Original Article

Randomized controlled trial: Role of glycerin suppository for promoting feeding tolerance in preterm very low birth weight neonates

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ABSTRACT

Background: Feeding intolerance is a common problem in preterm infants delaying establishment of full enteral feeding (FEF). Sustained parenteral nutrition has many disadvantages. To promote feeding tolerance, glycerin suppository is being used. **Aims:** (a) To compare the efficacy of glycerin suppository versus no intervention in preterm, very low birth weight (VLBW) neonates in achieving FEFs, i.e., 180 ml/kg/day for at least 24 hrs both the groups. (b) Correlation of glycerin suppository with time to regain birth weight, necrotizing enterocolitis, and adverse effects following glycerin suppository. **Materials and Methods:** The present study is a prospective randomized control trial; study population - 50 VLBW (birth weight between 1000 and 1500 g) or preterm (gestational age between 28 and 32 weeks) neonates randomized to either glycerin suppository group or non-intervention group. Intervention group – glycerin suppository (1 g) once daily from day 2 to day 14 of life or non-intervention along with intermittent oral feeds and standardized care. **Results:** A total of 58 neonates were assessed for eligibility, 50 randomized to either glycerin suppository group or control group, 19 neonates in both the groups were analyzed for outcome. Mean time to achieve FEFs was 11.57±1.21 days in glycerin suppository group and 11.84±1.25 days in control group which was not statistically significant (p=0.441; RR=0.67; 95% confidence interval=−0.539, 1.079). There was no significant difference observed in secondary outcomes. **Conclusion:** Prophylactic glycerin suppositories did not reduce the time to achieve FEFs in preterm VLBW neonates in our setting.

Key words: *Enteral feeding, Feeding intolerance, Necrotizing enterocolitis, Prematurity, Rectal suppositories*

Premature birth occurs at the time of rapid fetal growth and nutrient accumulation and therefore, establishing postnatal nutrition is essential to achieve appropriate growth and maintain biochemical normality [1]. There are significant risks with parenteral nutrition such as infection, cholestasis, hepatic dysfunction, thinning of gut mucosa, and impairment of enzyme production [2,3]. A delay in reaching full enteral feeding (FEF) is linked to poor outcome in preterm neonates including postnatal growth restriction and failure to thrive, especially in extremely low birth weight (ELBW) neonates [4,5]. An increased length of time to reach also significantly associated with a poor mental outcome in preterm neonates at 24 months corrected age [6]. Feeding intolerance is a common problem encountered in preterm infants. It may be seen as an early sign of necrotizing enterocolitis (NEC), sepsis, or other serious conditions, or it may result from gut immaturity [7,8]. The late passage of meconium also delays the establishment of oral feed and exaggerates the enterohepatic circulation of bilirubin [9].

To promote feeding tolerance and to prevent NEC, various strategies have been used such as administration of antenatal steroids, early initiation of enteral feeds, exclusive use of breast milk, mode of administration of feeds (continuous versus bolus feeds), and use of prokinetic and probiotic agents [10]. In addition to these modalities, glycerin laxatives (enema or suppositories) have also been used to encourage the passage of meconium, decrease gastrointestinal transit time, and improve feeding tolerance in preterm neonates [11]. We hypothesized that glycerin suppository by acting as an osmotic laxative will facilitate early meconium evacuation and accelerate feed tolerance. Our study was an effort to compare the efficacy of glycerin suppository versus no intervention in preterm very low birth weight (VLBW) neonates in improving feeding tolerance and to provide an accurate picture of the outcome.

