RESEARCH PAPER

Glycerin Suppository for Promoting Feeding Tolerance in Preterm Very Low Birthweight Neonates: *A Randomized Controlled Trial*

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Objective: To compare the efficacy of glycerin suppository versus no suppository in preterm very-low-birthweight neonates for improving feeding tolerance.

Design: Randomized controlled trial.

Setting: Level III neonatal unit from Mumbai, India.

Participants: 50 very-low-birthweight (birth weight between 1000 to 1500 grams) preterm (gestational age between 28 to 32 weeks) neonates randomized to glycerine suppository (*n*=25) or no intervention (*n*=26).

Intervention: Glycerin suppository (1g) once a day from day-2 to day-14 of life or no suppository, along with intermittent oral feeds and standardized care.

Primary outcome: Time required to achieve full enteral feeds (180 mL/kg/d).

Results: Baseline characteristics of neonates like gestational age, birthweight, gender and age at the time of introduction of feeds were comparable in both groups. The mean (SD) duration to reach full enteral feed was 11.90 (3.1) days in glycerin suppository group and was not significantly different (*P*=0.58) from control group, [11.33 (3.57) days]. Glycerin suppository group regained birth weight 2 days earlier than control group but this difference was not significant (*P*=0.16). There was no significant difference in duration of hospital stay or occurrence of necrotizing enterocolitis amongst the two study groups.

Conclusion: Once daily application of glycerin suppository does not accelerate the achievement of full feeds in preterm very-low-birthweight neonates.

Keywords: *Low birthweight, Prematurity, Feed intolerance, Necrotizing enterocolitis.*

Achieving optimal enteral feeding is crucial for the growth of the newborn, and delay in establishing full enteral feed is associated with adverse short term and long term outcomes [1]. Advancement of enteral nutrition in preterm neonates is hampered by gastric residuals and feeding intolerance. Gastrointestinal hypomotility and non-development of coordinated peristalsis are the postulated reasons for feeding intolerance [2-5].

Various feeding strategies (like trophic feeding and slow feeding advancement), medications (like antenatal steroids and prokinetics), and meconium evacuation are used to improve feeding intolerance [6-9]. Immature intestinal motor mechanism and neurotransmitter system is considered to be responsible for delay in passage of meconium in preterm infants. Retained thick tenacious meconium leads to functional obstruction, abdominal distension, gastric residuals and feeding intolerance [10-12]; and total meconium evacuation may improve feeding volume [11,13,14]. We hypothesized that glycerin suppository – by acting as osmotic laxative – will facilitate early meconium evacuation and accelerate feed tolerance and advancement in preterm very-low-birthweight (VLBW) neonates. Our specific objective was to compare the efficacy of glycerin suppository *versus* no glycerin suppository in preterm VLBW neonates on time required to achieve full enteral feeds.

METHODS

This randomized controlled trial was conducted in a Level III neonatal unit in Mumbai, India from March 2010 to April 2011. The study was approved by the hospital's Academic research ethics committee. Infants were enrolled after obtaining written informed consent from parents or legal guardians.

Infants admitted to neonatal intensive care unikt (NICU) on day-1 of life, with a birthweight between 1000 to 1500 grams, and gestational age between 28 to 32 weeks were eligible for inclusion in the study. Infants with gastrointestinal or other systemic malformations were excluded. Infant with hemodynamic instability and features of shock were also excluded.

Eligible neonates were randomized to either glycerin suppository group or control group. Those in the glycerin suppository group received the drug at a dose of one infant glycerin suppository (Hallens Infant Glycerin Suppository 1g, Meridian Enterprises) once a day from day-2 of life onwards. Those assigned to control group were not given

