Management of patent ductus arteriosus in preterm infants

Preterm bebeklerde patent duktus arteriozus'un tedavi yöntemleri

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ABSTRACT

Objective: To evaluate the incidence of symptomatic patent ductus arteriosus (PDA) in preterm infants, and the results of the intravenous indomethacine treatment and surgery.

Methods: Among 394 preterm infants (<37 weeks), symptomatic PDA was diagnosed by echocardiography in 51 babies and they were examined retrospectively. All infants were managed conservatively and then IV indomethacine was given to non-responders (n=30). Surgical closure was performed in 12 babies.

Results: The incidence of symptomatic PDA in preterm infants was 12.9%: median age: 3 days, mean birth weight: 1434±540 g (540-2900g) and mean gestational ages (GA) 30.9±3.3 weeks (23-37 weeks). With indomethacine, ductal closure was achieved in 70% infants. Early clinical improvement was observed in all cases that underwent surgery and most of them had a low birth weight (< 1500 g) and an early gestational age (< 32 weeks). None of them died due to operation.

Conclusion: The incidence of symptomatic PDA is high in preterm infants. Treatment with indomethacine improves ductal closure and associated with few reversible adverse effects. In the other hand, early clinical improvement and high success rate was achieved after surgery. If indomethacine fails to achieve ductal closure, decision of surgery must be made immediately. *(Anadolu Kardiyol Derg 2006; 6: 28-33)*

Key words: PDA, preterm infants, indomethacine, ductal ligation

ÖZET

Amaç: Preterm bebeklerde semptomatik patent duktus arteriozus (PDA) insidansının belirlenmesi, intravenöz indometazin ve cerrahi tedavi yöntemlerinin sonuçlarının değerlendirilmesi amaçlanmıştır.

Yöntemler: Kliniğimizde izlenen 394 preterm (< 37 hafta) bebekten 51'inde ekokardiyografik inceleme ile semptomatik duktus açıklığı belirlendi ve semptomatik PDA' lı bu bebekler retrospektif olarak incelendi. Tüm bebekler konservatif tedavi yöntemleri (sıvı kısıtlaması ve diuretik tedavi) ile tedavi edildi, daha sonra bu tedaviye cevap alınamayan olgularda (n=30) intravenöz indometazin (0.2 mg/kg/doz x 3) uygulandı. Cerrahi tedavi ise 12 bebekte uygulandı.

Bulgular: Semptomatik PDA insidansı preterm bebeklerde % 12.9 idi. Semptomatik PDA'lı preterm bebeklerin mediyan postnatal yaşı: 3 gün, ortalama doğum ağırlığı: 1434±540 g (540-2900 g) ve ortalama gestasyonel haftaları: 30.9±3.3 hafta (23-37 hafta) idi İndometazin tedavisi ile %70 olguda duktal kapanma saptanmıştır. Cerrahi tedavi uygulanan bebeklerin çoğunun gestasyonel yaşları < 32 hafta ve doğum ağırlıkları < 1500 g olmasına karşın tümünde erken klinik düzelme sağlanmış ve cerrahi tedaviye bağlı ölüm gözlenmemiştir.

Sonuç: Preterm yenidoğan bebeklerde semptomatik PDA insidansı yüksektir. İntravenöz indometazin uygulaması PDA'nın tedavisinde etkili bir yöntemdir ve az sayıda hastada geri dönüşümlü yan etkileri izlenmiştir. Diğer taraftan, cerrahi tedavi ile erken klinik düzelme ve yüksek başarı sağlanmıştır. İndometazin tedavisi ile duktal kapanma sağlanamayan olgularda cerrahi tedavi kararı alınmasında gecikilmemelidir. *(Anadolu Kardiyol Derg 2006; 6: 28-33)*