MATERIALS AND METHODS

This randomized controlled trial (RCT) was conducted in neonatal intensive care unit (NICU) of a tertiary care hospital in western Uttar Pradesh, India, from October 2014 to November 2015. The study was approved by Institutional Ethics Committee. All infants admitted to NICU within 36 h of birth, with a birth weight between 1000 and 1500 g or gestational ages between 28 and 32 weeks, were eligible for inclusion in the study. Infants with gastrointestinal or other systemic malformations and infants with hemodynamic instability were excluded from the study. When a patient meeting inclusion criteria was admitted, the doctor on

duty obtained the written informed consent from parents or legal guardian. Eligible neonates were randomized to either glycerin suppository group or control group. Randomization was done by lottery method. Chits numbered from 1 to 20 were prepared, placed in a box, and a single chit was drawn from the box. It was presumed that, if we get even number, the child would be placed in study group, and if we get an odd number, child would be placed in control group.

The glycerin suppository administration was performed by designated study staff nurse or resident doctor on duty. Those in the study group received the drug at a dose of one infant glycerin suppository (infant glycerin suppository 1 g, Bhartia Pharmaceuticals) once a day from day 2 to day 14 of life, irrespective of the passage of stools. Those who were assigned to control group did not receive any suppository and no intervention was done in this group. Feeds were started in both the groups when they became clinically stable, usually between 2nd and 5th day of life. The feeds were given in the form of intermittent boluses every 3 h through orogastric or nasogastric infant feeding tube. All infants received either expressed breast milk (EBM) and/or preterm infant milk formula (Lactodex LBW, Raptakos, Brett & Co. Ltd.); EBM was preferred whenever available. The initial feeding volume was 10-20 ml/kg/day and the volume was increased daily by 10-20 ml/kg/day, if tolerated until complete enteral feeding was achieved i.e., 180 ml/kg/day. Feeding was withheld as per clinical condition (suggestive of NEC or other intra-abdominal pathology) or if gastric residuals exceeded 50% of previous feed volume. Standards of care of NICU did not change throughout the study period. Grading up of intravenous fluids and starting of trophic feeds was done as before as per standard protocol of NICU.

The primary outcome was the time required to achieve FEFs, i.e., 180 ml/kg/day for at least 24 h in both the groups. The secondary outcome was the correlation of glycerin suppository with NEC, time to regain birth weight and adverse effects if any following the glycerin suppository. Sample size was calculated using the formula for the hypothesis of 2-parallel sample means. With the existing feeding practices, the average time taken by an infant with birth weight of 1000-1500 g to reach full feeds was 13 days (standard deviation [SD] 3 days). We hypothesized that the glycerin suppository group will reach full feeds by day 10 (SD 2.8 days) of life. For a difference of 3 days, with an error of 0.025 and power of 80%, the estimated sample size was 19 in each group. To account for lost to follow-up, 25 infants were to be enrolled in each group. Data was analyzed by SPSS software version 22.0 (SPSS Inc., Chicago, IL, USA). Continuous measures between groups were compared using two-sample t-test. Chi-square (χ^2) test was used to compare proportions. p value<0.05 was considered statistically significant.

RESULTS

A total of 50 neonates were randomized and allocated to either glycerin suppository group or control group. The flow chart of the study participants is shown in Fig. 1. The baseline characteristics of the study participants were similar in both the groups as shown in Table 1 and include birth weight, gestational age, sex, administration of antenatal steroids, mode of delivery, age at the introduction of feeds, type of milk received and hyperbilirubinemia. A total of 19 neonates in both the groups were analyzed for the outcome of the study. The outcome of the two study groups is shown in Table 2.

DISCUSSION

The results of our RCT did not show any statistically significant difference in the time to achieve FEF in glycerin suppository group as compared to control group and suggest that the use of glycerin suppository to evacuate meconium does not reduce the time to reach FEF in preterm LBW neonates versus those not

