factors that contribute to feeding intolerance are many and include immature motility of the gut and increased viscosity of meconium. Enhancement of the passage of the first stool (meconium) might enhance the ability of the preterm infant tolerating his feeds and might help reduce the time on intravenous fluids. Our review included two studies addressing our objective. We found that glycerin enema given to preterm infants apophylactically did not shorten the time to reach full feeding nor decreased the time to discharge. Having said so, the available data are still quite limited to make a strong conclusion.

BACKGROUND

Description of the condition

Feeding intolerance is a common clinical problem in preterm infants which occur in all infants below 29 weeks (Ringer 1996). It may be an early sign of necrotizing enterocolitis (NEC), sepsis, or other serious conditions, or may result from gut immaturity. The definition of feeding intolerance varies and is based on assessment of the amount and colour of gastric residuals and associated clinical manifestation (Jadcherla 2002). It usually manifests with gastric residuals, vomiting, abdominal distension and delay in passage of meconium (Newell 2000; Patole 2005). Factors that contribute to feeding intolerance include poor coordination of suckling and swallowing, incompetent lower oesophageal sphincter, small gastric capacity and delayed gastric emptying time, intestinal hypomotility (Mansi 2011), immaturity of the intestinal motor mechanisms (Newell 2000), and increased viscosity of meconium. Timing of the first and last meconium stool is critical for oral feeding tolerance and proper gastrointestinal function (Meetze 1993). In contrast to term infants, many preterm infants pass their first meconium only after considerable delay up to 27 days (median, 43 hours) (Meetze 1993; Wang 1994). Consequences of feeding intolerance include prolonged need for total parenteral nutrition (TPN), infection, liver damage secondary to TPN and prolonged stay in the hospital (Stoll 2002; Unger 1986). Therefore, the priority is to establish full enteral feeds as soon as possible in preterm infants (Kaufman 2003). In an observational study in 2007, Shim et al reported that the routine use of glycerin enema resulted in infants achieving full enteral feeds earlier than in the control group (median 16.0 vs. 22.9 days; P<0.001) with a hazard ratio (HR) of 2.9 [95% confidence interval (CI) 1.8, 4.8]. Further, this difference was larger for infants with BW < 1,000 g (median 17.3 vs. 28.1 days, P<0.001). The rate of sepsis was also lower in the glycerin enema compared to the control group (7.7 vs. 27.8%; p = 0.02) in VLBW infants (Shim 2007).

Description of the intervention

Glycerin laxatives in the form of enemas or suppositories are widely used in neonatal intensive care units (Zenk 1993). They act by virtue of the mildly irritant action of glycerol (BNF 2010) and are used to enhance bowel evacuation to prevent or manage feeding intolerance. The safety of glycerin has been proven by long-

term clinical use (Shim 2007). It is relatively inexpensive and does not require medical device for administration or close monitoring. The possible side-effects include hyperosmotic damage to the bowel epithelial cells which may manifest by hematochezia, occult bleeding, or even perforation.

How the intervention might work

Glycerin laxatives stimulate the passage of meconium by acting as an osmotic dehydrating agent and increasing the osmotic pressure in the gut and stimulate rectal contraction (Gilman 1990).

Why it is important to do this review

In a recent review on glycerin use in preterm infants, the reviewers identified two studies; one randomised controlled trial (RCT) and one observational study. They concluded that the evidence regarding the effectiveness of glycerin laxatives for improving feeding intolerance is inconclusive in infants at ≤ 32 weeks gestational age or weighing ≤ 1500 g at birth (Shah 2011).
Despite the widespread utilization of glycerin laxatives in very low birth weight (VLBW) infants, the effectiveness of its use in not proven. Therefore it is important to critically review the literature regarding its effectiveness and safety for feeding intolerance in VLBW infant.

OBJECTIVES

1) To assess the effectiveness and safety of glycerin laxatives (enemas/suppositories) for preventing feeding intolerance in VLBW infants.

2) To assess the effectiveness and safety of glycerin laxatives (enemas/suppositories for treating feeding intolerance in VLBW infants.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized or quasi-randomised controlled trials that have evaluated the effectiveness of glycerin laxatives for feeding intolerance in VLBW infants were included.

Types of participants

Studies of VLBW infants (<1500 g at birth) who received glycerin laxatives for preventing or treating feeding intolerance were included. We accepted all definitions of feeding intolerance.
For studies using gestational age only, we accepted ≤ 32 weeks as equivalent to VLBW infants.
For studies using glycerin for treatment of feeding intolerance, we included any postnatal age.
For trials using glycerin for prevention of feeding intolerance, we accept age of enrolment up to 72 hours of age.

Types of interventions

Prophylactic or therapeutic glycerin laxatives versus placebo or no treatment in VLBW infants. For the purpose of this review, any dose of glycerin enemas/suppositories, preparation or mode of administration were accepted.

Types of outcome measures

Primary outcomes

Time to full enteral feeds (days) (tolerating ≥ 120 ml/kg/day of enteral feeds with no additional IV fluids or TPN).