Anahtar kelimeler: PDA, preterm infant, indometazin, duktal ligasyon

Introduction

Patent ductus arteriosus (PDA) is recognized more often in developing countries with increasing survival of preterm babies. In preterm infants, the normal mechanism of ductal closure does not function effectively, leading to persistent patency of the ductus arteriosus. Clinical findings are related to the degree of left to right shunting through the ductus. Presence of PDA is a contributing factor to the development of feeding intolerance, necrotising enterocolitis (NEC), intracranial hemorrhage (ICH), decreased glomerular filtration rate and bronchopulmonary dysplasia in preterm infants (1-5). Almost 70 % of preterm infants delivered before 28 weeks of gestation require either medical or surgical closure of a PDA (2,4). In this study we evaluated the incidence of symptomatic PDA in preterm infants, and the results of the intravenous (IV) indomethacine treatment and surgical

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closure in terms of PDA closure rate, complications and mortality in preterm infants with symptomatic PDA.

Methods

One thousand three hundred and ninety eight newborn infants were admitted to neonatal intensive care unit between January 1999 and May 2003. Among them 394 infants had gestational age ≤ 37 weeks and they were regarded as preterm. Computer based medical records of the preterm infants presenting with symptomatic PDA, documented by color flow Doppler (CFD) echocardiographic examination, were retrospectively analyzed. Infants with complex cardiac defects were excluded. Gestational ages (GAs), birth weights (BWs), Apgar scores, evidence of a respiratory distress syndrome (RDS) (necessitating ventilator assistance and a surfactant treatment at the first week of age), intraventricular hemorrhage, chromosomal abnormality, clinical risk index of babies (CRIB) were analyzed (6).

Pretreatment assessment for the ductus

The clinical diagnostic criteria of symptomatic ductus were presence of a systolic or a systolodiastolic murmur, tachycardia (160/ minute), hyperdynamic precordium, bounding arterial pulses, cardiomegaly or a need for assisted ventilation.

Echocardiographic findings: 2-dimensional, M-mode, pulsed Doppler and CFD examinations were performed using commercially available echocardiographic equipments (Hewlett Packard, Model Sonos 5500 cardiac imager, Andover Massachusetts, USA and Diagnostic Ultrasound Equipment, Model SSH-140 A, Toshiba Sonolayer, Tokyo Japan) with available transducers. Images were obtained at the standard parasternal, suprasternal, apical and subcostal four-chamber views. Detection of a mosaic jet flow signals within the ductus at the parasternal short-axis view indicated the presence of a PDA. When CFD imaging showed the ductal shunting, the diagnosis was confirmed by continuous and/or pulsed Doppler analysis, which indicated the timing and direction of the flow within the ductus. Internal ductal diameter was measured as the maximum thickness of a mosaic jet flow at the parasternal short axis. By using 2- dimensional echocardiography, the structural heart defects and associated cardiac abnormalities were also searched. M-mode echocardiography was used for calculation of dimensions of left ventricle, aortic root and left atrium were measured, and the left atrial to aortic root ratio..

Treatment protocols: Fluid intake was guided by the body weight, postnatal weight loss, urine volume, serum sodium concentration, and serum osmolarity. Daily fluid intake was initiated as 70 ml per kilogram and increased by 20 ml per kilogram each day to a maximum of 130 ml per kilogram per day by the end of the first week. All patients were treated with fluid restriction. Furosemide was given in dose of 1 mg/ kg per day if necessitated. After conservative therapy, the treatment strategies were divided in one of 2 ways; 1) Administration of prostaglandin inhibitors, 2) Surgical closure of a ductus.

