JPESON
Journal of Perinatal Society of Nepal

ORIGINAL ARTICLE

Role of Injectable Paracetamol for Closure of Patent Ductus Arteriosus in Preterm Neonates admitted in a Tertiary Care Hospital

Sunil Raja Manandhar, Dipendra Rai
Neonatology Unit, Paediatrics Department, Kathmandu Medical College Teaching Hospital

ISSN: 2976-1050 (Online)
ISSN : 2976-1042 (Print)

Received : 20 May, 2023
Accepted : 22 Jun, 2023

Online Access

DOI: 10.59881/jpeson18

Funding Source : None

Conflict of Interest : None

Corresponding Author

Dr Sunil Raja Manandhar
Professor and HOD,
Preceptor, DM Neonatology,
Kathmandu University,
Paediatrics Department,
Kathmandu Medical College
Teaching Hospital
Email: drsunilraja@gmail.com

ABSTRACT

Background: Ductus Arteriosus is a vascular connection between the pulmonary artery and descending aorta and it is one of the important shunt in fetal circulation. Closure of DA after birth is very important for circulation adaptation to the extra-uterine life. Patent Ductus Arteriosus (PDA) innewborns is a pathological condition and it is more prevalent in preterm and LBW babies.

Objective: The objective of this study is to assess the role of injectable paracetamol in closure of hemodynamically significant PDA (hs- PDA) in preterm neonates.

Methods: A prospective analytical study done at Kathmandu Medical College Teaching Hospital from Nov 2022- April 2023. Ethical clearance was received from the Institutional Review Committee of Kathmandu Medical College (Ref: 18102022/1). Convenient sampling method was applied and statistical analysis was done with Statistical package for social sciences 19 version. A total of 45 preterm babies with hs-PDA diagnosed by 2D Echocardiography were treated with injectable paracetamol and subsequent closure were evaluated.

Results: Hs-PDA closure was observed in 84.4% (38) babies with no siginificant side effects noted with injectable paracetamol therapy and 36 (80%) babies were discharged after successful completion of injectable paracetamol therapy.

Conclusion: This study highlighted the effcicacy of injectable paracetamol as one of the alternative treatment in the closure of hs-PDA in preterm babies as it is easily available with very less side effects.

Keywords: *Injectable paracetamol; hemodynamically significant patent ductus arteriosus; preterm neonates*

INTRODUCTION

Ductus Arteriosus (DA) is a vascular connection between the pulmonary artery and descending aorta and it is one of the important shunt in fetal circulation.[1] Closure of DA after birth is very important for circulation adaptation to the extra-uterine life. In healthy full termnewborns DA generally undergoes functional closure between 24 and 72 hours of life.[2] However failure to close the DA resulting in Patent Ductus Arteriosus (PDA) in newbornsis a pathological condition. The incidence of PDA is inversely proportional to birth weight and gestational age.[3] In preterm infants it varies between 40% to 60% on the third day of life.[4] PDA in preterm babies can be lead to various complications such as respiratory distress syndrome (RDS), prolonged need for mechanical ventilation, pulmonary haemorrhage, Bronchopulmonary dysplasia (BDP), necrotizing enterocolitis (NEC), impaired renal function, intra-ventricular haemorrhage (IVH), periventricular leukomalacia (PVL) etc.[5] Hemodynamically significant PDA (hs-PDA) is a common complication affecting more than 40% preterm infants with high morbidity and

Citation
Manandhar SR, Rai D. Role of Injectable Paracetamol for Closure of Patent Ductus Arteriosus in Preterm Neonates admitted in a Tertiary Care Hospital. J. Per. Soc. Nepal 2023;02(01):29-31. DOI: 10.59881/jpeson18

mortality.[4] To prevent such complications, the practice of DA closure is a common approach and it is performed first pharmacologically and in case of drugs failure or contraindication, require surgical closure.[2]

Pharmacological closure with non-steroidal anti inflammatory drugs (NSAIDs) eg. Ibuprofen and Indomethacin, is one of the treatment for PDA closure in preterm infants. However, NSAIDs are not effective in 25-30% of preterm babies and have serious side effects eg.transient renal function impairment, diminished platelet aggregation, hyper-bilirubinemia and gastrointestinal bleeding and perforation.[6] Due its side effects, now a days, Injectable Paracetamol is emerging as an alternative drugs pharmacologically for PDA closure. The role of Paracetamol, an inhibitor of the peroxidase component of prostaglandin-H2 synthetase, has been proposed for the treatment of PDA over the last 8 yrs.[7] So, the main objective of this study is to assess the role of Injectable Paracetamol in closure of hemodynamically significant PDA (hs- PDA) in preterm neonates.

