Paracetamol for Patent Ductus Arteriosus in Preterm or Term Infants

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Abstract: The aim of this study was to present our experience with intravenous paracetamol for closing of PDA in neonates contraindicated to ibuprofen or ibuprophen had failed and no candidates for surgical ligation. We conducted study in the Neonatal Intensive Care Unit (NICU) Dr. Zainoel Abidin Hospital and Harapan Bunda Hospital in Banda Aceh, from January to December 2017 with hemodynamic significant PDA (hsPDA). All the subject received 15 mg/kg/6 h intravenous paracetamol for 3 days for ductal closure, and evaluation ductal with echocardiography on the 5th day after the regiment. Seventy-two (72) neonates were diagnosed of hsPDA, mean gestational age (GA) of 34.26 weeks and mean birth weight of 1945.69 grams, female babies were 39 (54.2%) and male babies were 33 (45.8%). Preterm babies were 45 (62.5%) and full-term babies were 27 (37.5%). Twenty- six (36.1%%) babies had closed PDAs on the 5th days evaluation, 11 babies (15.3%) had twice regiment , closed PDA at the 10th days evaluation, and 35 babies (48.6%) had more closed PDA after three or four regiment. Successful closure on paracetamol was achieved in 51 babies (70.8%). And 21 (29.2%) had failed PDA closure. Paracetamol is an effective option in closure PDA and should be a first-line therapeutic option when there are contraindications for ibuprofen.

1 INTRODUCTION

Ductus Arteriosus (DA) is a heart problem that is frequently noted in the first few weeks or months after birth. It is characterized by the persistence of a normal fetal connection between the aorta and the pulmonary artery which allows oxygen-rich (red) blood that should go to the body to recirculate through the lungs. Closure of ductus arteriosus after birth is very important for circulation adaptation to the extra-uterine life. In healthy full-term newborns DA generally undergoes functional closure between 24 and 72 hours of life (Anngreni et al., 2014). Prolonged condition of PDA in preterms can be associated with important complications, such as severe respiratory distress syndrome (RDS), prolonged need for assisted ventilation, pulmonary hemorrhage, bronchopulmonary dysplasia (BDP), necrotizing enterocolitis (NEC), renal function damage, intra-ventricular hemorrhage (IVH), periventricular leukomalacia (PLV), To prevent such complications, the practice of DA closure is common and it is performed at first pharmacologically, but, in case of drugs failure or contraindication, with surgical (Anggreni et al., 2014; Allegaert et al., 2013; Brunner et al., 2013).

Despite years of researches and clinical experience on PDA management, many unresolved issues about its evaluation and treatment, with consequent heterogeneity of clinical practices in different centers, still remain, particularly regarding timing and modality of intervention. In fact, the available strategies vary from prophylactic treatment to early or delayed therapy. Pharmacological closure with non-steroidal anti-inflammatory drugs (NSAIDs), mainly ibuprofen and indomethacin, is currently the standard of care for PDA closure in preterm infants.. However, NSAIDs are not effective in around 25-30% of patients and they can have side effects such as transient renal function impairment, diminished platelet aggregation, hyperbilirubinemia, and gastrointestinal bleeding and perforation (Allegaert et al., 2013; Brunner et al., 2013). Recently, there is

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a growing interest in paracetamol for PDA closure and it has been suggested as an alternative drug to treat PDA. Finding the optimal pharmacological treatment for PDA closure in very low birth weght (VLBW) continues to remain challenging .The role of paracetamol, an inhibitor of the peroxidase component of prostaglandin-H2 synthetase, has been proposed for the treatment of PDA (Brunner et al., 2013; Weisz et al., 2014).

Hammerman *et al*. reported for the first time the use of paracetamol for closing of PDA (Hammerman C et al., 2011) Since then, many studies have reported similar efficiency of paracetamol to cyclooxygenase (COX) inhibitors for closing PDA and less adverse events (Dani et al., 2016). The large number of study reported the alternative treatment for closed the ductus (Dani et al., 2016; El-Khuffash et al., 2014; Oncel et al., 2013).

Since 2014, paracetamol is a standard practice used at Dr. Zainoel Abidin Hospital and Harapan Bunda Hospital for closure of PDA and has been found in standard operational procedures at Neonatal Intensive Care Unit, so there have been no studies on the effectiveness of the drug in PDA closure. So, the aim of this study was to present our experience with Paracetamol intravenous (IV) for closing PDA in preterm neonates or mature neonates presenting contraindication to ibuprofen or ibuprofen had failed and had feeding intolerance.