1) Administration of prostaglandin inhibitors: The standard 3-dose course of indomethacine treatment was given at a dose of 0.2 mg/kg/ in 12-hour intervals during a 48-hour period by intravenous route (Indocid IV, Merck, West Point). In three preterm infants, ibuprofen treatment was given at a dose of 10 mg/kg in 12 hour intervals during a 48- hour period by peroral route (Ibufen PO, Knoll, İstanbul). Infants having any contraindication (urine output < 1 ml /kg /hour during the preceding 8 hours; serum creatinine > 1.6 mg/dl; serum urea nitrogen concentration> 40 mg /dl; platelet count < 75.000/mm3, presence of hemorrhagic diathesis or NEC or cerebral/ pulmonary hemorrhage) were not treated with prostaglandin inhibitors. The levels of serum creatinine, total serum bilirubin, hematocrit and platelet count were measured daily. Fluid intake and urine volume were monitored while the infants were receiving their medication.

Evaluation of the response: After the third dose of indomethacine infants were examined (between 12 and 24 hours) for the presence of ductus-related signs and echocardiogram was performed. According to the initial response of the pharmacological treatment, infants were divided into 3 groups; 1) Closed ductus group consists of patients with absence of clinical signs, no murmur, normal precordial activity and normal systemic pulse pressure with no evidence of turbulent flow on CFD 2) Partially closed ductus - absence of clinical signs but presence of a small amount of left-to-right turbulent flow on CFD examination, 3) Non-responders group was constituted of patients with clinically patent ductus and a large amount of left-to-right turbulent flow evident on CFD examination. If indomethacine failed to achieve ductal closure, surgical closure of a ductus was performed in infants having symptomatic ductus arteriosus.

Reopening: The echocardiographic examination was repeated if there was any suspicion of failure of the ductus to close, or if reopening was suspected after initial closure.

2) Surgical closure of a ductus: If the infant 1) had severe symptoms including bradycardia, systemic hypotension, pulmonary hypertension, diastolic steal (reverse flow velocity in distal aorta), anuria or NEC; 2) had any contraindication to use indomethacine , or 3) if prostaglandin inhibitors failed to attain ductal closure; surgical closure of a ductus was performed.

Concomitant treatment: For treatment of hypotension refractory to fluid therapy dopamine or/and dobutamine infusion was started at a dose of 2-20, 5-10 mcgr/kg/minute respectively. Infants received surfactant and assisted ventilation when there was RDS or respiratory insufficiency.

Results

Selecting the cases by a pre-elimination based on clinical findings and then performing CFD echocardiography revealed that the incidence of symptomatic PDA was 3.6% (51) of total neonatal intensive care unit (NICU) admission. Three hundred and ninety four of 1398 infants had less than 37 weeks of GA and the incidence of symptomatic PDA was 12.9% (51/394) in preterm infants. Two hundred and fourteen out of 1398 infants had a BW < 1500 g and 236 out of total NICU admission had a GA < 34 weeks. The incidence of symptomatic PDA was 14.9% in infants with < 1500 g BW (32/214) and 17.7% in infants < 34 weeks GA (42/236). The median age of diagnosis of 51 preterm infants with PDA was 3.0 days (range: 1-30 days). All but three infants with PDA were diagnosed within the first two weeks of ages. The mean BW and GA of the neonates were 1434 ± 540 g and (540 - 2900 g) and 30.9 ± 3.3 weeks (23-37 weeks) respectively.

There were 25 girls and 26 boys. Twenty nine out of 51 (56.9%) preterm infants had a BW less than 1500 g and they were regarded as very low BW infants (VLBW), 21 babies had BWs ranged between 1500 and 2500 g and they were regarded as low BW infants (LBW). Fifth minute Apgar scores were analyzed in

41 infants, ranging between 5 and 10. Three very critical infants had high CRIB scores, (ranging between 10 and 15). At the time of diagnosis, 32 infants (62%) had RDS, 23 infants had an evidence of an infection (either early neonatal sepsis or neonatal pneumonia), 2 infants had an evidence of an intracranial hemorrhage diagnosed by cranial ultrasonography, 5 infants had NEC determined by clinically and laboratory assessment. One infant was diagnosed as Down syndrome, one had Pierre Robin syndrome and one had multiple extracardiac abnormalities (tracheo-eosophageal fistula and anal atresia).

