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Original Article

Assessment of enteral nutrition in preterm infants with patent ductus arteriosus undergoing medical treatment

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ABSTRACT

Objective: The aim of this study was evaluate the effect of enteral nutrition during treatment in preterms under 32 weeks of gestation with patent ductus arteriosus receiving medical treatment.

Material and Methods: Preterm newborns born before 32 weeks of gestation who received medical treatment for patent ductus arteriosus were categorized into three groups based on their enteral feeding status during treatment: Group A (not fed), Group B (fed <60 ml/kg/day), and Group C (fed ≥60 ml/kg/day). Gastrointestinal system problems and neonatal morbidities were compared with nutritional status. In this retrospective study, 105 patients were included.

Results: Gastrointestinal intolerance was more common in group A, which was never fed (p=0.017) and the time to full enteral nutrition was the longest in this group (p=0.024). In the most fed group C, the time to regain birth weight was the longest (p=0.002). Daily weight gain was the lowest in patients in group A (p=0.022) and mortality was the most common in this group (p=0.003). There was no statistically significant difference in the incidence of bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular hemorrhage and sepsis between fed and unfed infants.

Conclusion: No statistically significant adverse effects of enteral feeding were observed in preterms treated medically for patent ductus arteriosus. This study shows that enteral feeding does not increase gastrointestinal or neonatal morbidities, and that feeding during treatment appears to be safe.

Keywords: Enteral feeding, newborn, patent ductus arteriosus, preterm infant

INTRODUCTION

Patent ductus arteriosus (PDA) is the most common cardiovascular disorder in preterm neonates. Its incidence has been reported to be 79% in extremely low birth weight babies (1). Physiologically, almost all infants have an open duct at birth. The ductus arteriosus connects the proximal left pulmonary artery to the descending aorta just distal to the origin of the left subclavian artery, near where it arises from the main pulmonary artery (2). After birth, the duct closes functionally within 12-24 hours and anatomically within 2-3 weeks (3,4). Low oxygen and high prostaglandin sensitivity in the ductus of preterm infants lead to impaired closure or reopening of the closed ductus by decreasing constriction (5,6). An unclosed duct steals blood flow from the descending aorta to the pulmonary arteries and consequently decreases organ perfusion. Hypoperfusion has been clinically associated with necrotizing enterocolitis, cerebral ischemia, intraventricular hemorrhage, and pulmonary hemorrhage in newborns (7-9). Therefore, hemodynamically significant ductal patency can be treated conservatively, medically, or surgically.

The aim of medical treatment is the inhibition of prostaglandin synthesis (10). The prostaglandin-H2 synthetase enzyme, which has two active sites, cyclooxygenase (COX) and peroxidase

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(POX), produces circulating prostaglandins that regulate ductal patency (11,12). Among nonsteroidal anti-inflammatory drugs, indomethacin and ibuprofen exert their therapeutic effects by acting on the COX site, while paracetamol targets the POX site. Nonsteroidal anti-inflammatory drugs have many effects on COX, particularly in the cerebral, gastrointestinal, and renal regions (12,13). Surgical ligation is performed in infants with pharmacologically resistant PDA or in those with contraindications to medical therapy (14,15).

In the literature, there are many studies investigating the enteral nutrition status of babies with PDA receiving medical treatment (16-18). There is no complete consensus in the literature on this subject. The optimal management of enteral feeding in preterm infants with a hemodynamically significant patent ductus arteriosus (hsPDA) has long been a subject of considerable debate. Notably, substantial differences of opinion persist among neonatologists regarding this issue. In this study, we investigated the effects of enteral nutrition during treatment and neonatal morbidities in preterm infants with patent ductus arteriosus receiving medical treatment.

MATERIALS and METHODS

The study group consisted of <32-week preterm newborns who received treatment for patent ductus arteriosus between September 2019 and December 2021 at Ankara Bilkent City Hospital Pediatric Neonatalogy Clinic. Echocardiography (ECHO) was performed in all patients at 72 hours after the postnatal period. HsPDA was diagnosed according to the clinical and ECHO criteria (19). A pediatric cardiologist performed the ECHO examination. Doppler ECHO was performed using a GE Vivid 7 Pro 10S transducer (GE Healthcare, Salt Lake City, Utah). HsPDA was initially treated with either paracetamol or ibuprofen. Patients diagnosed with hsPDA by echocardiography received ibuprofen as the first line for treatment. Paracetamol was administered when ibuprofen was contraindicated. All patients were re-evaluated with clinical and echocardiographic findings after the first course. Patients with persistent hsPDA at the end of the evaluation were treated with the second and third courses. Surgical ligation was performed in patients with persistent hsPDA despite 3 courses of paracetamol or ibuprofen treatment.