Secondary outcomes

1. Duration of hospital stay (days)
2. Mortality (death during hospital stay).
3. Stage II or III necrotizing enterocolitis (NEC) (as per Bell's criteria) (Bell 1978).
4. ROP (grade≥1).
5. Requiring oxygen at 36 corrected gestational age (CGA).
6. PDA
7. IVH (grade≥2).
8. First stool after>48 h
9. Weight at discharge home (g/day).
10. Late onset sepsis (positive blood or cerebrospinal fluid cultures beyond 72 hours of age) (Stoll 2004).
11. Duration of total parenteral nutrition (TPN) (days).
12. Cholestasis [defined as serum conjugated bilirubin concentration greater than 1.0 mg/dL (17.1 micromol/L) if the total serum bilirubin is <5.0 mg/dL (85.5 micromol/L) or greater than 20 percent of the total serum bilirubin if the total serum bilirubin is >5.0 mg/dL (85.5 micromol/L)] at any time during hospital stay.
13. Any reported adverse effects by the authors e.g. diarrhoea, colonic perforation, malabsorption.

Search methods for identification of studies

Electronic searches

We formulated a comprehensive and exhaustive search strategy in an attempt to identify all relevant studies, regardless of language or publication status (published, unpublished, in press or in progress).

We searched the following databases: the Cochrane Central Register of Controlled Trials (Issue 3, 2013 of *The Cochrane Library*), MEDLINE (1950 to April 2013), EMBASE (1980 to April 2013), and CINAHL (1982 to April 2013). We restricted our search to all Randomised Control Trials without any language restriction.

The search strategy included text terms "preterm" OR "premature" OR "very low birth weight" OR "VLBW" OR "neonate" OR "newborn" OR "infan*" AND "Glycerin enema" OR "suppository" OR "glycerol".

Searching other resources

References from the studies identified and reviews on this topic were hand-searched for additional articles. We searched the database maintained by the United States National Institutes of Health (www.clinicaltrials.gov) and European trial registries to identify ongoing trials whose methods meet the criteria for inclusion in this review and recorded them in the review for future updates. We excluded the following types of articles: studies published only in abstract form, letters (without original data), editorials, reviews, lectures and commentaries. We did not consider unpublished studies.

Data collection and analysis

Selection of studies

The authors independently (JA, VS) reviewed all identified citations (study titles and abstracts) retrieved by the search strategy for relevance to the topic of this review. We reviewed the studies for relevance based on study design, types of participants, interventions and outcome measures. We removed duplicate trials and resolved any disagreement or discrepancies by discussion and by decision of third author (KA). We included the reasons for exclusion of potentially relevant studies in the table 'Characteristics of excluded studies'.

Data extraction and management

We designed a data extraction form and authors extracted data directly on the form. Extracted data included: author and citation, study location, gestational age of patients, birth weight, postnatal age at enrolment, inclusion/exclusion criteria within each study, the type and dose of glycerin laxatives used, sample size for the intervention and control groups and outcomes data (effectiveness and adverse events). We resolved discrepancies in data extraction by discussion and by decision of third author (KA).

Assessment of risk of bias in included studies

The risk of bias of the included studies was assessed using the method described by the Cochrane Collaboration (Higgins 2011). Each study was assessed under the following six domains:

1. Sequence generation (Was the allocation sequence adequately generated?) might lead to selection bias (biased allocation to interventions) due to inadequate generation;
2. Allocation concealment (Was allocation adequately concealed?) might lead to selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment;
3. Blinding of participants, personnel and outcome assessors (Was knowledge of the allocated intervention adequately prevented during the study?) might lead to performance bias due to knowledge of the allocated interventions by participants and personnel during the study or detection bias due to knowledge of the allocated interventions by outcome assessors;
4. Incomplete outcome data (Were incomplete outcome data adequately addressed?) might lead to attrition bias due to amount, nature or handling of incomplete outcome data;
5. Selective outcome reporting (Are reports of the study free of suggestion of selective outcome reporting?) might lead to reporting bias due to selective outcome reporting;
6. Other sources of bias (Was the study apparently free of other problems that could put it at a high risk of bias?).

An overall assessment for each study was made based on the findings of the six domains.

Two review authors (JA, VS) assessed each domain according to preset criteria and judge them as either "Low risk of bias", "High risk of bias", or "Unclear" (uncertain risk of bias). We resolved discrepancies in judgements by discussion. Review authors were not blinded to the study authors, locations of the studies, author funding, or study acknowledgements.

Measures of treatment effect

We calculated relative risk (RR), risk difference (RD), and the number needed to treat (NNT) or the number need to harm (NNH) along with the 95% confidence interval (CI) for dichotomous outcomes. For continuous outcomes the treatment effect is expressed as mean difference (MD) along with 95% CI.

Unit of analysis issues

We only considered parallel studies for this review.

Dealing with missing data

We contacted the primary author of the study to provide additional data in cases where the data were missing. Two review authors estimated the values from the graphs in studies where results were presented graphically and it was not possible to reach authors, or they were contacted and did not provide original data. If the numbers were not similar then results were presented as descriptive data in the results section.

When the results were provided as median and range; the data were converted to mean and standard deviation using established methods (Hozo 2005). A sensitivity analysis was conducted to determine the impact of imputed data.

Assessment of heterogeneity

We assessed between-study heterogeneity using the I-squared (I^2) and χ^2 statistics (Higgins 2003). I^2 values will be categorized in the following manner: less than 25%: not important, 25% to 49%: representing low heterogeneity, 50% to 74%: representing moderate heterogeneity, 75% to 100%: high heterogeneity (Higgins 2011). If I^2 values were greater than 75%, the magnitude and accompanying P value considered in the overall interpretation. In addition, at least two reviewers reassessed the included studies to determine if there were qualitative differences leading to heterogeneity that would prevent combining the results of the studies. If present, heterogeneity explored according to a priori subgroup analysis described.