By physical examination, hyperdynamic precordium was determined in 36 infants (70.5%), a systolic murmur was identified in 32 infants (62%) at the left upper sternal border. The systolodiastolic murmur was heard best at left upper sternal border in one case. In one case the murmur was also heard at the back. Twenty-five out of 51 cases (49%) had symptoms of heart failure. By chest roentgenogram, cardiomegaly was found in 15 cases.

Echocardiographic findings; At initial CFD echocardiographic examination, the diameter of the ductus ranged between 2.3 and 6 mm. Left atrial dilatation (left atrial dimension / aortic root dimension ratio > 1.3) was seen in 42 babies (range: 1.1 to 2.3). Associated cardiac abnormalities were pulmonary hypertension in four (7.8 %), ventricular septal defect in three (5.8%) and minor coronary artery anomaly in one infant (1.9%).

Results of the management

After conservative treatment, closure of the ductus was achieved in 8 of 51 infants (15.6%) (Fig.1). One infant with multiple extracardiac abnormalities was operated for tracheo-eosophageal fistula and died soon after operation. Two infants had a small PDA and did not require further treatment. Reversible hyponatremia occurred in 5 of 51 infants during therapy. Metabolic alkalosis was developed in two infants as a side effect of furosemide therapy. After conservative treatment (1-5 days), forty infants still had a symptomatic PDA and 80 % (n=32) of them also had RDS and received conventional respiratory support. They were managed in 1 of 2 ways;

1) Prostaglandin inhibitors: Out of 40, 30 infants were treated with indomethacine and 3 infants were treated with oral ibuprofen. In our study, because of few number of infants were treated with ibuprofen and intravenous form of ibuprofen is not available in our country, we could not compare the efficacy of two drugs.

Indomethacine group

Closure: With the indomethacine treatment ductus closure was achieved in 21 of 30 infants (70 %). Among these 30 infants,