Table 1: Baseline characteristics of the study participants

Characteristics	Glycerin suppository group (n=25)	Control group (n=25)	t value	p value/result
Birth weight, grams (SD)	1344 (208.3)	1362 (190.9)	t=0.3185	0.7515*
Gestational age, weeks (SD)	30.5 (2.63)	30.8 (1.3)	t=0.5113	0.6115*
Sex n (%)				
Male	14 (56)	16 (64)	χ^2=0.333	0.5638*
Female	11 (44)	9 (36)		
Antenatal glucocorticoids	20 (80)	21 (84)	χ^2=0.175	0.6757*
Mode of delivery n (%)				
Vaginal	12 (48)	13 (52)	χ^2=0.08	0.7772*
LSCS	13 (52)	12 (48)		
Age at introduction of feeds in days (SD)	4.0 (0.9)	4.24 (1.3)	t=0.7589	0.4516*
Type of milk received n (%)				
Breast milk only	16 (64)	17 (68)	χ^2=0.089	0.7654*
Breast milk+formula milk	9 (36)	8 (32)		
Hyperbilirubinemia	11 (44)	12 (48)	χ^2=0.175	0.6757*
Mortality	1 (4%)	2 (8%)	χ^2=0.000	1.000*

*p>0.05=Statistically not significant, χ^2=Chi-square, t=test value. SD: Standard deviation, LSCS: Lower segment cesarean section