Assessment of reporting biases

We described how we planned to investigate the possibility of selective outcome reporting bias and what might be founded for each included study. If the protocol was available, then outcomes in the protocol were compared to the published report. If the protocol was not available, then outcomes listed in the methods section of an article were compared to those whose results were reported. If the authors reported results that are not significant but do not provide data, bias is likely to occur. We planned to contacted authors of the study reports to obtain additional information although it may be unreliable (Chan 2004).

We assessed the methods as:

1. Adequate (where it was clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
2. Inadequate (where not all the study's pre-specified outcomes were not reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported incompletely and so cannot be used; study fails to include results of a key outcome that were expected to be reported);
3. Unclear (insufficient information to permit judgement).

Other sources of bias:

For each included study, we described any important concerns we have about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as yes; no; or unclear. If needed, we planned to explore the impact of the level of bias by undertaking sensitivity analyses.

Data synthesis

If appropriate, meta-analysis of pooled data was performed assuming a fixed effect model. Review Manager 5.2 software was utilized for statistical analysis. For estimates of typical relative risk and risk difference, we used the Mantel-Haenszel method. For measured quantities, we used the inverse variance method.

We have two primary comparisons:

1. Glycerin prophylaxis vs. placebo;
2. Glycerin treatment vs. placebo.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was planned a priori and the data were planed to be stratified by the following variables: birth weight (VLBW and extremely LBW infants), gestational age at birth (28-32 weeks and < 28 weeks), age at first treatment, intervention preparation (enemas or suppositories), and any other possible sources of heterogeneity.

Sensitivity analysis

Sensitivity analysis could not be performed because of the limited number of studies identified for inclusion in this review.

RESULTS

Description of studies

See tables Characteristics of included studies.

Prevention of feeding intolerance:

Participants

Two included studies (Haiden 2007; Khadr 2011) reported outcomes on 135 infants. The study by Haiden 2007 included infants <32 weeks gestation and <1500 g while the study by Khadr 2011 included infants >24 weeks gestation and <32 weeks gestation. Both studies excluded infants with major dysmorphic features, major congenital anomalies including gastrointestinal (GI) anomalies. The study by Khadr 2011 also excluded infants with hypoxic-ischemic encephalopathy (HIE) (stage >2).

Intervention

Included studies randomised infants to different preparations and dosages of glycerin. Haiden 2007 used glycerine enema while

Khadr 2011 used glycerin suppository. The dose for glycerin in the study by Haiden 2007 was 10 mL/kg saline containing 0.8 g/10mL glycerin while Khadr 2011 used a 250-mg glycerin suppository once daily for infants born between $24^{0/7}$-$27^{6/7}$ weeks and two 250-mg glycerin suppositories (500 mg) once daily for infants born between $28^{0/7}$- $31^{6/7}$. In the study by Haiden 2007 infants received glycerin enema if they did not spontaneously pass meconium during the first 12 h of life. A second enema was administered if the infant had not passed meconium during the 24 hours following the first enema. This process was continued until complete evacuation of meconium was achieved. In the study by Khadr 2011, the intervention group received glycerin suppository once daily per rectum for 10 days commencing at 24 h of age. In both trials the control group received no intervention.

Outcomes

The primary outcome for Haiden 2007 was the time when the last meconium was passed while for Khadr 2011 it was time to full enteral feeds from commencement of enteral feeds.

The secondary outcomes included feeding tolerance for Haiden 2007 and NEC, sepsis, feed intolerance, mortality, patent ductus arteriosus (PDA), intraventricular haemorrhage (IVH), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD) for Khadr 2011.

Treatment of feeding intolerance:

We did not identify any study that utilized Glycerin for treatment of feeding intolerance.

Results of the search

Our search on April, 1st, 2013 yielded two randomised trials meeting our inclusion criteria for prevention of feeding intolerance (Haiden 2007, Khadr 2011).

Included studies

Included studies are Haiden 2007 and Khadr 2011.

Excluded studies

We excluded two studies. Shim 2007 due to the observation nature of the study and Wang 2008 since the intervention was a combination of glycerin enema and Golden diplococci.

Risk of bias in included studies

See tables Risk of bias in included studies.

Allocation

Both studies (Haiden 2007; Khadr 2011) were at low risk for bias in random sequence generation. The study by Haiden 2007 was scored as unclear risk while the study by Khadr 2011 was categorized as low risk for allocation concealment.

Blinding

Both studies (Haiden 2007; Khadr 2011) were at high risk for performance bias as they were not blinded. As both studies were not applicable for independent outcome assessment, the risk of detection bias couldn't be evaluated.

Incomplete outcome data

Both studies (Haiden 2007; Khadr 2011) were at low risk for attrition bias.

Selective reporting

Both studies (Haiden 2007; Khadr 2011) were at low risk for reporting bias.

Other potential sources of bias

Both studies (Haiden 2007; Khadr 2011) were at low risk for other potential sources of bias.

Effects of interventions

Glycerin prophylaxis vs. placebo/no intervention (COMPARISON 1):

Time to full enteral feeds (days) (Outcome 1.1):

Two studies reported on this outcome (Khadr 2011; Haiden 2007). No statistically significant difference in the time to full enteral feeds between the two groups was noted [weighted mean difference (WMD), -1.45; 95% CI -3.88 to 0.98; P 0.91].