2 METHODS

This study took place in two hospital in Banda Aceh , i.e., dr Zainoel Abidin Hospital and Harapan Bunda Hospital. It was conducted from January to December 2017.Subject who met inclusion criteria were performed echocardiography, with hemodynamically significant of PDA (hsPDA), Echocardiography criteria of hsPDA were a ductal diameter ≥1.5 mm, a left atrium to aortic root ratio >1.5, and diastolic aortic retrograde flow. Bidimensional color Doppler echocardiography with GE Vivid Healthcare multi-frequency 7 MHz sector probe was used. All of the babies received paracetamol 15 mg/kg iv administration every 6 h for 3 consecutive days, reevaluation close of PDA done on day 5th. If ductus closure was confirmed by echocardiography, treatment was discontinued, and if PDA not closed , the regiment can be repeated with the same dose for 3 consecutive days too. Repetition like this regiment can only be done for 4 times. The categorized fail of PDA closed is repetition to 4 times regiment PDA not close.

Demographic features (gestational age/GA, gender, birth weight, height, Apgar score, delivery mode, antenatal steroids, MgSO4, age treatment/days of treatment, primary reason to use paracetamol, main outcome, adverse events, surgery, and invasive ventilation), times of treatment, response to treatment. Before and 24 hours after the end of paracetamol treatment, liver function tests were performed in all patients. In all cases, a written informed consent was obtained.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS). A descriptive analysis was done to elaborate subject demographics and clinical data. A p-value of 0.05 was used to determine significant association.

3 RESULTS

Between January and December 2017 , there were total of 72 preterm and full term babies who had hsPDA. with range gestational age (GA) 28, and 40 weeks. (mean 34.26 weeks)., the mean birth weight (BW) was 1945.69 g ranging from 870 to 4000 g. The fourty five (62.5%) babies were pre-term and the 27 (37.5%) were full term babies. Table 1 describes demographic characteristic among babies whose received paracetamol IV

In all patients, due to feeding- intolerance and clinic instability, iv paracetamol was started after obtaining informed consent signature. Complete closure was observed in 51 babies (70.8%). Of the 27 term – babies, the success of the closure of PDA was mor3 50% (15 babies). The mean postnatal age at the first iv paracetamol dose was 2.7 days, ranging from 1 to 4 days.

Bivariate analysis of closed the ductal and GA, BW, diameter PDA, days of treatment and times regiment had significant associations (Table 2).

Table 1: Characteristics of Subjects

Characteristics	Preterm babies N (%)	Term Babies N(%)
Sex		
Girls	26 (57.8)	13 (48.1)
Boys	19 (42.2)	14 (51.9)
Mean Gestational age (GA/weeks)	32.3	37.5
Mean Birth Weight (BW/grams)	1.022	1.666
Mean size of PDA (mm)	5.92	8.28
Mean days of treatment	3	2,14
Regiment		
One time	22 (48.9)	4 (14.8)
Twice	8 (17.8)	3 (11.1)
Three times	3 (6.7)	5 (18.5)
Four times	12 (26.7)	15 (55.6)
Close of PDA	36 (80)	15 (55.6)
Fail Close of PDA	9 (20)	12 (44.4)

Table 2: Bivariate analysis of close PDA in relation to GA, BW, size of PDA, days of treatment, and times regiment.

Variable	**P Values**
GA	0,015
BW	0,002
Size of PDA	0,020
Days treatment	0,001
Times regiment	0,000

GA: Gestational age, BW: Birth Weight

Tabel 3. Multivariate analysis of variable to predict close of PDA

	SE	P Value	R
GA	0,036	0,008	2,840
BW	0,000	0,001	3,650
Size of PDA	0,018	0,010	2,740
Days of treatment	0,100	0,000	3,930
Times regiment	0,044	0,000	6,170

