Original Article

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Paediatrics Section

Effect of Glycerine Suppository in Achieving Early Full Feeds in Premature Infants: A Randomised Controlled Trial

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ABSTRACT

Introduction: Achieving full feeds in premature infants is challenging as it can be delayed due to immaturity of their gut. Osmotic agents orally and as suppositories or enemas can be used to stimulate the passage of meconium to promote early feeding but there is little evidence to support this practice as studies have been inconclusive.

Aim: To determine the effect of using glycerine suppository in premature neonates on their time required to achieve full feeds in comparison with premature neonates with no glycerine suppository.

Materials and Methods: This study was a randomised, double blinded trial conducted on premature infants, with birth weight <1500 g and a gestational age <32 weeks. Study group received 500 mg glycerine suppository twice daily, started within 48 hours of life for 14 days, while Control Group (CG) received no intervention. The results were plotted in MS Excel and analysed using SPSS 22.

Results: Total 50 cases, 25 neonates in each group were analysed for the primary and secondary outcomes. Mean duration for full feeds was achieved by 11.1 days in the Glycerine Suppository Group (GSG) and 11.9 days in Control Group (CG) (p-value 0.2). While the duration of hospital stay was shorter in the GSG than the CG (38.4 days vs 40.7 days), but was not statistically significant (p-value 0.49).

Conclusion: There was no statistically significant difference seen between the groups in achieving Full Enteral Feeds (FEF). No differences were observed between the groups in regaining birth weight, duration of hospitalisation or incidence of complications including Necrotising Enterocolitis (NEC).

Keywords: Enteral feeding, Necrotising enterocolitis, Preterm birth

INTRODUCTION

Premature infants after birth require the establishment of appropriate nutrition during this crucial period of rapid growth [1]. Most are initially started with intravenous parenteral nutrition with progressive advancement of enteral feeds. It is crucial to establish early optimal enteral feeding in such premature neonates since there is an increased probability of infections, gut atrophy, cholestasis with increased hospitalisation and costs associated with prolonged parenteral nutrition [2]. Achieving full feeds is challenging and can be delayed due to feeding intolerance and the development of life-threatening NEC [3,4]. This might be due to the immature gut with intestinal hypomotility and in-coordinated peristalsis [5]. There are different strategies used to improve feeding tolerance like Minimal Enteral Nutrition (MEN), slow intermittent or continuous advancement of feeds, antenatal steroids, prokinetics drugs and early evacuation of meconium [6,7].

Meconium evacuation depends upon the maturity of the intestinal motor and neurotransmitter systems and is delayed in more immature preterms [8]. A thick, tenacious, sticky meconium may cause obstruction leading to abdomen distension with feeding intolerance [9,10]. Osmotic agents orally and as suppositories or enemas have been used to stimulate the passage of meconium to promote early feeding [11,12] but there is little evidence to support this practice as studies have been inconclusive due to inadequate methodology [13,14].

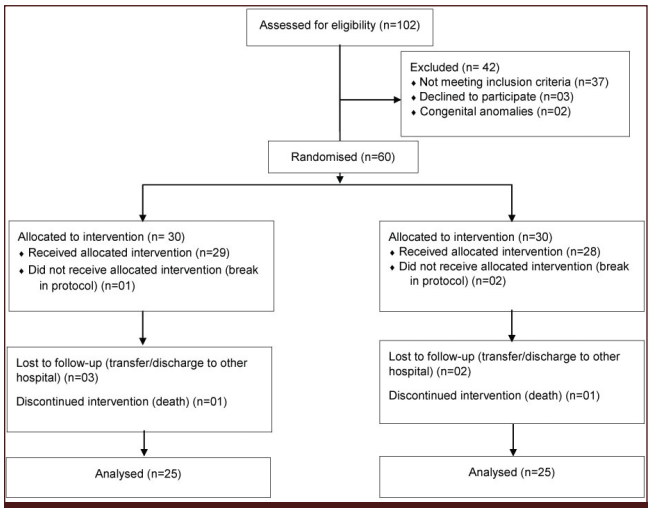
As further research was required, a randomised controlled trial was designed to observe the effect of using prophylactic glycerine suppository in premature neonates with the primary objective being the time required to achieve full feeds by preventing feed intolerance.

MATERIALS AND METHODS

A randomised double-blinded, placebo-controlled trial was done at the NICU of a teaching hospital of the armed forces at

Delhi from April 2014 to March 2017. The study was approved by the intuitional ethics committee (Letter no MHS/Trg/14/Paed-17).

The formula for hypothesis of 2-parallel sample means was used for calculating the sample size. For a difference of three days as taken from previous studies [13] with an error of 0.05 and power 90%, the sample size was estimated to be 24 in each group. To account for the loss of dropouts during the study period of 20%, a total of 30 cases were enrolled in each group [Table/Fig-1].



[Table/Fig-1]: CONSORT flow chart.