Duration of hospital stay (days) (Outcome 1.2):

Two studies reported on this outcome (Khadr 2011; Haiden 2007). No statistically significant difference in the duration of hospital stay was observed between groups (WMD, -0.38; 95% CI -9.68 to 0.95; 8.93; P 0.02].

Mortality (Outcome 1.3):

Only one study reported on this outcome (Khadr 2011). No statistically significant difference in mortality among study groups was observed (RR, 1.08; 95% CI 0.32 to 3.58; P 0.9).

NEC (any stage) (Outcome 1.4):

Only one study reported on this outcome (Khadr 2011). No statistically significant difference in NEC among study groups was observed (RR, 3.45; 95% CI 0.41 to 28.87; P 0.25).

ROP (grade ≥1) (n) (Outcome 1.5):

Only one study reported on this outcome (Khadr 2011). No statistically significant difference in ROP among study groups was observed (RR, 1.72; 95% CI 0.17 to 17.90; P 0.65).

Requiring oxygen at 36 weeks CGA (n) (Outcome 1.6):

Only one study reported on this outcome (Khadr 2011). No statistically significant difference in oxygen requirement at 36 weeks CGA among study groups was observed (RR, 1.19; 95% CI 0.57 to 2.48, P 0.65).

PDA (n) (Outcome 1.7):

Only one study reported on this outcome (Khadr 2011). No statistically significant difference in PDA among study groups was observed (RR, 0.86; 95% CI 0.54, 1.39, P 0.54).

IVH (grade ≥2) (n) (Outcome 1.8):

Only one study reported on this outcome (Khadr 2011). No statistically significant difference in IVH (grade ≥2) among study groups was observed (RR 1.29; 95% CI 0.63 to 2.65, P 0.48).

First stool after >48 h (n) (Outcome 1.9):

Only one study reported on this outcome (Khadr 2011). The administration of Glycerin resulted in a significant improvement of stool passage in the first 48 hours in treated infants (RR 0.38; 95% CI 0.19 to 0.77, P 0.007).

Weight at discharge home (g) (Outcome 1.10):

Only one study reported on this outcome (Haiden 2007). No statistically significant difference in weight at discharge home among study groups was observed (MD -62.00; 95% CI -317.49 to 193.49, P 0.63).

Late onset sepsis (Outcome 1.11):

Both included studies not reported on this outcome.

Duration of total parenteral nutrition (TPN) (Outcome 1.12):

Both included studies not reported on this outcome.

Cholestasis at any time during hospital stay (Outcome 1.13):

Both included studies not reported on this outcome.

Adverse effects (Outcome 1.14):

Both included studies reported no observed side effects to treatment such as diarrhoea, rectal bleeding, dehydration or intestinal perforation.

Glycerin treatment vs placebo/no intervention (COMPARISON 2):

No eligible studies were available for this comparison.

Subgroup analysis:

No subgroup analysis could be performed.

DISCUSSION

Summary of main results

Our review summarizes the evidence of efficacy and safety of glycerin laxatives for prevention or treatment of feeding intolerance in VLBW infants. We identified only two trials that evaluated the use of prophylactic glycerin laxatives. No eligible trials that evaluated the therapeutic use of glycerin laxatives for feeding intolerance were identified. We identified one ongoing study that is evaluating the use of prophylactic glycerin suppositories for feeding intolerance and will include it in updates of our review in the future. Our review showed that prophylactic glycerin laxatives administration did not reduce the time to achieve full enteral feeds and other secondary outcomes including duration of hospital stay, mortality, PDA, IVH, NEC, ROP, BPD and weight at discharge home. The administration of prophylactic glycerin laxatives resulted in improved stool passage in the first 48 hours of life in treated infants. No adverse effects were reported in included trials.

Overall completeness and applicability of evidence

The included trials are not sufficient to address our objectives adequately. The external validity of the review might be affected by the use of different preparations, dosing regimens, and duration of the intervention under study. In addition to passage of meconium; several factors could influence tolerance to feeds in the preterm host and therefore a multipronged approach may be required to facilitate feeding tolerance.

Quality of the evidence

The validity of our review's results is potentially compromised by the following: few studies addressing the topic of interest, limited sample size included in these studies (total of 135 infants from the two included studies) and the use of different preparations and dosing regimens of the intervention under study (the dose and duration of therapy may have not been adequate). Further in the study by Haiden 2007 ; protocol violation occurred in 23 participants (15 in the intervention group did not receive the enema while eight infants in the control group received enema). Even though the authors performed both intention-to-treat and per-protocol analyses with no difference in the outcome, this could have the potential to influence the outcome. In both included trials, healthcare professionals and participants were not blinded which could introduce bias.

Potential biases in the review process

This review utilized a very thorough and comprehensive search strategy. All attempts were made to minimize the potential of a publication bias. Only randomised or quasi-randomised controlled trials were included. To minimize the reviewer bias, all steps of this review were conducted independently by review authors.

Agreements and disagreements with other studies or reviews

Our review included two randomised controlled trials (Khadr 2011; Haiden 2007) in contrast to the recent review by Shah

et al (Shah 2011) that included one randomised controlled trial (Haiden 2007) and one observational study (Shim2007).
Our findings are in line with the review by Shah 2011 that the evidence of prophylactic glycerin laxative administration to improve feeding intolerance in VLBW infants is inconclusive.

AUTHORS' CONCLUSIONS

Implications for practice

Our review of available evidence for glycerin laxatives does not support the use of glycerin laxatives in clinical practice.

Implications for research

Further studies are needed to confirm or refute the effectiveness and safety of glycerin laxatives for feeding intolerance in VLBW infants.