GA: Gestational age, BW: Birth Weight

4 DISCUSSION

More recently, oral or iv administration of paracetamol (acetaminophen) gained attention in PDA treatment. How paracetamol acts for closing PDA still remains unclear, but it is known that it inhibits prostaglandin synthetase (Weisz et al., 2014; Hammerman et al., 2011; Dani et al., 2016). The role of paracetamol as an alternative treatment for closure of hsPDA has gained attention in recent years because of its superior safety profile in comparison to the cyclooxygenase inhibitors. Alternatively, paracetamol has been proposed to selectively inhibit a central isoform of COX3, but the existence of a functional human COX3 has been questioned (Hammerman et al., 2011; Dani et al., 2016; El-Khuffash et al., 2014; Oncel et al., 2013). The paracetamol also inhibits prostaglandin synthetase activity. Although its precise mechanism of action remains controversial. Theoretically, these differences would permit peroxidase inhibition to be optimally effective under conditions in which cyclooxygenase inhibition is less active or hypothetically, render it ideally suited for treatment in the PDA environment (Dani et al., 2016; El-Khuffash et al., 2014; Oncel et al., 2013; Oncel, Uras et al., 2013; Sinha et al., 2013).

Hammerman *et al*. reported for the first time several case reports on premature infants who received paracetamol achieving ductal closure (Hammerman et al., 2011). Since then, 24 case reports series have been reported and 6 randomized control trials (RCTs) showing paracetamol utility for ductal closure with similar results comparing to ibuprofen/indomethacin and fewer adverse events

(Anggreni et al., 2014; Hammerman et al., 2011). Study by Oncel *et al*. used paracetamol in 10 premature infants under than 30 weeks of GA with a 100% of effectiveness. Nevertheless, other authors did not achieve same striking results (El-Khuffash et al., 2014; Oncel et al., 2013). The most common dosage is 15 mg/k/dose/6qh.. Sinha R *et al* , used oral paracetamol but the result to closed ductal not satisfying (Sinha et al., 2013). In our study, all of the babies had problems feeding, therefore, paracetamol is given intravenously 15 mg/k/dose/q6h. We have reported a lower average ductal closure probably in our study do not separated between babies preterm and full term babies. No studies have reported the effectiveness of paracetamol for closure of PDA. Roofthooft DW *et al* study and Tekgündüz KS *et al* study did not show satisfactory results closed the ductal of paracetamol administration (Roofthooft et al., 2013; Tekgündüz et al., 2015). A recent report has reinforced the long-term neurodevelopmental safety of paracetamol in comparison to ibuprofen in 80 preterm neonates (Oncel et al., 2017). Considering the equivocal reports published until now and the promise offered by paracetamol as a safer alternative, this randomized, active controlled, masked, non-inferiority trial was planned. In our study, no subject had the neurodevelopmental problem after 6 month evaluation.

In our study all the neonates with hsPDA received treatment with intravenous paracetamol because this treatment was included in the standard operating procedures at the NICU. The result of our study show that there are many cases fail to close the PDA in full term babies compared with preterm babies (12 babies/44.4%). There are several reasons why PDA becomes unresponsive to the administration of Non-Steroidal Anti-Inflammatory Drug's (NSAIDs). The inflammatory process in the wall of a DA occurs soon after birth. It is associated with the influx of monocytes or macrophages into the walls of the DA witch later induces the prostaglandin and Nitrid-Oxcides (NO)- independent cytokines-mediated vasodilation (Hermes-DeSantis et al., 2006).

In preterm babies get very fantastic results with the success of PDA closure at 36 (80%), out of these, 22 babies (48,9%) only got one regiment while in the term babies the success of PDA closure in 15 babies (55,6%) received four times regiment. These result concluded that although paracetamol can affect the closure PDA in term babies, this drugs far more successful in preterm subjects.

The success of PDA closure also depends on the baby's weight, gestational age, size of PDA and on the day of administration drug. The small sample size is a limitation for our study, the single adverse event we noticed was a transient elevation in liver enzymes and not need medicine for this condition.

Our patients had oral feeding intolerance, so we use iv route. In our opinion, the oral route probably does not represent the optimal choice our subject. In these patients, gut immaturity together with oral feeding - intolerance can lead to unpredictable and possibly too low intestinal drug absorption.

The single adverse event we noticed was a transient elevation in liver enzymes in four pre-term babies as previously has been reported in literature, and they required no treatment.

5 CONCLUSIONS

Our results highlight that paracetamol could be come not only an alternative treatment in closing PDA but also the treatment of choice in several scenarios.in term babies. Nevertheless, one of the main limitations of this study is that it is with fewer subjects. studies are needed to know long-term consequences of using paracetamol for closing PDA and to answer important questions about the optimal dose, the best route of administration, safety and the implications in term babies.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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