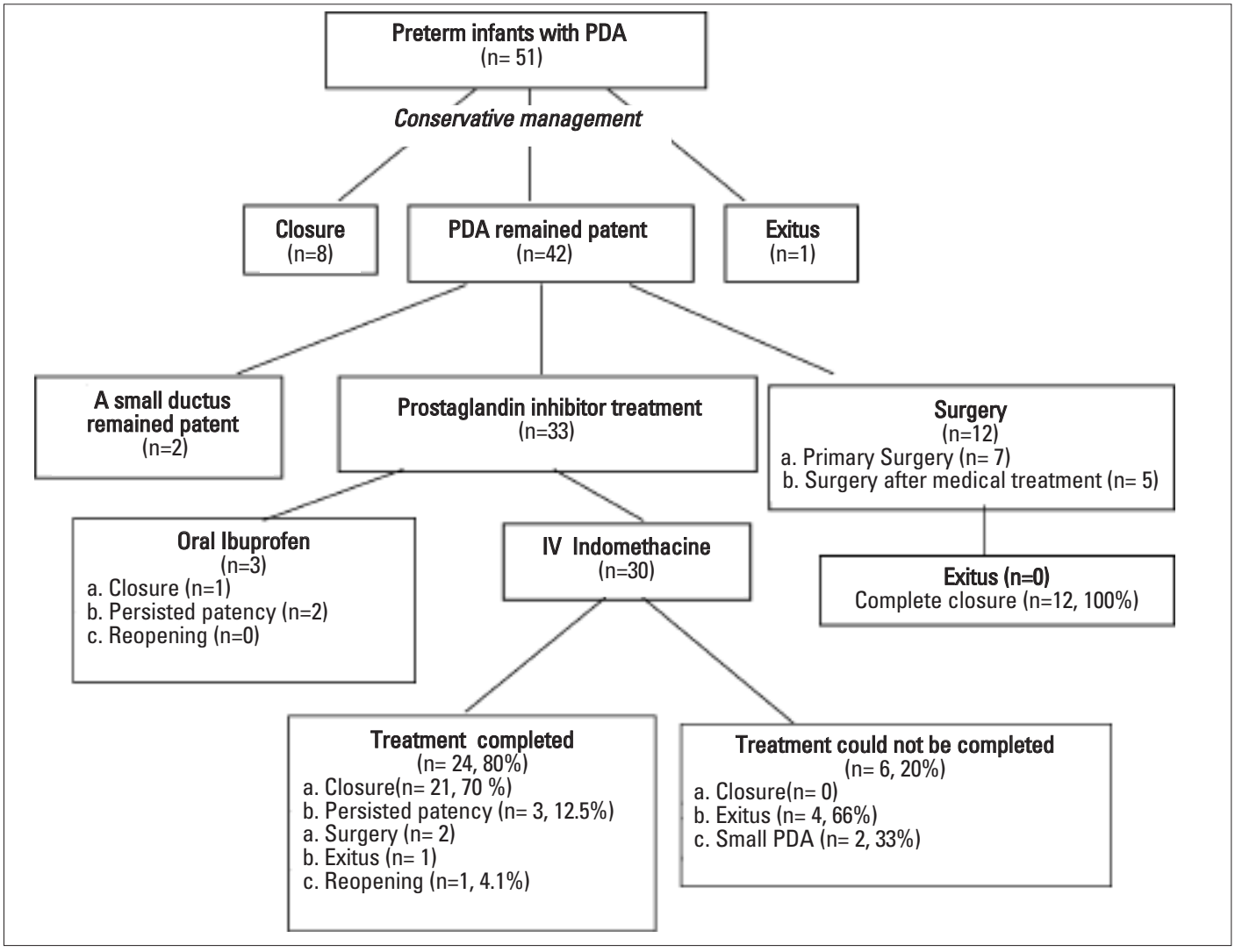

Figure 1. The results of management strategies for symptomatic patent ductus arteriosus (PDA) in preterm infants

24 infants completed standard (0.2 mg/kg per doses for 3 times) indomethacine treatment. Six infants could receive only one or two doses of indomethacine because of renal dysfunction. Thus, ductal closure was obtained in 21 of 24 infants (87.5%) who completed standard indomethacine treatment. Closure time ranged between 4 and 18 days of life. *Non-responders:* Large ductal shunting persisted in three infants who completed standard indomethacine treatment. Two of them underwent surgical ligation. The other infant died of sepsis soon after completing standard treatment. *Partly closed group;* Small and asymptomatic ductus arteriosus was detected in 2 cases and they did not require further intervention.

Exitus: Five infants receiving indomethacine died during the treatment period or soon after completing standard treatment. Out of 5 infants, four infants had high CRIB scores (> 8 points) within the first 12 hours and all died of fulminant sepsis.

Complications: During treatment with indomethacine, renal dysfunction occurred in six cases. After completion therapy with indomethacine, decreased urine output was observed in 11 cases and it resolved within the four days after therapy. Thus, poor renal function occurred in 55% of infants (17/30 cases). Among them peritoneal dialysis was performed in only one case and the treatment with indomethacine was discontinued in six cases (20%). Among these cases, NEC also developed in five cases (16.6%).

Although thrombocytopenia developed in 50% of cases (15/30), most of them had minor skin hemorrhage (n=10, 33%) or minor tracheal bleeding (n=3, 10%). Tracheal and intracranial hemorrhage was observed only in 2 infants (6.6%) and treatment with indomethacine was discontinued in these cases. They also had renal dysfunction and /or NEC.

Reopening was observed in only one case who received indomethacine at 5th day of life. Although ductal closure was obtained at 8th day of life, a PDA recurrence was observed at the 20th day of life. This case underwent an operation at the 23rd day of life.