Patients receiving PDA treatment were categorized according to their nutritional status during treatment into three groups: Group A was never fed, Group B was fed <60 ml/kg/d, and Group C was fed ≥60 ml/kg/d. All patients were fed with breast milk during hospitalization.

In our study, several clinical parameters- such as birth weight, gestational age, gender, mode of delivery, preterm premature rupture of membrane (PPROM), antenatal steroid usage and Apgar scores - were retrospectively obtained from hospital records and patient charts.. We also evaluated nutritional and respiratory outcomes such as time to regain birth weight, days to full enteral feeding, total parenteral nutrition requirement and duration, surfactant use, oxygen requirement and duration, mechanical ventilation use, gastrointestinal bleeding and major morbidities (pulmonary hemorrhage, respiratory distress syndrome [RDS], necrotizing enterocolitis [NEC] stage ≥2, bronchopulmonary dysplasia [BPD], intraventricular hemorrhage [IVH], retinopathy of prematurity [ROP]), as well as discharge weight.

Preterm newborns born at or after 32 weeks of gestation, as well as those with genetic anomalies, pre-existing gastrointestinal problems, or who died before completion of treatment, were excluded from the study.

Statistical analyses

The data were evaluated using the IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, N.Y., USA). In the descriptive statistics section, categorical variables are presented as numbers, percentages, and continuous variables are presented as medians (interquartile range). The conformity of continuous variables to normal distribution was evaluated using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Mann Whitney-U test was used for comparisons of continuous variables that did not conform to normal distribution. Pearson Chi-Square, Chi-Square with Yates correction, and Fisher exact chi-square tests were used to compare categorical variables. In this study, the statistical significance level was set as $p<0.050$.

RESULTS

A total of 105 neonates were included in the study and categorized into three groups: Group A (n =7), Group B (n = 50), and Group C (n = 48). The median gestational age at birth was 28 weeks (26.4–29.8), and the median birth weight was 1075 g (755–1400 g). The median gestational age was significantly lower in Group A [27 weeks (24.4–27.0)] compared to Group C [28 weeks (27.0–29.4)] ($p = 0.022$). In addition, the median birth weight was lowest in Group A [760 g (570–910)] compared to Group B [1050 g (700–1436)] ($p = 0.024$) and Group C [1115 g (860–1400)] ($p = 0.004$). Antenatal steroid administration was more prevalent in Group B (70%) than in Group C (47%) ($p = 0.044$). No statistically significant differences were observed among the groups in terms of 5-minute APGAR scores, PPROM incidence, surfactant use, or the occurrence of RDS (Table I).

Gastrointestinal system intolerance was significantly lower in Group C (35%) compared to Group A (85%) ($p = 0.017$) and Group B (68%) ($p = 0.02$). The median time to transition to full enteral nutrition was significantly shorter in Group C [12 days (11–16)] compared to Group A [29 days (17–29)] ($p = 0.024$) and Group B [17 days (11.5–25.5)] ($p = 0.023$). The median time to regain birth weight was significantly shorter in Group B [8 days (6–11.5)] compared to Group C [12 days (9.2–14)] ($p = 0.02$). The median TPN duration was highest in Group B

Table I: Descriptive characteristics of patients according to nutritional status

	Group A	Group B	Group C	p		
				B vs A	C vs A	C vs B
Number of patients	7	50	48	-	-	-
Birth week*	27 (24.4- 27.0)	28 (26.2-30)	28 (27- 29.4)	0.066	0.022	0.762[a]
Birth weight (grams)*	760 (570-910)	1055 (700-1436)	1115 (860-1400)	0.024	0.004	0.462[a]
Gender[†] Male Female	 1 (14) 6 (85)	 24 (4) 26 (52)	 30 (62) 70 (37)	0.122	0.035	0.215[b]
Birth by C/S[†]	7 (100)	48 (9)	40 (83)	-	-	0.049[b]
5[th] minute APGAR*	7 (6-7)	7 (5-7)	6 (6-7)	0.960	0.855	0.953[a]
PPROM[†]	0 (0)	6 (12)	9 (18)	-	-	0.518[b]
Antenatal steroid[†]	3 (42)	35 (70)	23 (47)	0.206	1.000	0.044[b]
Surfactant use[†]	6 (85)	44 (88)	41 (85)	1.000	1.000	0.937[b]
RDS[†]	6 (85)	45 (90)	42 (87)	0.562	1.000	0.943[b]

