Short-Term Outcome Of Different Treatment Modalities Of Patent Ductus Arteriosus In Preterm Infants. Five Years Experiences In Qatar

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Citation

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Abstract

Background:
The incidence of patent ductus arteriosus (PDA) ranges from 40 to 60 percent in infants born before 28 weeks' gestation. In recent years, there has been growing debate regarding the need to treat PDA during the neonatal period.
Objective:
To study the short-term outcome of PDA treated with different treatment modalities in preterm infants of = 32 weeks gestational age.
Methods

: This study is a descriptive retrospective chart review conducted at NICU Women's Hospital, Hamad Medical Corporation, State of Qatar. The files of all infants born in the hospital with a gestational age of = 32 weeks and a diagnosis of PDA over a five-year period, January 2003 to December 2007 were reviewed.
Results:
For the five-year period, a total of 82 cases of PDA were diagnosed in infants of = 32 weeks' gestational age. Pharmaceutical intervention was used in 63/82 infants (76%), 20/82 infants (24%) required surgical ligation after failed medication, while the PDA in 32 infants (39%) closed spontaneously. Medication was successful in only 30/63 cases (47%). Large PDA significantly increased the mortality, IVH, and ROP (P value 0.002-0.003). However, PDA size had no protective effect on BPD or NEC (P value 0.54, 0.06, respectively). Infants who received medication or surgery experienced no significant difference in all adverse outcomes except for ROP, which had a P value of 0.003. Preterm infants =32 weeks who had spontaneous closure of their PDA experienced a lower rate of CLD, ROP, NEC and IVH (p<0.001-0.045).
Conclusion:
The results suggest that conservative treatment of PDA is the first-choice approach before resorting to medical and surgical treatment.

ABBREVIATIONS

BPD = Bronchopulmonary dysplasia
CHD = Congenital heart disease
CPAP= Continuous positive air-way pressure
IVH = interventricular hemorrhage
NEC = necrotizing enterocolitis
NICU = Neonatal intensive care unit
PDA = Patent ductus arteriosus
PEEP = positive end expiratory pressure
ROP = retinopathy of prematurity

INTRODUCTION

Ductus arteriosus is a vascular connection between the main pulmonary artery and aorta. The ductus arteriosus closes spontaneously in most near- and full-term infants during the first three days of life. However, in preterm infants, it remains patent during the first week of life.[1] Patent ductus arteriosus (PDA) is a common congenital heart defect in preterm infants. The incidence of PDA in preterm infants is increasing due to the improved survival rate of infants born with an extremely low birth weight. Similarly, incidence is inversely proportionate to gestational age; in preterm

infant's = 28 weeks, the incidence is as high as 60 percent.[2]

The Cochrane review 2008 showed that the available clinical trials were unable to establish an obvious relationship between different neonatal morbidities, whether secondary to the hemodynamic changes that occur with left-to-right shunt through the PDA or to the therapies used to close the PDA.[3] In a small randomized controlled trial conducted 25 years ago, the investigators suggested that persistent PDA is associated with increased pulmonary morbidity.[4]

The debate regarding optimum management of patent ductus arteriosus in preterm infants has increased in recent years. The majority of clinicians attempt to close clinically significant PDAs using either indomethacin or ibuprofen. If the PDA does not close or reopens after pharmaceutical therapy, then some clinicians consider surgical closure.[5] The decision to surgically close a "significant" PDA is complicated by recent experiences, indicating that surgery of any kind in newborns is associated with poor neurodevelopmental outcomes. Some preterm infants seem to be unable to tolerate a PDA ligation, perhaps because of acute physiological changes that are imposed on the cardiovascular system that has adapted to the PDA.[6,7]

Current conservative measures that have been adopted by some clinicians include adjustment of the ventilation by reducing inspiratory time, increasing positive end expiratory pressure (PEEP), and fluid restriction.[8]

The objective of this study is to assess the short-term outcome of different PDA treatment modalities in premature infants of = 32 weeks' gestation.

METHODS

This study is a descriptive retrospective chart review. All records of preterm infants of <37 weeks' gestation admitted to NICU at Hamad Medical Corporation, Qatar, within a five-year time period, January 2003 to December 2007, were reviewed and assessed. The NICU had 8604 admissions within this time period. From those admissions, a total of 495 patients had congenital heart disease. PDA was diagnosed in 82 cases of infants born before 32 weeks.

