

## Original Research

# Transpyloric Feed in Reflux-Associated Apnea in Preterm Newborns: A Prospective Study

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### Abstract

#### Background

The etiological correlation between gastroesophageal reflux (GER) and apnea is controversial. We conducted a prospective interventional study designed to address the controversy.

#### Methods

Preterm neonates with apnea at a tertiary care center, who had clinical features of GER without any other comorbidities likely to cause apnea, were included in the study. The enrolled neonates underwent continuous transpyloric tube feeding for 72 hours. The primary outcome measure was the difference in the number of apneic episodes pre- and post-initiation of nasoduodenal (ND) feeding. Secondary outcome measures included the incidence of necrotizing enterocolitis, other gastrointestinal disturbances, and mortality.

#### Results

Sixteen preterm neonates were included in the study. A substantial proportion (n =11, 68.8%) of the included neonates had a reduction in the number of apneic episodes. There was a significant decrease in the mean number of apneic episodes from 1.75 ( $\pm 0.837$ ) to 0.969 ( $\pm 0.957$ ) ( $P = .007$ ). The median number of apneas was 1.5 (IQR 0.875) before and 0.5 (IQR 0.875) after ND feeds. There were no serious adverse events observed that were attributable to transpyloric feeding.

#### Conclusion

This prospective study suggests that in a selected group of preterm neonates with reflux-associated apnea, transpyloric feeding can be an effective therapeutic modality.

#### Keywords

prematurity; newborn; gastroesophageal reflux; apnea; transpyloric feeding

## Introduction

Apnea is common in premature neonates.<sup>1</sup> Between 7 and 54% of babies born between 30 and 35 weeks of gestational age have apnea and almost every infant born at less than 29 weeks has apnea.<sup>2,3</sup> While apnea may be physiological in premature babies, gastroesophageal reflux (GER) is often implicated as a cause of apnea in this population. However, the causal relationship between apnea and GER remains controversial.<sup>4</sup> While earlier studies supported this relationship, several recent reports are con-

tradictory.<sup>5-11</sup> It is difficult to establish a chronological relationship between the occurrence of reflux and the onset of apnea. This difficulty is further complicated by the fact that both reflux and apnea commonly coexist in premature infants.<sup>4</sup> Hence, while the association between these events can be established, it is hard to prove that reflux is the cause of apnea.

Two retrospective studies have reported transpyloric feeds, which reduce reflux, to be effective in reducing apnea in premature babies.<sup>12,13</sup>

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We designed this prospective study to test the hypothesis that transpyloric feeds may help reduce apnea in selected premature newborns.

## Methods

A prospective interventional single-center study was done at the Medical College Hospital, Kolkata, India, a tertiary care hospital in eastern India, between May 2015 and November 2015. This study was approved by the Institutional Ethics Committee for Human Research of Medical College Kolkata. Written informed consent was obtained from the parents/legal guardians of all participants. The trial was registered with Clinical Trials Registry-India (CTRI/2015/03/005656).

Inclusion criteria included preterm (gestational age less than 37 weeks) neonates born at the institution and admitted to the neonatal intensive care unit (NICU) were included in the study if, 1) They were on enteral feeds of more than 20 ml/kg/day. 2) They had at least one episode of apnea. 3) They had clinical features of GER (regurgitation, possetting, back arching, choking, coughing, unexplained crying and irritability). 4) They did not meet any of the exclusion criteria.

Exclusion criteria included neonates born outside the hospital, those on mechanical ventilation, and those with major congenital anomalies. Neonates with comorbidities that can cause apnea such as sepsis, hypoglycemia, hypothermia, dyselectrolytemia, patent ductus arteriosus, intracranial hemorrhage, etc were also excluded.

For assessment of gestational age, a dating ultrasound scan done prior to 20 weeks of gestation was used whenever available. When a dating scan was not available, the date of maternal last menstrual period was used for calculation, after ascertaining that the mother had regular menstrual cycles. Postnatal gestational age assessment was also done using the new Ballard score.

For the purpose of the present study, apnea was defined as cessation of respiration for longer than 20 seconds or shorter duration in the presence of cyanosis or bradycardia.<sup>1</sup> These episodes were confirmed by the vital records

and events log of the neonatal intensive care unit (NICU). A clinical diagnosis of suspected GER was made by the attending neonatologist. Institutional protocols regarding the initiation and progression of enteral feeds in preterm neonates were followed without any change.

Transpyloric placement of the non-weighed polyurethane feeding tube was done at the bedside by the previously described technique.<sup>12</sup> Appropriate placement of the tube was confirmed with an abdominal X-ray. The neonates had continuous transpyloric feeding of human milk with a pump for 72 hours. There was no change in the volume of feeds during the study period. A Star 55 multi-para monitor (Skanray/Larsen & Toubro, Mysore, India) was used for monitoring vitals. Vitals and events records were collected from the bedside events log as well as the trends log of the multi-para monitor.