2) Primary surgical closure of ductus: Primary surgical closure of ductus was performed in 7 infants having symptomatic ductus arteriosus soon after the diagnosis was made (median postnatal age - 16 days, range 4-35 days). Except two babies all infants were diagnosed within the first eight days of life. In these babies mean GA was 31.0 ± 3.3 weeks (range 27-37 weeks) and mean BW was 1564 ± 712 g (range 820-2900g). Before the surgery renal dysfunction, tracheal hemorrhage and NEC were seen in 5, 1 and 1 cases respectively.

Due to unresponsiveness to prostaglandin inhibitors (n=4) and ductal reopening (n=1), additional five infants were also operated. A total of 12 babies with a mean GA of 31±3.2 weeks (range 27-37 weeks) and mean BW of 1472±708 g (range 820-2900 g) underwent surgery (median postnatal age - 16 days, range - 4-35 days). It was remarkable that among 12 infants, 8 infants had low BW (< 1500 g), low GA (< 32 weeks) and were receiving conventional respiratory support (both intermittent positive pressure ventilation and surfactant treatment). An extubation was achieved at a mean time of 6 days (range: 1 to 17 days) after ligation in all except one.

Complications of surgery: After operation, transient renal dysfunction was seen in 3 infants, two infants developed NEC and one of them underwent operation for NEC. Two cases developed sepsis. Recurrent nerve paralysis was observed in one case. After operation, transient systemic hypertension was observed in one case. Among these 12 infants, only two infants died of sepsis. One of them who had multiple cardiac defects (a large VSD and ASD) underwent surgical ligation at 11th day of life but he died of fulminant sepsis on 14th day of life. The other case underwent an operation at 23rd day of life but he died of fulminant sepsis at the 50th day of life. None of the infants died due to operation. Overall success rate with ductal ligation was 100%.

Overall success and mortality rates with all management modalities were 78% and 17%, respectively.

Discussion

Patent ductus arteriosus in premature infants have been the subject of many investigations and it appears in 45% of infants under 1750 g BW and in about 80% of infants under 1200 g BW (1). In a national collaborative study, Gersony et al (4) reported that a symptomatic PDA developed in 21% of 3559 babies under 1750 g. In our study, selecting the cases based on clinical findings and then performing CFD echocardiographic examination, the incidence of symptomatic PDA was determined in 14.9% of infants with BW < 1500 g and 17.7 % of infants with GA< 34 weeks.

Indomethacine is the conventional pharmacological treatment for the closure of patent ductus in preterm infants and it is administered either prophylactically or very early after recognition of the presence of a PDA (5). A number of different dosing regimens have been used, and local institutional practices vary. The reported rate of ductal closure with indomethacine was between 53 % and 91% (4, 5, 7-14). Gersony et al (4) reported that indomethacine resulted in closure of the ductus in 79 % of the 135 treated infants, whereas in the same time scale, only 28% had closed spontaneously in the control group. They found that relapse occurred in 26% of responders, many of whom did not require further intervention. If reopening appears after initial closure, repeat courses of indomethacine can be administered, but if ductal patency persists and the infant remains symptomatic, decision of surgical ligation must be made immediately.

In our study, with using indomethacine, closure of the ductus was achieved in 70% infants and most of them also had RDS and received conventional respiratory support. Subsequent ductal reopening was seen in only one case that required an operation later. Due to unresponsiveness to indomethacine additional two infants were also operated on. Five cases died during indomethacine treatment or in the post treatment period. Among them, four infants had either high CRIB score, poor renal function or an evidence of infection before the treatment and all received ventilatory support and could not complete the standard 3 doses of indomethacine therapy. Ductal closure was obtained in 21 of 24 infants (87.5 %) who completed standard indomethacine treatment.