The initial diagnosis of PDA was based on clinical criteria, which are hemodynamic instability, respiratory instability or a combination of both. The hemodynamic criteria included blood pressure instability, bounding peripheral pulses, poor tissue perfusion, and metabolic acidosis. The respiratory criteria included difficulty in weaning from the ventilator, increased ventilatory support, frequent episodes of apnea, carbon dioxide retention and the occurrence of pulmonary hemorrhage. All these cases underwent a routine confirmation by echocardiography. The size of the PDA was classified into three categories: insignificant or small if the diameter was = 1-1.5mm, moderate if the diameter was = 1.5-3mm, and large if the diameter was = 3mm.[9] Management modalities were divided into conservative, medical or surgical. The conservative approach included optimizing ventilation, restricting the total fluid intake to 130 ml /kg/day and augmenting positive pressure ventilation. The pharmaceutical intervention included using either intravenous Indomethacin or oral ibuprofen. Patients who failed conservative and pharmaceutical treatment while still clinically compromised were candidates for surgical ligation.

The outcomes were assessed by analyzing the percentage of infants with PDA, modalities of treatment and major adverse outcome of these modalities. The rate of occurrence of NEC (modified Bell staging 1–3),[10] IVH, BPD, ROP and mortality rate were also documented. Data obtained from the patient files were entered into a computerized statistical program (SPSS12®)

This study was approved by the Institutional Review Board. A waiver of informed consent for participation was obtained from the ethical committee, since it is a chart review study.

RESULTS

STUDY DEMOGRAPHIC

A total of 82 infants of = 32 weeks' gestation of equal gender distribution were identified out of 147 infants with isolated PDA. The mean gestational age was 26.9 (±2.41) and the mean birth weight was 1020 ± 353grams (Table 1).

TREATMENT MODALITIES IN PRETERM INFANTS

A total of 63 infants received medical treatment with a closure rate of 47 percent, and 20 infants required surgical ligation for their PDA after it failed to close by medication (31%). A total of 13 PDA cases failed to close in response to medication but closed later spontaneously (late spontaneous closure). Conservative treatment was successful in only 19/82 infants (23%) of those who received no treatment. However, the overall spontaneous closure, including late spontaneous closure, was 32/82 (39%) (Figure 1).

RESPONSE OF DIFFERENT PDA SIZE TO DIFFERENT TREATMENT MODALITIES

Figure 2 shows the number of PDAs that were successfully closed according to different size and treatment modalities. Twelve out of those with a large PDA closed spontaneously (26%); moderate PDAs have the same percentage of spontaneous closure (26%).

COMPLICATIONS RELATED TO TREATMENT MODALITIES

When comparing combined surgical and medical treatment to conservative treatment (Table 2), the rate of adverse outcome is significantly lower in the latter group with a P value of 0.001 to 0.05. Neither the medication approach nor the surgical approach showed any significant protection against adverse outcomes when compared, except in ROP, where the P value is 0.003 (Table 3).

EFFECT OF PDA SIZE ON NEONATAL OUTCOME

Adverse outcomes have been significantly influenced by the size of the PDA, where the larger the size, the higher the possibility of developing an adverse outcome (Table 4).

Figure 1

Table (1) Demographic features of the study population =32 weeks

Variables	Total Number = 82
Female	41(50%)
Mean gestational age	26.9±2.41weeks
Mean birth weight	1020 ±353 grams
Mechanical ventilation*	64(79%)
CLD	30 (36%)
IVH	25 (69.5%)
NEC	16 (19.5%)
ROP **	46 (56.1%)**
Thrombocytopenia	18 (22%)
Mortality	18 (21%)

* Including CPAP. **ROP of all grades

Figure 2

Table (2) Neonatal outcome comparing spontaneous closure versus non spontaneous closure

	Spontaneous (32)& %	Non spontaneous N(50) & %	P value
Mortality	3 (9.3%)	15 (30%)	0.05
CLD	3 (9.3%)	27 (54%)	0.001
IVH	6 (18.7%)	25 (50%)	0.009
NEC	1 (3.1%)	15 (30%)	0.007
ROP	5 (15.6%)	41 (82%)	0.001

*P value in favor of spontaneous.

**All grades

Figure 3

Table (3) Neonatal outcome in babies' =32weeks comparing medication versus surgery

	Medication N (30) & %	Surgery N (20)& %	P value
Mortality	9 (30%)	6 (30%)	0.75
CLD	16 (53.3%)	11 (55%)	0.86
IVH	19 (63.3%)	6 (30%)	0.04
NEC	10 (33.3%)	5 (25%)	0.75
ROP	29 (96.6%)	12 (60%)	0.003

**All grades

Figure 4

Table (4) Effect of PDA size on neonatal outcome = 32 weeks

	Small + moderate N (35)& %	Large N (47)& %	P value
Mortality	3 (8.5%)	15 (31.9%)	0.02
CLD	11 (31.4%)	19 (40.4%)	0.54
IVH	4 (11.4%)	21 (44.6%)	0.003
NEC	3 (8.5%)	13 (27.6%)	0.06
ROP	13 (37.2%)	29 (61.7%)	0.006

Figure 5

Figure 1.Response of PDA cases according to different treatment Modalities.