The primary outcome measure was the incidence of apneic episodes post-intervention. Secondary outcome measures included incidence of gastrointestinal disturbances, necrotizing enterocolitis, and mortality post-intervention.

## Statistical Analysis

Data analysis was done using R Version 3.3.0. Descriptive statistics were used to summarize important variables under study. The normal distribution of the differences between the mean number of apneic episodes post- and pre-intervention was confirmed by the Shapiro-Wilks test ( $P = .770$ ). Hence, a paired *t*-test was used to compare the mean number of events post- and pre-intervention. Linear regression studies were done as multifactorial analyses for confounding factors that could possibly affect the change of apnea. Two-tailed *P* values were used unless explicitly stated otherwise. A *P* value less than or equal to .05 was considered to be statistically significant.

## Results

Seventeen preterm neonates aged between 4 to 23 days were enrolled in the study, one was excluded due to intolerance of transpyloric feeds (excessive vomiting). Sixteen neonates (10 male, 62.5%) were included in the final per-protocol analysis.

The mean gestational age of the study population was 31.885 ±1.96 (range 28-35) weeks. Eight preterm neonates (50%) were very preterm (gestational age 28-31 weeks). No extremely preterm neonate (gestational age < 28 weeks) was included in the study.

The mean (+SD), median (interquartile range, IQR), and range of the birth weights were 1.35 (±0.34) kg, 1.225 (1.11-1.525) kg, and 1-2.3 kgs, respectively. Ten (62.5%) of the preterm neonates were very low birth weights (less than 1.5 kg).

Approximately one-third (31.59 %) of the infants were born by Caesarean section, while the rest were born vaginally. Antenatal complications were reported in 2 cases (antepartum hemorrhage and prolonged rupture of membranes, respectively). Three of the 16 preterm neonates had moderate perinatal asphyxia. Nasoduodenal (ND) feeding was started at a median age of 2.5 (IQR 2.0) days. Seven of the 16 infants were on complete enteral nutrition.

Eleven of the 16 (68.75%) neonates had a documented reduction in the number of apneic episodes with transpyloric feeding (Figure 1). The median number of apneas was 1.5 (IQR 0.88) before and 0.5 (IQR 0.88) after ND feeds. The mean number of apneic episodes decreased

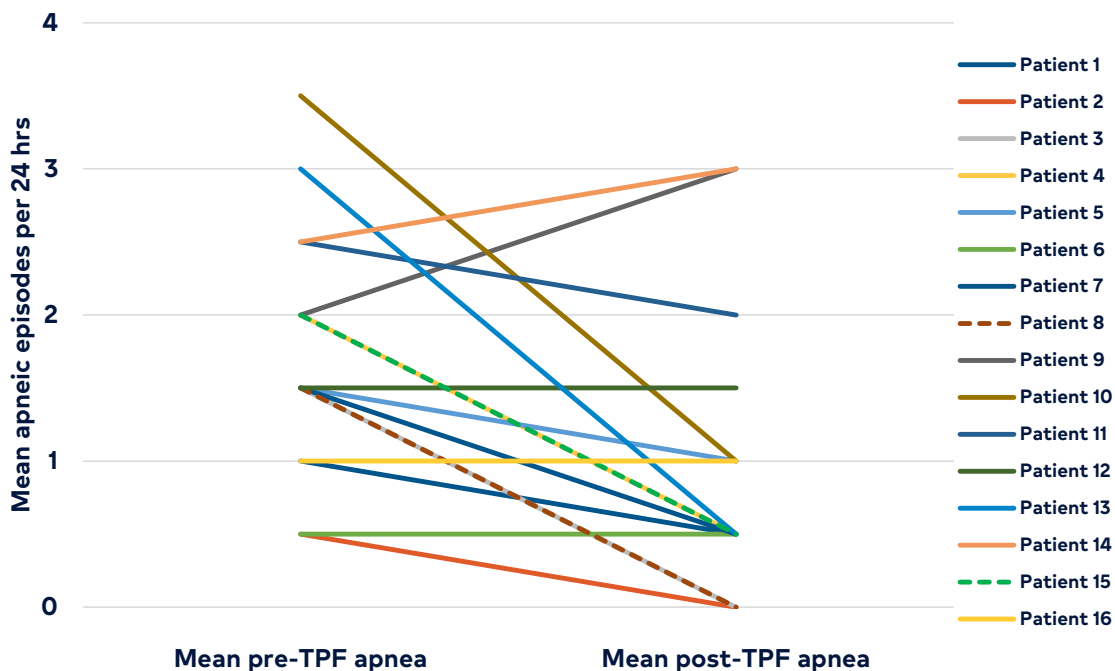
from 1.75 (±0.84) to 0.97 (±0.96) (mean difference 0.78, 95% CI for mean difference 0.25-1.31, *P* = .007).

No other covariates such as sex, gestational age, etc were found to be significantly related to the number of apneic events by linear regression analysis (Table 1). The *F*-test or the overall statistic for regression has a significant *P* value greater than .05.