any suppository, only a sham procedure was performed (no active placebo). Sequence was generated using random allocation software in variable blocks of 2 or 4, by a statistician who was not part of the study. Randomization allocation concealment was achieved by creating sequentially numbered sealed opaque envelopes that contained the randomization codes. When a patient meeting inclusion criteria was admitted in the unit, doctor on duty obtained written informed consent from parents. The serially numbered opaque sealed envelope was opened by the designated study staff nurses. Access to these envelopes was only limited to these designated study staff nurses. Nursing staff involved in care of infant, on-duty resident doctors and consultants involved in the care of infant were blinded to study intervention. The glycerin suppository administration or sham procedure was performed by designated study staff nurses (two) behind curtains. This intervention was continued till day 14 of life irrespective of passage of stools. Glycerin suppository or sham intervention was withheld if there was hemodynamic instability. These two study nurses were otherwise not involved in day-to-day clinical management of these infants. Feeds were started in both groups of infants when they were clinically stable, usually between 3rd to 5th day of life. The feeds were in the form of intermittent boluses every 2 hours through orogastric infant feeding tube. All infants received either expressed breast milk (EBM) and/or preterm infant milk formula (Lactodex LBW, Raptakos, Brett and Co. Ltd.); EBM was preferred, if available. The initial feeding volume was 20 mL/kg/day and the volume was increased daily by 20 mL/kg/day, if tolerated until complete enteral feeding was achieved (180 mL/Kg/day). Feeds were withheld if clinical signs and symptoms suggestive of necrotizing enterocolitis (NEC) or other intra-abdominal pathology were suspected. Feeding was withheld as per clinical condition or if gastric residuals exceeded 20% of previous feed volume. EBM was fortified with a commercial powder preparation (Lactodex HMF, Raptakos, Brett and Co. Ltd) once full feeds were tolerated by infant. Feeding policy was similar in both study groups.

Standards of care of infants in the NICU did not change throughout the study period. Grading up of intravenous fluids, parenteral nutrition and starting of trophic feeds was done as before as per the standard protocol of the unit. The regimen of parenteral nutrition used for both groups remained same and it consisted of solution of 10% dextrose, amino acids and electrolytes. Parenteral nutrition was started on day-2 of life in all infants and advanced daily to meet each infant's total estimated fluid and nutritional requirements.

The primary outcome was time required by the infant to achieve full enteral feeds. (when the infant tolerated a volume of 180 mL/kg/day for at least 24 hours). Secondary outcomes were: time required to regain birth weight, age of achieving a weight of 1700 grams, necrotizing enterocolitis (Bell classification) [15], proportion of infants in whom feeds were withheld for any reasons, and age at the time of discharge from hospital. All infants were followed up till the time of discharge from the hospital or transfer to other hospital. All the data were recorded in predesigned study case record forms.

Sample size was calculated by using the formula for the hypothesis of 2-parallel sample means. In our unit, with the existing feeding practices, the average time taken by an infant with birth weight of 1000 to 1500 gram to reach full feeds was 15 days (SD 3 days). We hypothesized that the glycerin suppository group will reach full feeds by day 12 of life. For a difference of 3 days, with an error of 0.05 and power 90%, the estimated sample size was 22 in each group. To account for loss to follow up, 25 infants were to be enrolled in each group.

Data were analyzed by using IBM SPSS version 18 software. Categorical variables were compared using the Fisher's exact test. Continuous measures between groups were compared using two sample *t* test or Mann-Whitney U test as appropriate. *P* value <0.05 was considered significant.

RESULTS

The flow chart of participants in the study is presented in ***Fig.* 1**. A total of 50 infants were randomized; 25 to glycerin suppository group and 25 to control group.

The baseline clinical and demographic characteristics of the two study groups were similar (***Table* I**). ***Table* II** depicts the outcomes in the two study groups. The time required to reach full enteral feeds was similar in both groups. Glycerin suppository group regained birth weight 2 days earlier than control group but this difference was not statistically significant. The age of achieving a weight of 1700 grams, proportion of infants with NEC, proportion of infants in whom feeds were withheld, and age at discharge from hospital were similar in both study groups.

DISCUSSION

In this randomized controlled trial on 50 VLBW neonates, we could not detect any difference in time required by the infant to achieve full enteral feeds in children receiving glycerin suppository and those not receiving it.

We did not enroll infants <1000 grams in our study because of perceived risk and difficulty in administering 1g infant glycerin suppository in this population. The main limitations of our study was the assessment of only short term outcomes. Moreover, our study was not powered for