ACKNOWLEDGEMENTS

None

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Haiden 2007

Methods	Open randomised controlled trial
Participants	Inclusion criteria: BW <1500 g and GA < 32 week. Infants were further stratified according to their GA (< or > 28 weeks) Exclusion criteria: Infants with major congenital malformations and known gastrointestinal abnormalities were excluded
Interventions	Intervention group: Infants who failed to spontaneously pass meconium in the first 12 hours of life received glycerin enema (10 ml/kg saline containing 0.8g/10ml glycerin). A urinary catheter (CH 8) lubricated with petrolatum was inserted into the rectum (2 cm in infants < 1000 g and 3 cm in infants weighing 1000-2000) to administer the enema. A second enema was administered if the infant failed to pass meconium during the 24 hours following the enema. The procedure was repeated until complete evacuation of meconium was achieved defined as passage of 2 stools without macroscopic evidence of meconium within 24 hours Control group: No intervention was performed
Outcomes	Primary: The time when the last meconium was passed Secondary: Feeding tolerance
Notes	Austria

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomised
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not Blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Khadr 2011

Methods	Open randomised controlled trial
Participants	Inclusion criteria: Inborn preterm infants between $24^{0/7}$ to $31^{6/7}$ weeks gestation Exclusion criteria: Infants with major dysmorphic features, structural gastrointestinal anomalies or hypoxic ischemic encephalopathy > stage 2 were excluded
Interventions	Intervention group: Infants received a 250-mg glycerin suppository once daily if born between $24^{0/7}$ to $27^{6/7}$ or two 250-mg glycerin suppositories (500 mg) once daily if born between $28^{0/7}$ to $31^{6/7}$ weeks. Suppositories were administered daily for a total of 10 days commencing at 24 hours of age Control group: Infants received no intervention
Outcomes	Primary outcome: Time to full enteral feeds from commencement of enteral feeds (days) Secondary outcome NEC, Sepsis, Feed intolerance, Mortality, PDA, IVH, ROP, BPD
Notes	Study was conducted in Wishaw General Hospital in Lanarkshire, UK ISRCTN47065764 Eudract_number:2005-000302-31

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A set of study numbers and treatment allocation cards were generated by a research nurse at the beginning of the study. Each study number was paired with a treatment card and sealed in an opaque envelope and stratified by gestational age ($24^{0/7}$ to $27^{6/7}$ and $28^{0/7}$ to $31^{6/7}$ weeks). The envelopes were then shuffled and stacked by gestational age prior to commencement of study
Allocation concealment (selection bias)	Low risk	Used consecutive sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Shim2007	Observational study
Wang 2008	They studied glycerine enema and Golden diplococci in the same group

Characteristics of ongoing studies *[ordered by study ID]*

Khadawardi 2013

Trial name or title	Efficacy of prophylactic glycerin suppositories for feeding intolerance in very low birth weight preterm infants: a randomised trial
Methods	Multicenter randomised controlled clinical trial
Participants	Inclusion criteria: 1. Preterm infants with birth weight < 1250g 2. Inborn or outborn infants 3. < 72 hours of age Exclusion criteria: 1. Congenital malformations 2. Acute abdomen needing surgical intervention 3. Severity of illness such that death is likely in the first few days after birth 4. Inability to get the parental consent
Interventions	In treatment group, a glycerin suppository will be given rectally (¼ of glycerin chip) every 12 hours. The therapy will not be discontinued until 48 hours after reaching full enteral feeds are established at140cc/kg/day In control group will receive routine NICU medical care without any specific intervention for the study
Outcomes	The primary outcome is days to achieve full enteral feeds (breast milk or formula) by nasogastric tube or by mouth (140 cc/kg/day) Secondary outcomes include: 1. Incidence of feeding intolerance, which is defined by the presence of gastric residual volumes > 50 % of the previous feed for two consecutive feeds in addition to two of the following (abdominal distension > 1 cm, abdominal tenderness, vomiting, bile stained aspirate) 2. Incidence of NEC, defined as clinical signs plus pneumatosis intestinalis on abdominal radiograph or Bell stage II 3. Incidence of late onset sepsis, defined as clinical signs in addition to at least one positive sterile site culture (blood culture, urine or CSF) beyond 72 hours of age 4. Incidence of neonatal hyperbilirubinaemia, defined as level of bilirubin requiring treatment with phototherapy according to the bilirubin chart used in the participating unit 5. Duration of NICU length of stay, defined as day from admission till discharge home
Starting date	2013

Khadawardi 2013 (*Continued*)

Contact information	Emad Khadawardi
Notes	Saudi Arabia NCT01799629

DATA AND ANALYSES

Comparison 1. Glycerin prophylaxis vs placebo/no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to full enteral feeds (days)	2	135	Mean Difference (IV, Fixed, 95% CI)	-1.45 [-3.88, 0.98]
2 Duration of hospital stay (days)	2	135	Mean Difference (IV, Fixed, 95% CI)	-0.38 [-9.68, 8.93]
3 Mortality	1	54	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.32, 3.58]
4 NEC, any	1	54	Risk Ratio (M-H, Fixed, 95% CI)	3.45 [0.41, 28.87]
5 ROP (grade ≥1), n	1	54	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [0.17, 17.90]
6 Requiring oxygen at 36 weeks CGA, n	1	54	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.57, 2.48]
7 PDA, n	1	54	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.54, 1.39]
8 IVH (grade ≥2), n	1	54	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.63, 2.65]
9 First stool after >48 h, n	1	54	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.19, 0.77]
10 Weight at discharge home (g)	1	81	Mean Difference (IV, Fixed, 95% CI)	-62.0 [-317.49, 193.49]

Analysis 1.1. Comparison 1 Glycerin prophylaxis vs placebo/no intervention, Outcome 1 Time to full enteral feeds (days).