:** *Median (IQR),* **†:** *n(%),* **[a]:** *Mann Whitney U test was applied,* **[b]:** *Chi Square test was applied,* ***C/S: *Ceserrian Section,* ***PPROM:*** *Preterm premature rupture of membranes,* ***RDS:*** *Respiratory distress syndrome*

Table II: Effects of nutritional status in preterms receiving PDA treatment

	Group A	Group B	Group C	p		
				B vs A	C vs A	C vs B
Number of patients	7	50	48	-	-	-
GIS intolerance*	6 (85)	34 (68)	17 (35)	0.662	0.017	0.002[b]
NEC (stage 2 ≥) within 7 days of treatment*	2 (28)	7 (14)	3 (6)	0.304	0.116	0.318[b]
Time to reach full enteral transition (days)[†]	29 (17-29)	17 (11.5-25.5)	12 (11-16)	0.208	0.024	0.023[a]
Time to reach birth weight (days)[†]	9 (4-11)	8 (6-11.5)	12 (9.2-14)	0.661	0.050	0.002[a]
TPN duration (days)[†]	12 (8-29)	15 (10-24.5)	12 (9-14.7)	0.567	0.810	0.047[a]
Daily weight gain (grams)[†]	15 (6-15.2)	17.5 (13.8-21.4)	17.8 (14.2-22.2)	0.029	0.022	0.823[a]
GIS bleeding*	1 (14)	5 (10)	1 (2.1)	0.562	0.240	0.205[b]
Pulmonary hemorrhage*	3 (42)	9 (18)	6 (12)	0.154	0.078	0.635[b]

:** *n(%),* **†:** *Median(IQR),* **[a]:** *Mann Whitney U test was applied,* **[b]:** *Chi Square test was applied,* ***GIS: *Gastrointestinal System,* ***NEC:*** *Necrotizing Enterocolits,* ***TPN:*** *Total Parenteral Nutrition*

Table III: Neonatal morbidities in preterms receiving PDA treatment

	Group A	Group B	Group C	p		
				B vs A	C vs A	C vs B
Number of patients	7	50	48	-	-	-
IVH*	4 (57)	13 (26)	14 (29)	0.180	0.200	0.901[b]
ROP*	2 (28)	16 (32)	29 (60)	1.000	0.220	0.009[b]
BPD*	3 (42)	36 (72)	38 (79)	0.191	0.061	0.555[b]
Proven sepsis*	4 (57)	26(52)	20(41)	1.000	0.686	0.411[b]
NEC (stage 2 ≥)*	2 (28)	11 (22)	4 (8.3)	0.653	0.163	0.110[b]
Surgical NEC*	1 (1)	3 (6)	3 (6)	0.417	0.429	1.000[b]
Duration of invasive ventilation (days)[†]	10 (7-28)	11 (6-20.2)	23.5 (4.25-3)	0.817	0.343	0.215[a]
Oxygen duration (days)[†]	12 (8-74)	39 (21-60.2)	69 (31.2-93.7)	0.576	0.042	0.003[a]
Discharge day (days)[†]	78 (76-78)	66 (51-83)	78 (55-111.5)	0.203	0.831	0.091[a]
Mortality*	4 (57)	15 (30)	3 (6.3)	0.206	0.003	0.006[b]

:** *Median (IQR),* **†:** *n(%),* **[a]:** *Mann Whitney U test was applied,* **[b]:** *Chi Square test was applied,* ***IVH: *Intraventricular hemorrhage,* ***ROP:*** *Retinopathy of Prematurity,* ***BPD:*** *Bronchopulmonary Dysplasia,* ***NEC:*** *Necrotizing Enterocolitis*

[15 days (10–24.5)] compared to Group C [12 days (9–14.5)] (p = 0.047). The median daily weight gain was lowest in Group A [15 g (6–15.2)] compared to Group B [17.5 g (13.8–21.4)] (p = 0.029) and Group C [17.8 g (14.2–22.2)] (p=0.022). No statistically significant differences were observed among the groups with respect to NEC (stage ≥ 2) within 7 days of treatment, GIS bleeding, or pulmonary hemorrhage (Table II).

The effect of nutrition on neonatal morbidities is shown in Table III. ROP incidence was highest in Group C (60%) compared to Group B (32%) (p=0.009). The median duration of oxygen therapy was highest in Group C [69 days (31.2–93.7)] compared to Group A [12 days (8–74)] (p = 0.042). Mortality was lowest in Group C (6.3%) compared to Group A (57%) (p = 0.003) and Group B (30%) (p = 0.006). No statistically significant differences were observed among the groups with regard to IVH, BPD, proven sepsis, NEC (stage ≥ 2), surgical NEC, invasive ventilation duration, or length of hospital stay.