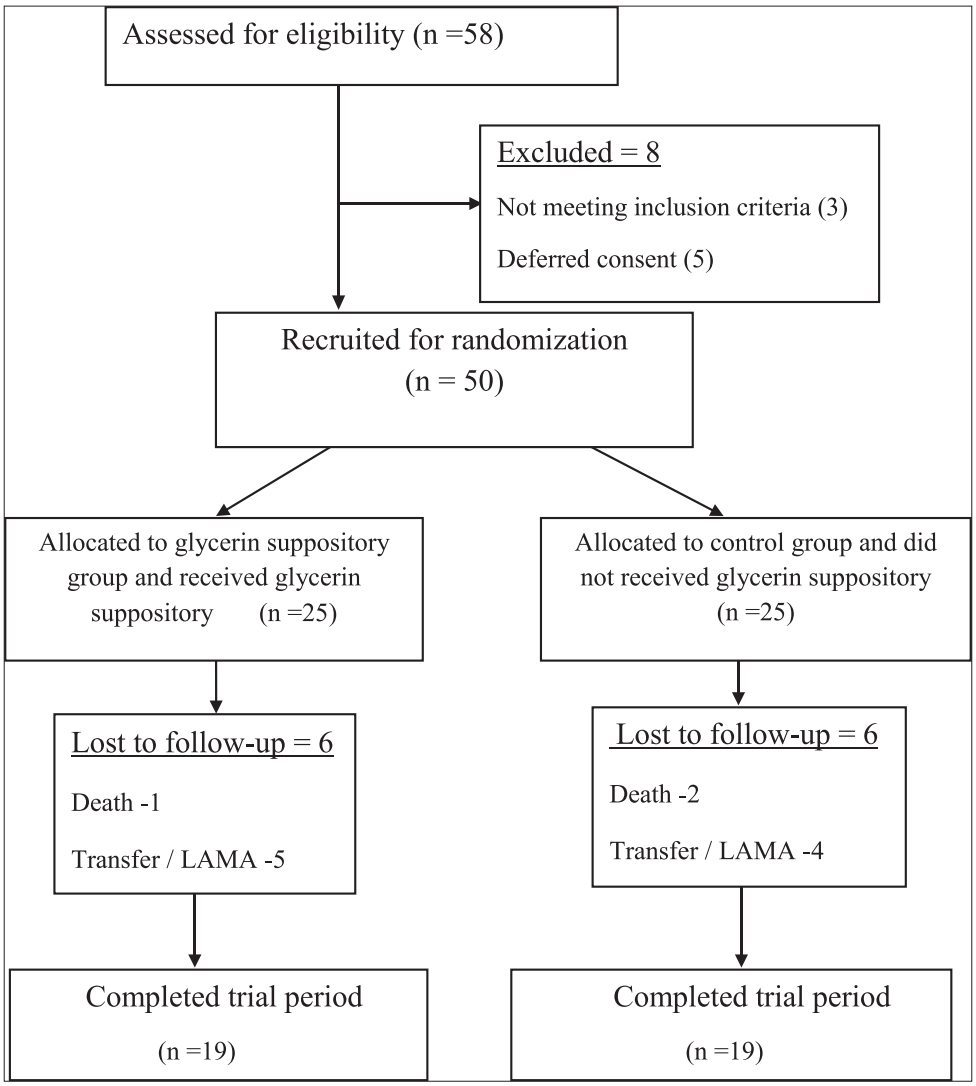

Figure 1: Flow chart of the study participants

Table 2: Comparison of outcomes in glycerin suppository group and control group

Outcome	Glycerin suppository group (n=19)	Control group (n=19)	p value	Relative risk (95% CI)
Mean time to reach FEF in days (SD)	11.57 (1.21)	11.84 (1.25)	0.4416	0.67 (−0.539-1.079)
Feeds withheld, n (%)	4 (21)	3 (15.7)	0.6757	1.33 (0.343-5.170)
NEC, n (%)	1 (5.2)	2 (10.5)	0.5637	0.50 (0.049-5.061)
Mean time to regain birth weight in days (SD)	14.15 (1.58)	14.21 (1.57)	0.9069	0.11 (−0.976-1.096)
Adverse effect	0	0		

SD: Standard deviation, FEF: Full enteral feeding, NEC: Necrotizing enterocolitis, CI: Confidence interval

receiving it. There was also no significant difference observed in the secondary outcome between the two groups. An observational cohort study by Shim et al. reported a significant positive effect on feeding tolerance and sepsis prevention in VLBW infants. The study group achieved FEF significantly faster than the control group (16 days vs. 22.9 days) [4]. Haiden et al. in a RCT found that repeated daily application of small volume diluted glycerin enemas does not accelerate meconium evacuation and FEF in VLBW infants [12].

Khadr et al. in a non-blinded RCT showed that the median time to full feeds was 1.6 days shorter in the glycerin suppository group; however, it was not statistically significant. The study concluded that regular glycerin suppositories did not reduce the time to FEF in infants born at <32 weeks gestation, and no significant differences were observed in secondary outcomes such as incidence of sepsis, NEC, duration of oxygen requirement, growth or age at discharge [3]. A double-blinded RCT by Shinde et al. concluded that once-daily application of glycerin suppository does not accelerate the achievement of full feeds in preterm VLBW neonates [11]. Meconium retention is believed to result in gastric residuals, distention of abdomen and delayed passage of food, possibly by enteroenteric reflexes leading to

delayed gastric emptying [13,14]. The passage of first meconium only reflects the function of terminal bowel and achievement of total meconium evacuation which is delayed in preterm infants also correlates better with feed tolerance [15].

The findings of our trial are also not unexpected as the normal function of the upper as well as lower gastrointestinal tract is essential for complete evacuation of meconium, and also feeding tolerance and interventions such as a glycerin suppository or small volume enemas do not have an effect on the right colon or the small bowel [14]. Whether combination of therapies targeting both upper and lower gastrointestinal tract would result in benefits needs investigation. A more frequent application (e.g., twice daily) or higher dose may be more effective in accelerating meconium evacuation [16]. Our study has some limitations also. The clinicians were not blinded to treatment allocation, introducing an element of bias. ELBW neonates were not included in the trial because of the perceived risk and difficulty in the administration of glycerin suppository in this population.

CONCLUSION

Regular once-daily administration of glycerin suppositories to preterm VLBW neonates for 14 days did not significantly reduce the time to achieve FEF in our setting. There was also no impact observed on secondary outcomes including the incidence of NEC, hyperbilirubinemia, time to regain birth weight, feed intolerance, and any adverse effect and mortality with the use of glycerin suppository. Our findings do not support the routine use of prophylactic glycerin laxatives in clinical practice to promote feeding tolerance in preterm low birth weight neonates. Additional studies are needed to confirm the effectiveness and safety of glycerin laxatives for the prevention and treatment of feeding intolerance.

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