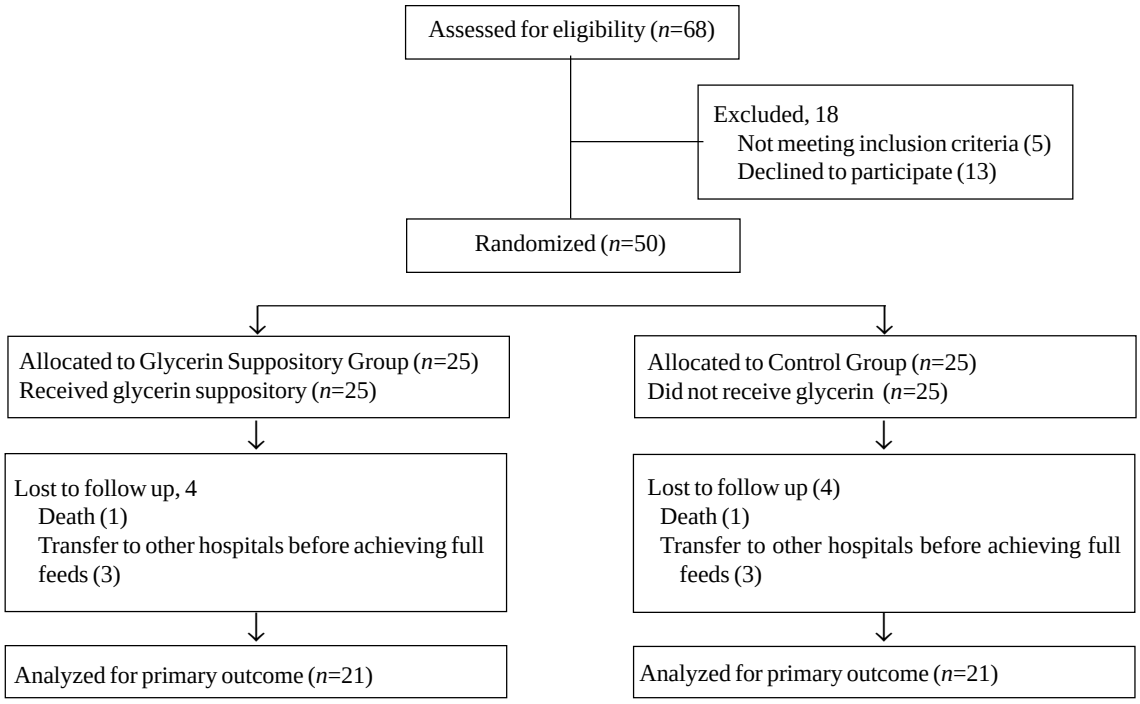

FIG.1 *Flow of participants in the study.*

outcomes like NEC. We calculated sample size for 3 days reduction in time required to reach full enteral feeds. A smaller reduction that may still be clinically meaningful may have been missed as it requires a large sample size.

Shim, *et al*. [4], in an observational study, reported a significant reduction in time to achieve full enteral feeds. A recent randomized controlled trial by Khadr, *et al*. [1] showed that the median time to full feeds was 1.6 days shorter in glycerin suppository group; however, it was not statistically significant. Haiden, *et al*. [6] used gastrografin osmotic contrast for evacuation of meconium in preterm infants, and observed that the median time to reach full enteral feedings was shorter in intervention group as compared to control group. Two systematic reviews evaluating glycerin suppository for meconium evacuation did not report any benefit on feeding intolerance or hyperbilirubinemia [16,17]. It may be possible that glycerin application every 24 hour until complete achievement of full feeds may be too low to be efficient. A more frequent application (*e.g.*12 hourly) or higher dose may be more effective in accelerating meconium evacuation [18]. It is also possible that meconium evacuation cannot be accelerated by suppositories because rapid and sufficient meconium passage indicates a correct functionality of the digestive tract.

In conclusion, once daily application of glycerin suppository does not seem to offer any advantage in premature infants in terms of accelerating achievement of full enteral feeding.

TABLE I BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE STUDY PARTICIPANTS

Characteristic	*Glycerin Suppository Group (n=25)*	*Control Group (n=25)*
Birth weight (g)*	1179 (142)	1237 (161)
Gestational age (wks)*	29.7 (1.3)	29.7 (1.1)
Males, *n* (%)	13 (52%)	16 (64%)
Antenatal glucocorticoids	19 (76%)	20 (80%)
LSCS delivery	16 (64%)	14 (56%)
Age at introduction of feeds (d)*	5.5 (2.2)	5.5 (2.8)
Type of milk received		
Breast milk only	18 (72%)	19 (76%)
Breast milk+Formula milk	7 (28%)	6 (24%)

** Values in mean (SD).*

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WHAT IS ALREADY KNOWN?

- Glycerin suppository is useful in early evacuation of meconium in term and preterm infants.

WHAT THIS STUDY ADDS?

- Daily application of glycerin suppository in preterm infants (gestational age 28-32 weeks) does not have any advantage in accelerating full enteral feeding.