All premature neonates, less than 32 weeks of gestation and weighing less than 1500 gm were eligible for the study. Neonates with major congenital malformation, systemic metabolic diseases and haemodynamic instability with features of shock, on inotropes, nitric oxide, prostaglandins, neutropenia (absolute neutrophil count $<0.5\times10^9$/L) and with suspected coagulopathy (bleeding from any orifice) or confirmed coagulopathy (international normalised ratio >1.4, prothrombin time >16 s, partial thromboplastin time >59 s (preterm 80s or greater in first day of life), fibrinogen <1.5 g/L, platelet count $<100\times10^9$/L) were excluded from the study [15]. Written consent from parent was obtained after explaining the study procedure. Enrolled neonates were randomised into an intervention group, who received glycerine suppository (GSG) and the control group (CG). The randomisation sequence was generated using a web-based program with allocation using a sealed opaque in blocks of six which contained three each subject of the two groups.

All neonates were admitted to the NICU and received standard initial care and investigations. The neonates in the intervention group (GSG), were administered a glycerine suppository 500 mg, which was made by cutting a 1 gm suppository (Pentasa 1 gm, Serum Biotec Ltd.,). This was given twice daily starting within 48 hours (day 2) of life by the nursing staff in charge specifically. The tip was first lubricated with water and then placed in the neonate's rectum. Their buttocks were held together for 30 seconds to prevent this suppository for being spontaneously ejected. Treatment was continued up to 14 days of life. Those assigned to the CG, were not given any suppository.

Double blinding was achieved by placing suppository in diaper as a sham procedure to ensure that the treatment appeared to have been given, to other staff and residents involved in the care of these neonates. The interventions were withheld on the deterioration of the status of the enrolled neonates.

A gastric tube was routinely inserted orally during the first hour of birth in all neonates. Subsequently, all babies received MEN within the next 12 hours which was 1 mL feed every 4 hourly. Following these feeds were started if they remained clinically stable, usually between 2nd to 5th days of life. The feeds were preferably Expressed Breast Milk (EBM) and if unavailable/ or inadequate then formula milk was used. This feed was given through an orogastric tube in an intermittent 2 hourly boluses which were initially started at 10 mL per kg and then subsequently increased daily by 10-20 mL/kg/day until full enteral feeding (140 mL/kg/day) was achieved [16]. The EBM was fortified with commercially available powder (Lactodex HMF, Raptakos, Brett and Co., Ltd.,). The feeding policy remained similar for the two groups throughout the study period. The neonates were monitored daily as per the standards of NICU care along with laboratory investigations for infections during the study.

As it was hypothesised that early use of glycerine suppository would decrease the time for achieving FEF in premature neonates, hence the primary outcome was days required for FEF on fortified EBM or formula feeds. Secondary outcomes were the time required to regain birth weight, NEC (Bell classification) [17], weight on discharge and outcome.

STATISTICAL ANALYSIS

These results were recorded and then analysed by using SPSS software version 22.0 (SPSS Inc., Chicago, IL USA). Results of outcome variables were expressed in mean and SD in tables and were compared using the Fisher's-exact test. Two sample t-test or Mann-Whitney-U test as appropriate were used and a p-value <0.05 was considered significant.

RESULTS

A total of 102 Very Low Birth Weight (VLBW) preterm infants (less than 1500 gm) were evaluated for study. Of these 37 had to be excluded as these neonates either were sick with shock or had metabolic derangements or bleeding manifestations as described in the exclusion criteria. Two neonates had obvious structural anomies and were excluded. Parents of 03 neonates

declined to participate in the study. The remaining 60 infants were randomised evenly to GSG and CG. Of the enrolled cases, 5 in each arm did not complete the study due to transfer to a different centre, break in study protocol and death.

The remaining 25 neonates in the GSG and 25 neonates in the CG were studied and evaluated. There was no difference in the baseline characteristics of these two groups which included birth weight, type of delivery, antenatal steroids, and type of milk feeds [Table/Fig-2]. The mean gestational age were 30.1 weeks in GSG group compared to 30.3 weeks in CG group. Similarly, comparable mean weights of 1191 gm and 1243 gm were observed in GSG and CG groups.

Characteristics	Glycerine Study Group (GSG) N=25	Control Group (CG) N=25	p-value
Birth weight in gms, mean (SD)	1191 (146)	1243 (159)	0.23
Gestational age in weeks, mean (SD)	30.1 (1.5)	30.3 (1.66)	0.65
Sex (%)			
Male	14	13	0.78
Female	11	12	
Antenatal steroids (%)	22 (88)	21(84)	0.68
Mode of Delivery (%)			
Vaginal	16 (64)	18 (72)	0.54
Caesarean section	9 (36)	7 (28)	
Types of Milk (%)			
Breast milk only	15 (60)	17 (68)	0.55
Breast milk plus formula feed	10 (40)	8 (32)	

[Table/Fig-2]: Demographic characteristics of the study participants.