DISCUSSION

Patent ductus arteriosus is the most common cardiovascular disease in preterm newborns. In the preterm population, where ductal closure is delayed, ductus-related systemic hypoperfusion effects and related complications are observed. Gastrointestinal system problems are one of these complications. There is no consensus in the literature regarding nutritional management in infants with PDA. In a study by Louis et al.(17) in 415 preterms receiving indomethacin for PDA treatment, patients were divided into three groups: never fed, ≤60 ml/kg/d, and >60 ml/kg/d fed. The effect of enteral feeding on the gastrointestinal system and neonatal morbidities were evaluated, it was found that enteral feeding volume change during and after treatment did not affect the incidence of NEC, gastrointestinal system intolerance, or prematurity-related morbidities. In the same study, the duration of transition to full enteral nutrition and total parenteral nutrition (TPN) duration was found to be the longest in patients receiving low enteral feeding volume (17). Kelleher et al. (20) investigated the incidence of spontaneous intestinal perforation in 15751 LBW infants who received prophylactic indomethacin treatment in the first 3 days of life to prevent PDA and IVH. Infants who received early enteral feeding reached full enteral nutrition on a shorter day, and the total duration of parenteral nutrition was found to be less, regardless of indomethacin treatment (20). In our study, the duration of transition to full enteral nutrition was found to be the longest in group A and the shortest in group C, and a statistically significant difference was found (C vs A p=0.024, C vs B p=0.023). The shortest duration in group A may be related to the highest mortality rate in group A patients.

In a study by Clyman et al. (16) with 177 preterms with PDA receiving indomethacin or ibuprofen, patients were divided into two groups as trophic fed and non-fed, and the effect of nutrition on gastrointestinal effects and morbidities were evaluated. The study showed that there was no significant difference in NEC rates or other neonatal morbidities between the two groups, but it took 2.8 days to reach full enteral nutrition in the trophically fed group (16). In this study, gastrointestinal intolerance was found in 85.7% of patients in group A, 68.0% in group B, and 35.4% in group C (A vs C p=0.017, B vs C p=0.002). In this study, there was no statistically significant difference in NEC incidence among the groups. However, NEC was observed more often in infants who were fed less. Daily weight gain was highest in group C and lowest in group A. Although the time to reach birth weight was the longest in group C, the patients in group C had the highest discharge weight. The discharge weight was 2210 g in group B and 2784 g in group C patients. The longer time to reach birth weight in the most fed group may also be related to the long-term preterm morbidities of the patients. In this group, ROP, ventilation time, oxygen exposure, and discharge times were higher in other groups resulting in a prolonged hospital stay. This study contributes to the literature in this regard. The main limitation of this study is its retrospective design. Because of the small number of patients, further and larger scale studies are needed.

CONCLUSION

PDA can be associated with severe gastrointestinal complications such as feeding intolerance, gastrointestinal perforation, and necrotizing enterocolitis, which pose a major challenge in the nutritional management of preterm infants. Guidelines should be developed to clearly define the administration and course of enteral nutrition and target nutrient intake before, during, and after the medical treatment of PDA. In preterm infants with PDA, fluid restriction is used in the management of PDA, but this may lead to inadequate nutrient intake. This may lead to long-term adverse effects such as impaired growth and development in preterm infants.

The results of this study suggest that feeding during medical therapy does not significantly affect mesenteric blood flow and splanchnic oxygenation after enteral feeding in infants with PDA. We may recommend that enteral feeding should not be interrupted; rather, it should be initiated or continued in infants with PDA.

In preterm infants who received medical treatment, it was observed that gastrointestinal system intolerance and mortality were less, the transition time to full enteral feeding was shorter, and daily weight gain was higher in those who received enteral feeding during treatment. In this study, it was not observed that feeding increased the incidence of BPD, IVH, sepsis, and NEC. In addition, feeding during PDA treatment did not have a negative effect on the duration of invasive ventilation, inotrope use, or discharge day. This study shows that feeding during the medical treatment of PDA is beneficial and does not increase gastrointestinal and neonatal morbidities.

Ethics committee approval

This study was granted ethical approval by Ankara Bilkent City Hospital Ethics Committee under reference number E2-21-1162 on December 22, 2021.

Contribution of the authors

Study conception and design: ***BNK,AK,CT;*** data collection: ***BNK, AK, EAD, HAG;*** analysis and interpretation of results: ***BNK, AK ,BC ,EAD, HAG;*** draft manuscript preparation: ***BNK, BC, CT.*** All authors reviewed the results and approved the final version of the article

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Conflict of interest

The authors declare that there is no conflict of interest.

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