Review: Glycerin laxatives for prevention or treatment of feeding intolerance in very low birth weight infants

Comparison: 1 Glycerin prophylaxis vs placebo/no intervention

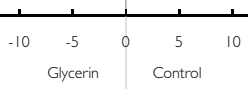
Outcome: 1 Time to full enteral feeds (days)

Study or subgroup	Glycerin N	Glycerin Mean(SD)	Control N	Control Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Haiden 2007	39	26 (18.75)	42	27 (17.5)		9.4 %	-1.00 [-8.91, 6.91]
Khadr 2011	29	7.4 (6.6)	25	8.9 (2.2)		90.6 %	-1.50 [-4.05, 1.05]
Total (95% CI)	**68**		**67**			**100.0 %**	**-1.45 [-3.88, 0.98]**

Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.91); I^2 =0.0%

Test for overall effect: Z = 1.17 (P = 0.24)

Test for subgroup differences: Not applicable

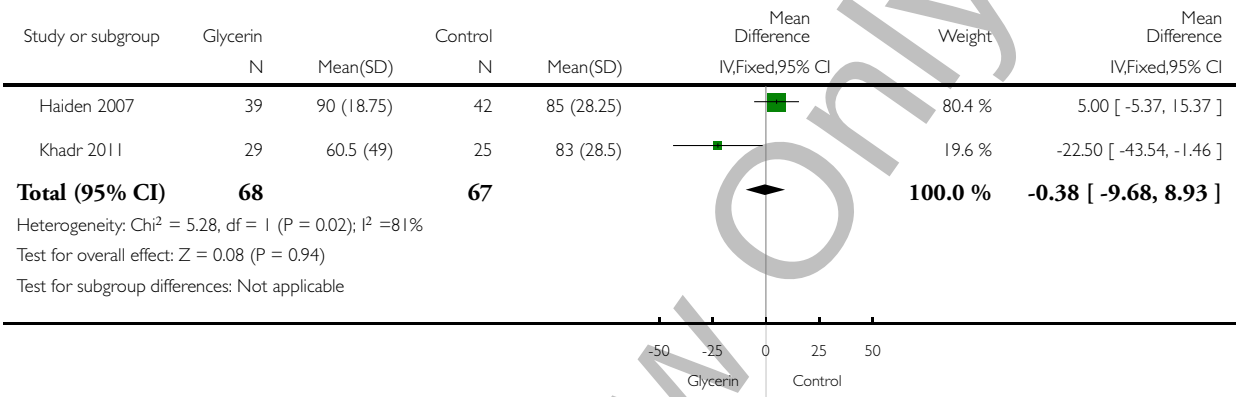


Analysis 1.2. Comparison 1 Glycerin prophylaxis vs placebo/no intervention, Outcome 2 Duration of hospital stay (days).

Review: Glycerin laxatives for prevention or treatment of feeding intolerance in very low birth weight infants

Comparison: 1 Glycerin prophylaxis vs placebo/no intervention

Outcome: 2 Duration of hospital stay (days)

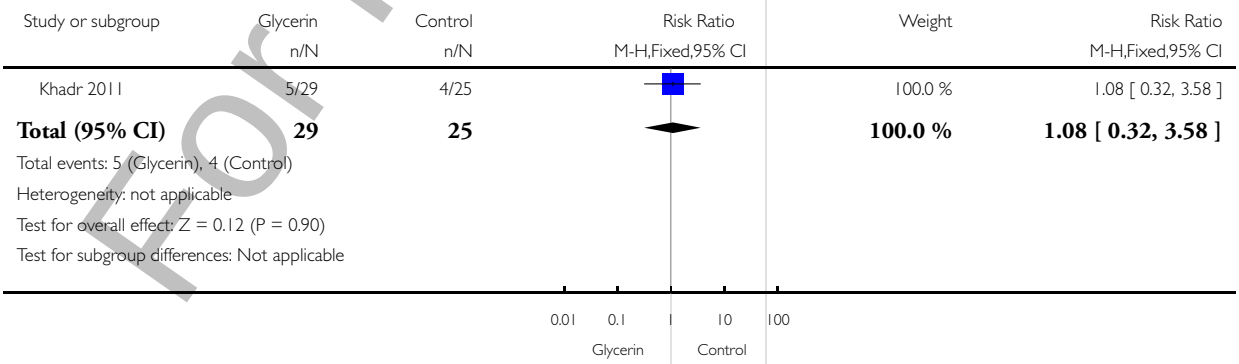


Analysis 1.3. Comparison 1 Glycerin prophylaxis vs placebo/no intervention, Outcome 3 Mortality.