Vasoconstriction induced by bolus injection of indomethacine reduces organ perfusion and has been related to the well-known side effects of indomethacine (7, 9, 15, 16). In our study, renal dysfunction occurred in six cases (20%) and NEC develo-

ped in five of them (16.6%). The treatment with indomethacine was discontinued in these six cases. After completion the therapy with indomethacine, reversible renal dysfunction was also observed in 11 cases. Christmann et al (15) reported that there was a transient, but significant reduction in urine output after bolus injection of indomethacine. They found that in contrast to bolus injections, during continuous infusion of indomethacine (over 36 h) there was no significant change in all arteries measured. To avoid 'indomethacine-related side effects, Dumas et al (17) analyzed the different dosages and found lower indomethacine doses as effective as standard protocols. They reported that preterm neonates (<34 weeks) receiving daily intravenous doses of indomethacine, 0.1 mg/kg, started at the age of 4-5 days, the initial success rate of ductal closure was 84.7%, of which 6.5% reopened.

Recently, ibuprofen has been used to treat haemodynamically significant PDA in preterm infants and researchers reported that both oral and intravenous use of ibuprofen were as effective as indomethacine. (2, 3, 7-11,18)

Surgical closure of ductus is suggested if indomethacine fails to achieve ductal closure or if there is any contraindication for indomethacine use, in the presence of severe symptoms (1, 5). In many centres, it is accomplished in the neonatal intensive care unit (NICU), thus avoiding potential problems associated with transporting a sick premature infant to and from operating room (19, 20). Mortier et al (20) reported their experience in 33 premature infants with PDA who have been operated in their NICU over a six-year period. They observed no operative or immediate postoperative deaths and reported hospital mortality was 6%. Respiratory compromise, blood flow fluctuations, intracranial hemorrhage, infection, chylothorax, recurrent nerve paralysis and death are the risks associated with surgical closure (1, 5). If carried out early, it will reduce the time before extubation and discharge from the NICU (19, 20, 21). In the study of Satur et al (21) a total of 122 infants with a mean GA of 27 weeks and mean BW of 960 g, underwent surgical closure. Ninety percent of them were on ventilatory support and extubation was achieved at a median time of 10 days after ligation. They also reported that there were no deaths associated with the operation.

Little et al (19) compared ductal ligation and indomethacine treatment by means of weight, physical findings, echocardiographical findings of infants, success/complications of treatment, and length of hospital stay. They examined 212 infants owing a median GA of 26 weeks and BW weight of 836 g. They found that no measurement, except PDA diameter, was predictive of medical failure or need for reoperation and weight <1.000 g was a predictor of medical treatment failure. They reported that with indomethacine, PDA closure was observed in 88 of 167 cases (53%). Indomethacine complications (73%) included thrombocytopenia (36%), increase in blood urea nitrogen (31%), sepsis (30%), oliguria (25%), hyponatremia (25%), intracranial hemorrhage (16%), pulmonary interstitial emphysema (11%), NEC (8%), intestinal perforation (4%) and bleeding (3%). Overall 36% babies required operations and they had few complications included pneumothorax (4%), intracranial hemorrhage (4%), bleeding (4%), NEC (1%) and wound infection (1%). They concluded that ductal ligation may be preferable, especially in very low BW babies, because it is associated with low morbidity.

In our study surgical closure of a ductus was performed in 12 infants. It was remarkable that most of them had low BW (< 1500 g), low GAs (< 32 weeks) and all were dependent on ventilatory support, and extubation was achieved at a mean time of 6 days after ligation. After operation, transient renal dysfunction was seen in 3 infants, two infants developed NEC. Two cases developed sepsis. Recurrent nerve paralysis was observed in only one case. After operation, transient systemic hypertension was observed in one case. None of the infants died due to operation.

Conclusion

The incidence of symptomatic PDA is high in preterm infants. Conservative treatment and IV indomethacine improve ductal closure and are associated with few adverse effects. In our study, we also observed that early clinical improvement and high success rate were achieved with surgical ligation. If indomethacine fails to achieve ductal closure or if infants have any contraindication indomethacine use, decision of surgical ligation must be made immediately.

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