The only adverse effect of transpyloric feeding was vomiting in 1 of the patients (5.88%) which resolved after cessation of transpyloric feeding. This subject was excluded from the analysis.

### Discussion

GER has often been suggested as the cause of apnea in prematurity. Though both GER and apnea are common in preterm neonates, to date their causal and temporal relationships remain inconclusive. The interpretation of prior studies is challenging due to the varying methods used for diagnosing and defining GER. While apnea is well defined, it is now accepted that GER is basically a clinical diagnosis, as there is no gold standard test for GER in infants.<sup>14</sup> Barium contrast studies are not recommended and esophageal pH monitoring techniques are limited by their inability



**Figure 1.** A line plot shows the mean number of apneic episodes during the study. Abbreviation: TPF = transpyloric feed

**Table 1.** Summary of Linear Regression Analysis

Variable	Coefficient (Std. error)	t-score	P value
Sex = male	0.45 (0.54)	0.83	.433
Gestational age, weeks	0.27 (0.13)	2.05	.075
Birth weight, kg	-0.01 (0.72)	-0.02	.988
Age at start of transpyloric feeding, days	-0.06(0.05)	-1.22	.256
Mode of delivery = ND	-0.35(0.69)	-0.51	.626
Perinatal asphyxia = No	0.13 (0.48)	0.26	.799
Complete enteral feeding = No	-0.32(0.49)	-0.64	.538
Overall			
Adjusted $R^2 = 0.5244$ , $F$ statistic = 3.363 on 7 and 8 DF, $P$ value = .055			
ND = nasoduodenal feed			

to detect non-acid reflux episodes.<sup>14,15</sup> Multiple intraluminal impedance (MII), a novel pH-independent technique for diagnosing reflux, has not correlated well with symptoms.<sup>16,17</sup> A recent study suggested that only 10% of babies with clinical reflux behavior had documented reflux events detected by MII.<sup>18</sup>

In this study, we used clinically accepted reflux symptoms as the inclusion criteria instead of complex and still unproven diagnostic modalities. Instead of diagnosing reflux, we attempted to reduce reflux to document its effect on apnea.

We used transpyloric feeds to decrease reflux which is well supported by the literature. Radiolabeled formula infusion studies have shown that direct small bowel feeding reduces the likelihood of reflux.<sup>19</sup> Transpyloric feeding has been shown to be comparable to fundoplication in reducing reflux in older children.<sup>20</sup> Jejunal feed has been recommended by the European Society of Pediatric Gastroenterology Hepatology and Nutrition as an alternative to fundoplication to prevent aspiration.<sup>21</sup> Building on previously published retrospective studies, our study is the first prospective study evaluating the efficacy and safety of transpyloric feeding in preterm neonates for apnea that coexisted with clinical reflux. Our results suggest that this intervention is effective in a selected group of infants.

Eleven of the 16 preterm neonates in our study had a reduction in the number of apneic episodes with transpyloric feeding. There was also

a significant reduction in the mean number of apneic episodes in the pre- and post-intervention periods. This result compares well with the available literature. In a retrospective study, Misra et al observed a reduction in apnea in 12 out of 15 premature neonates treated with transpyloric feeding due to clinically suspected GER.<sup>12</sup> These authors also reported a significant decrease in the mean number of apneic episodes. Similarly, Malcolm et al showed a reduction in the combined number of apnea episodes from 4 to 2.5 in 72 hours pre- and post-transpyloric feeding, respectively, in a retrospective report on 72 very low birth weight neonates.<sup>13</sup>

The precise mechanisms of decreased apnea with transpyloric feeding remain unknown. Rosen et al reported significantly more reflux episodes during transpyloric feeding periods.<sup>22</sup> However, this increase was in relation to the non-feeding periods. The total number of reflux events and the number of full column reflux events, possibly associated with apnea, were actually reduced in these neonates on transpyloric feeding than those reported in newborns with reflux.<sup>22,23</sup>

No significant adverse events were associated with transpyloric tube insertion or feeding, such as necrotizing enterocolitis as reported by Malcolm et al.<sup>13</sup> One participant had vomiting with the transpyloric feed that resolved on removal of the tube. A recent systematic review reported no difference in rates of intestinal perforation or necrotizing enterocolitis but increased mortality in neonates on transpyloric feeding.<sup>24</sup> However, the higher likelihood of

mortality in the transpyloric group was mostly attributed to 1 study, which likely suffered from selection bias.

The limitations of this study include a small sample size. Though there was no control group, the before-after design meant that each subject served as its own control. Lastly, the present study, being unblinded, was prone to the risk of assessor's bias. However, objective, electronically recorded data from the vitals monitor was used for the purpose of the study to help mitigate any bias.

## Conclusion

This prospective study shows that transpyloric feeding may reduce apneic episodes in preterm neonates with clinical features of GER. Further research including randomized controlled trials with a larger sample size is needed to better evaluate this simple intervention.

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This study was presented at Digestive Disease Week 2019 and published as an abstract in the proceedings.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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