Review: Glycerin laxatives for prevention or treatment of feeding intolerance in very low birth weight infants

Comparison: 1 Glycerin prophylaxis vs placebo/no intervention

Outcome: 3 Mortality

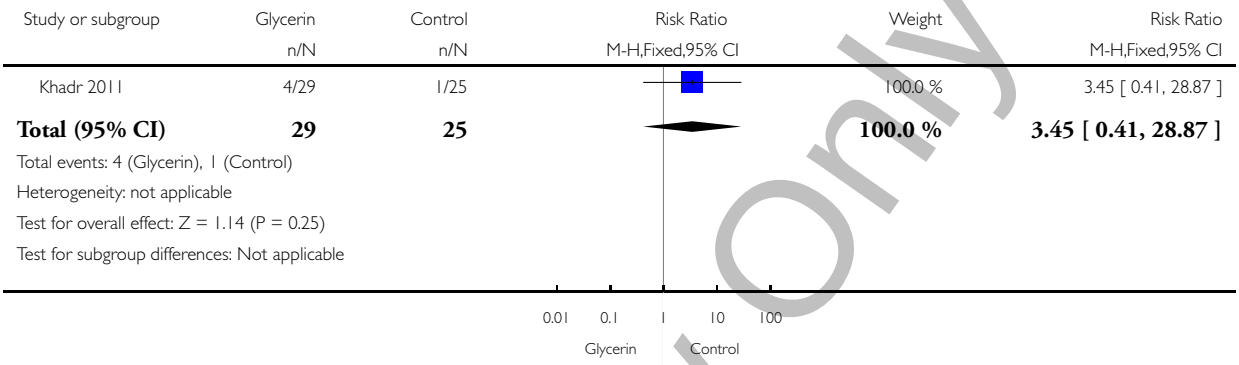


Analysis 1.4. Comparison 1 Glycerin prophylaxis vs placebo/no intervention, Outcome 4 NEC, any.

Review: Glycerin laxatives for prevention or treatment of feeding intolerance in very low birth weight infants

Comparison: 1 Glycerin prophylaxis vs placebo/no intervention

Outcome: 4 NEC, any

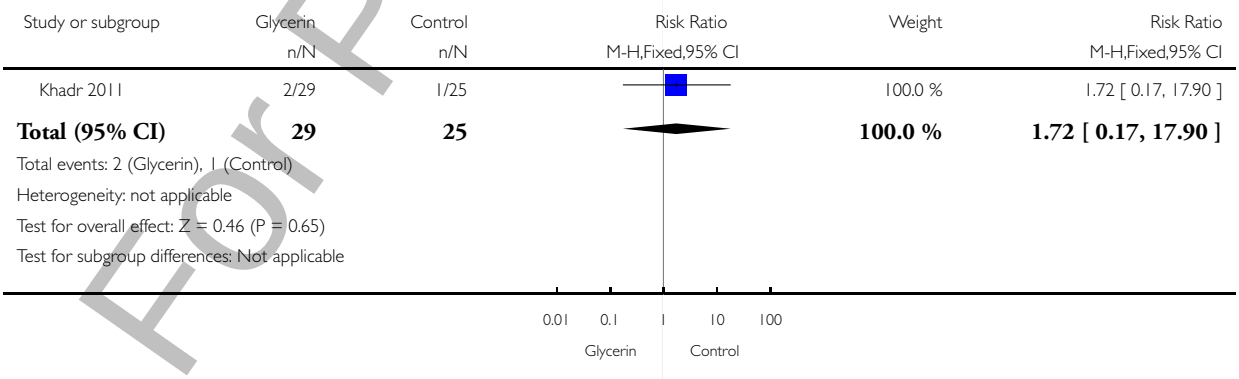


Analysis 1.5. Comparison 1 Glycerin prophylaxis vs placebo/no intervention, Outcome 5 ROP (grade ≥1), n.

Review: Glycerin laxatives for prevention or treatment of feeding intolerance in very low birth weight infants

Comparison: 1 Glycerin prophylaxis vs placebo/no intervention

Outcome: 5 ROP (grade ≥1), n

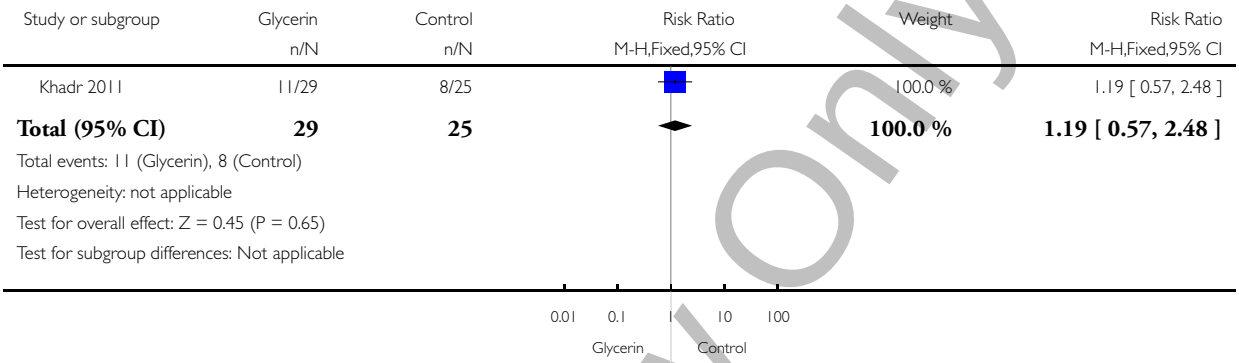


Analysis 1.6. Comparison 1 Glycerin prophylaxis vs placebo/no intervention, Outcome 6 Requiring oxygen at 36 weeks CGA, n.