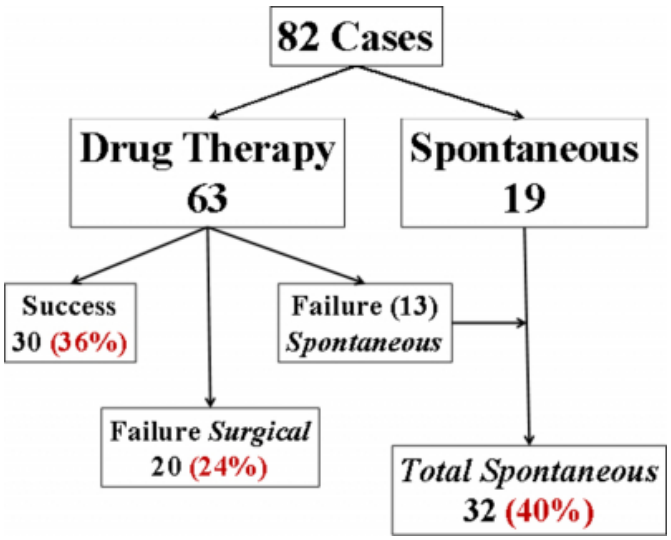
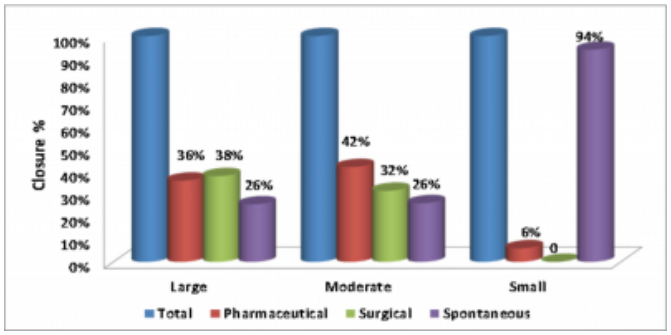


Figure 6

Figure 2. Number of PDA successfully closed according to Size and treatment modality.



DISCUSSION

In preterm infants, patency of the ductus arteriosus may represent a normal physiologic adjustment to allow shunting from either systemic-to-pulmonary circulation (e.g., in the first day of life) or from pulmonary-to-systemic circulation (e.g., in the presence of severe lung disease).[11]

Several studies have discussed medical and surgical treatment; however, few studies have evaluated the outcome of currently popular conservative treatment, which includes adjusting ventilation and fluid restriction.[8] The spontaneous closure reported in the current study was 23 percent of affected preterm infants of = 32weeks. This rate is not comparable with the rate reported in the literature by Sophie et al., who reported a spontaneous closure rate of 67 percent of the ductus arteriosus in moderately premature infants.[8]

However, this gap could be narrowed if the author factored in the 13/63 infants (20%) in whom the PDA was not completely closed after medication and closed later spontaneously without need for further courses of medication (late spontaneous closure) to bring the overall rate of spontaneous closure to 39 percent. This rate of spontaneous closure is comparable to the rate reported by Josh and his colleagues. They reported a rate of spontaneous permanent DA closure of >34 percent in extremely low birth weight neonates.[12]

Ronald and his colleagues recommended that the therapies designed to close the ductus arteriosus are contraindicated in some settings and should not be considered a standard of care at any time until these therapies are proven to decrease long-term clinical morbidities in randomized, placebo-controlled trials.[11] This is reflected in this study's results, which showed no significant difference when the medication and surgical approach were used in terms of decreasing all morbidities. On the other hand, when comparing the medication and surgical approach with conservative management, there was a statistically significant reduction in all forms of morbidities. This result is supported by the lack of evidence that the treatment of patent ductus arteriosus results in long-term benefit.[13]

Interestingly, the ROP was significantly increased in those patients who received medication of P value 0.003. This can be explained by the need for prolonged respiratory support while receiving medication. Large PDAs have no protective role in comparison to other PDA size in decreasing morbidities. This can be explained by the fact that these infants were subjected to long-term medical treatment with possible long-standing pathology and hazardous surgical intervention.

Both pharmacologic and surgical treatment options exist for closing a PDA, both of which have their own morbidities. Treatment of a PDA is not gentle and has not been shown to prevent any morbidity associated with prematurity.[14]

In conclusion, acknowledging the limitations of this retrospective analysis, the rate of PDA closure achieved with conservative treatment at the center was comparable to the rates previously reported with drug management. This conservative approach resulted in ensuring PDA closure, and it did so without exposing the neonates to potential side effects of drug treatment. Although the result is a retrospective chart review analysis, the authors changed their

approach to the treatment of small and moderate PDA by placing more emphasis on the conservative approach before exposing the infants to other active interventions. Further confirmation by way of a properly randomized controlled trial is warranted.

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