TABLE II COMPARISON OF OUTCOMES IN GLYCERINE SUPPOSITORY VS. CONTROL GROUPS

* *Outcome*	*Glycerin suppository group (n=21)*	*Control group (n=21)*	*Relative risk (95% CI)*
Time to full enteral feeds (d)	11.9 (3.1)	11.3 (3.6)	0.57 (-1.52 to 2.66)
Time to regain birth weight (d)	15.7 (4.1)	17.1 (1.3)	-1.45 (-3.35 to 0.45)
Age of achieving weight of 1700 g (d)	41.6 (9.7)	36.3 (8.8)	5.32 (-0.46 to 11.10)
NEC stage 2 or more, *n*	0/21	1/21	0.33 (0.01 to 7.74)
NEC stage 1, *n*	2/21	0/21	5.0 (0.25 to 98.27)
Feeds withheld, *n*	7/21	4/21	1.75 (0.60 to 5.10)
Duration of hospital stay (d)	53.7 (14.4)	48.9 (14.8)	4.8 (-4.31 to 13.91)

* *Values in mean (SD).*

REFERENCES

1. Khadr SN, Ibhanesebhor SE, Rennix C, Fisher HE, Manjunatha CM, Young D, *et al*. Randomized controlled trial: impact of glycerin suppositories on time to full feed in preterm infants. Neonatology. 2011;100:169-76.
2. Leaf A. Introducing enteral feeds in the high-risk preterm infant. Semin Fetal Neonatal Med. 2013:18;150-4.
3. Bisset WM, Watt J, Rivers RP, Milla PJ. Postprandial motor responses of the small intestine to enteral feeds in preterm infants. Arch Dis Child. 1989;64:1356–61.
4. Shim SY, Kim HS, Kim DH, Kim EK, Son DW, Kim BI, *et al.* Induction of early meconium evacuation promotes feeding tolerance in very low birthweight infants. Neonatology. 2007;92:67-72.
5. McClure RJ, Newell SJ. Randomised controlled trial of trophic feeding and gut motility. Arch Dis Child Fetal Neonatal Ed. 1999;80:54-8.
6. Haiden N, Norooz F, Klebermass-Schrehof K, Horak AS, Jilma B, Berger A, *et al*. The effect of an osmotic contrast agent on complete meconium evacuation in preterm infants. Pediatrics. 2012;130:e1600-6.
7. Patole S. Strategies for prevention of feed intolerance in preterm neonates: a systematic review. J Matern Fetal Neonatal Med. 2005;18: 67-76.
8. McGuire W, Henderson G, Fowlie PW. Feeding the preterm infant. BMJ 2004;329: 1227-30.
9. Costalos C, Gounaris A, Sevastiadou S, Hatzistamatiou Z, Theodoraki M, Alexiou EN, *et al*. The effect of antenatal corticosteroids on gut peptides of preterm infants – a matched group comparison: corticosteroids and gut development. Early Hum Dev. 2003;74:83-8.
10. Yamauchi K, Kubota A, Usui N, Yonekura T, Kosumi T, Nogami T, *et al*. Benign transient non organic ileus of neonate: Eur J Peditr Surg. 2002;12:168-74.
11. Seigel M. Gastric emptying time in premature and compromised infants. J Pediatr Gastroenterol Nutr. 1983:2 Suppl 1; s236-40.
12. Dimmitt RA, Moss RL. Meconium diseases in infants with very low birth weight. Semin Pediatr Surg. 2000;9:79-83.
13. Mihatsch WA, Franz AR, Linder W, Pohlandt F. Meconium passage in extremely low birth weight infants and its relationship to very early enteral nutrition. Acta Paediatr. 2001;90:409-11.
14. Neu J, Zhang L. Feeding intolerance in very low-birth weight infants: what is it and what can we do about it? Acta Paediatr. 2005;94:Suppl.93-9.
15. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, *et al.* Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg. 1978; 187:1-7.
16. Shah V, Chirinian N, Lee S. EPIQ evidence review Group; Does the use of glycerin laxatives decrease feeding intolerance in preterm infants? Paediatr Child Health 2011;16:e68-70.
17. Shrinivasjois R, Sharma A, Shah P, Kava M. Effect of induction of meconium evacuation using per rectal laxative on neonatal hyperbilirubinemia in term newborn; A systemic review of randomized controlled trials. Indian J Med Sci. 2010;65:278-85.
18. Emil S, Nguyen T, Sills J, Padilla G. Meconium obstruction in extremely low-birth weight neonates: guidelines for diagnosis and management. J Pediatr Surg; 2004; 39:731-7.