Review: Glycerin laxatives for prevention or treatment of feeding intolerance in very low birth weight infants

Comparison: 1 Glycerin prophylaxis vs placebo/no intervention

Outcome: 6 Requiring oxygen at 36 weeks CGA, n

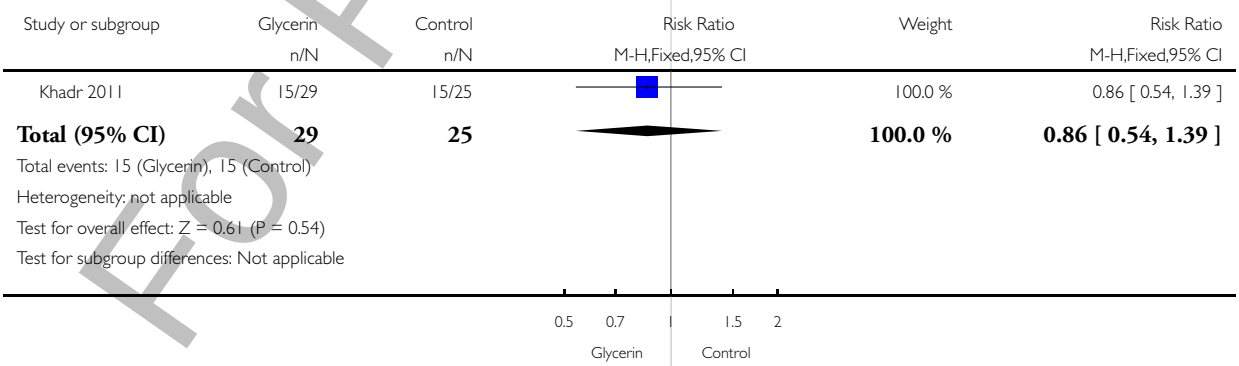


Analysis 1.7. Comparison 1 Glycerin prophylaxis vs placebo/no intervention, Outcome 7 PDA, n.

Review: Glycerin laxatives for prevention or treatment of feeding intolerance in very low birth weight infants

Comparison: 1 Glycerin prophylaxis vs placebo/no intervention

Outcome: 7 PDA, n



Analysis 1.8. Comparison 1 Glycerin prophylaxis vs placebo/no intervention, Outcome 8 IVH (grade ≥2), n.

Review: Glycerin laxatives for prevention or treatment of feeding intolerance in very low birth weight infants

Comparison: 1 Glycerin prophylaxis vs placebo/no intervention

Outcome: 8 IVH (grade ≥2), n

Study or subgroup	Glycerin n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Khadr 2011	12/29	8/25		100.0 %	1.29 [0.63, 2.65]
Total (95% CI)	**29**	**25**		**100.0 %**	**1.29 [0.63, 2.65]**

Total events: 12 (Glycerin), 8 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.70 (P = 0.48)
Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Glycerin prophylaxis vs placebo/no intervention, Outcome 9 First stool after >48 h, n.

Review: Glycerin laxatives for prevention or treatment of feeding intolerance in very low birth weight infants

Comparison: 1 Glycerin prophylaxis vs placebo/no intervention

Outcome: 9 First stool after >48 h, n

Study or subgroup	Glycerin n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Khadr 2011	7/29	16/25		100.0 %	0.38 [0.19, 0.77]
Total (95% CI)	**29**	**25**		**100.0 %**	**0.38 [0.19, 0.77]**

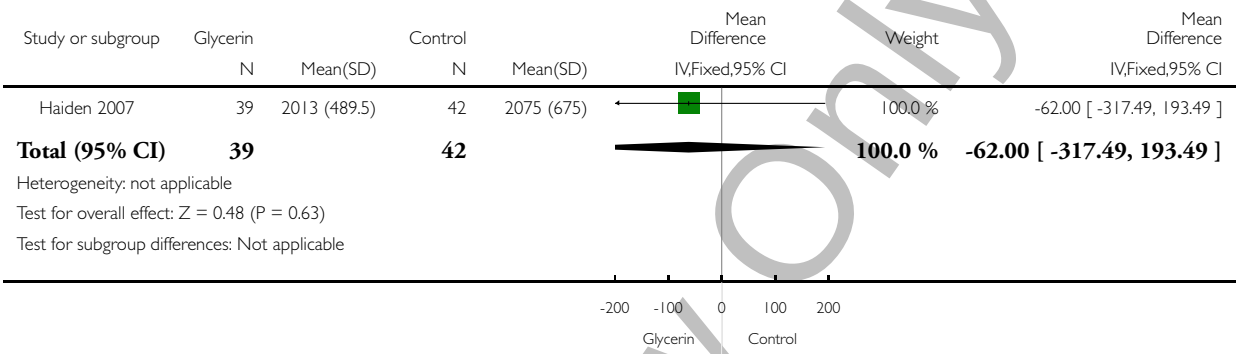
Total events: 7 (Glycerin), 16 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 2.70 (P = 0.0070)
Test for subgroup differences: Not applicable

Analysis 1.10. Comparison 1 Glycerin prophylaxis vs placebo/no intervention, Outcome 10 Weight at discharge home (g).

Review: Glycerin laxatives for prevention or treatment of feeding intolerance in very low birth weight infants

Comparison: 1 Glycerin prophylaxis vs placebo/no intervention

Outcome: 10 Weight at discharge home (g)



CONTRIBUTIONS OF AUTHORS

All authors contributed to the research idea, design, protocol development and writing. JA and VS searched the literature and performed the data extraction. JA, AA and KA analysed the data. JA wrote the manuscript that was reviewed by all authors.

DECLARATIONS OF INTEREST

None to declare

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None