Cases in each group were analysed for the primary and secondary outcome of the study which included passage of first and last day of meconium, introduction of enteral feeds, day on which full feed achieved, duration of hospital stay, discharge weights and any complications noted including NEC [Table/Fig-3]. There was no statistically significant difference between the groups in achieving FEF at 11.1 and 11.9 days in GSG and CG groups, p-value 0.2. Average duration of regaining birth weight was higher at 17.13 days in CG group compared 15.87 days in GSG group; however, it was statistically not significant. Likewise, the duration was also higher in CG group at 40.7 days as compared to 38.4 days in GSG group (p-value 0.49). No significant difference was observed between the groups in increased incidence of NEC [Table/Fig-3].

DISCUSSION

Current randomised controlled study was done on 50 premature neonates and found no benefit of using prophylactic glycerine

Variables	Glycerine Study Group (GSG) n=25	Control Group (CG) n=25	p-value	Relative Risk (95% CI)
Passage of first Meconium, days of life, mean (SD)	1.9 (0.5)	1.89(0.6)	0.94	1.08 (0.62-1.88)
Last Meconium, days of life, mean (SD)	7.57 (1.9)	8.12	0.41	0.58 (0.27-1.23)
Introduction of feeds, days of life, mean (SD)	1.1 (0.3)	1(0.2)	0.17	1.25 (0.74-2.09)
Full Feeds, days of life, mean (SD)	11.1 (1.31)	11.9 (2.8)	0.2	0.83 (0.44-1.56)
Birth weight regained, days of life, mean (SD)	15.87 (2.83)	17.13 (3.7)	0.18	1.33 (0.80-2.20)
Duration of hospital stay, days of life, mean (SD)	38.4 (11.4)	40.7 (12.1)	0.49	0.92 (0.50-1.67)
Discharge Weight in gm mean (SD)	2031 (211)	2119 (237)	0.17	0.75 (0.38-1.45)
NEC Stage 1-n (%)	2 (8)	3 (12)	0.68 (X^2=0.16)	0.75 (0.19-3.01)
NEC Stage 2 or more- n (%)	1 (4)	1 (4)		

[Table/Fig-3]: Comparison of outcomes between the study GSG and CG.

suppository in decreasing the time required to achieve FEF compared to those who did not. There was also no significant difference observed in the secondary outcomes as in early discharge or weight gain, length of hospital stay or increased risk of complications. The result of this study though was, in contrast, to study by Shim SY et al., who reported faster time to full feeds than their CG (16 days vs 22.9 days) in their VLBW infants, possibly due to use of glycerine enemas which though are more effective but are comparatively more invasive in nature [18]. This was also reported by Pietz J et al., and their protocol included regular use of glycerine suppositories if there was no meconium for 24 hours (study conducted in US) and they reported one of the lowest incidences of NEC in VLBW in United States NICUs [19]. Their rationale was to prevent the development of intestinal distension that could affect intestinal flow leading to NEC.

The index study was similar to the observations made by Shinde S et al., but they used once daily glycerine suppository in their randomised controlled trial in a higher dose [13] and suggested for more frequent dosing which was done in the index study. Other studies had also advocated a higher

or more frequent dose similar to the index study [20]. No significant benefit with the use of glycerine suppository was also reported by Shah V et al., [11]. In a study by Khadr SN et al., the GSG had a shorter median time to achieve full feeds by 1.6 days but it was not statistically significant [2]. In a recently conducted systemic review on the use of glycerine enemas and suppositories, there was no difference observed in terms of meconium evacuation, time to FEF or increased complications, but meta-analysed data revealed a non-significant trend towards increased risk of NEC with active treatment [14]. The authors felt that these trials were underpowered and had methodological issues as the trials terminated at an arbitrary point of time without completion of meconium evacuation due to which the evidence was inconclusive and further research was required. Some authors have advocated oral osmotic agents for proper evacuation of meconium with the rationale that glycerine suppositories or enemas would not affect the small intestine and colon [12]. They too observed these osmotic agents like gastrografin did not accelerate meconium evacuation in premature infants, had a higher stool frequency with accelerated full feeding and shortened stay but there was some increase in NEC. With the data available for potential increase in NEC with their use, even occasional intermittent use should be avoided until further trials are undertaken to evaluate their safety.

LIMITATION

The study couldn't analyse the complications and quantify the risks associated due to smaller sample size. Another possible limitation is that the study involved VLBW including extremely low birth weight infants whose gut maturity differs considerably and can have different meconium evacuation profiles. The authors observed osmotic agents to be more helpful in extreme preterms with severely delayed meconium evacuation which may be studied in future.

CONCLUSION

The present study findings do not support the routine prophylactic use of glycerine suppository in premature infants as it did not promote early achievement of FEF. However, it may have a role in subset of neonates such as extreme preterm with delayed meconium passage which warrants further studies to achieve benefits and risks in adequately powered trials.

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