METHODS

This is a prospective analytical study done at Neonatology unit, Paediatrics Department, Kathmandu Medical College Teaching Hospital (KMCTH) over the period of six months duration(Nov 2022- April 2023). Ethical clearance was received from Institutional Review Committee (IRC) of Kathmandu Medical College (Ref. 18102022/01) and written consent was taken from the parents after explainingtreatment requirement for hs-PDA, its consequences and possible complications. Preterm (26-36 wks) babies born at KMCTH and outside KMCTH were included in the study. Syndromic preterm babies were excluded as their genetic factors may interfere the data quality. Data were entered in Excel and analysis was done in SPSS 19, point estimate at 95% confidence interval was calculated along with frequency, mean, standard deviation and p value <0.05 taken as statistically significant.A cross tabulation relation of reponse to inj. Parcetamol and none response were analysed with respect to various neonatal charecteristics.

The sample size was calculated as follows;

$$N = \frac{Z^2 \times P \times Q}{d^2}$$

Where,

N = Sample size

Z = 95% Confidence Interval Constant = $(1.96)^2$

P = Prevalence of PDA in preterm babies in previous study =20 % *Arlettaz R et al[8]

Q = 1- P

d = 12 %error = $(0.12)^2$

$$N = \frac{(1.96)^2 \times 0.20 \times (1 - 0.2)}{(0.12)^2}$$

$$N = \frac{3.84 \times 0.20 \times 0.8}{0.0144} = \frac{0.6144}{0.0144} = 42.66 = 43$$

Total Sample size = 45 preterm neonates with hs-PDA were included in the study.

Hemodynamically significant PDA (hs-PDA) is defined as:

Clinically having the following one or more criteria:[9]

1. Hyper dynamic precordium
2. Systolic murmur
3. Bounding peripheral pulses
4. Wide pulse pressure
5. Unexplained oxygen requirement Fio2 > 40%
6. Tachypnea (Respiratory rate > 60 breaths/min)

2D ECHO examination having following all three criteria:[9]

1. PDA diameter ≥ 1.5mm
2. LA/Ao≥1.5
3. Diastolic turbulence (increased diastolic flow 0.2-0.4m/s) on colordoppler in left pulmonary artery[10]

2D Echo was done via Portable ECHO machine Logi Q E multi-frequency containing 7 MHz neonatal probe manufactured by GE healthcare Ltd, USA. PDA size is measured in 2D image from the transductal diameter over the maximum constriction site(narrowest dimension) at the pulmonary end of ductus.[11]Preterm neonates (in-born/out-born) admitted in the neonatal unit of KMCTH, diagnosed by 2D-Echo within first 72 hours of life ashaemo-dynamically significant PDA (hs-PDA)with PDA size ≥1.5 mm received intravenous Injectable paracetamol @15mg/kg/dose QID (6hourly) for 72 hours.[9] The babies were assessed daily clinically and by 2D-Echo over the period of treatment till 72 hrs to assess the subsequent closure of hs-PDA. If the PDA closure is confirmed by Echocardiography, Injectable paracetamol treatment was discontinued, and if PDA is not closed, then the treatment regime is continued for next 72 hrs (3 more consecutive days). If, after six consecutive days, still ductus is not closed, then it was labeled as PDA not closed.ThePDA closure wasdefined when there was no blood flowshunting in Ductus Arteriosus in color doppler examination by 2D Echo.

Demographic features (Gestational age, gender, birth weight, Apgar score, delivery mode, antenatal steroids received by mother, age of treatment started, days of treatment, primary reason to use paracetamol, main outcome, adverse events and invasive ventilation), times of treatment, response to the treatment were noted. Liver function test (LFT) before and 24 hours after the end of paracetamol treatment were done in all babies. The required treatment and management of preterm babies with its morbid conditions were done according to treatment protocol of the neonatal unit of KMCTH.

RESULTS

Over the six month period, a total of 45 babies with hedynamically significant PDA were included in thestudy. Among them 26babies were inborn whereas 19 babies were outborn. Similalry, 26 (57.8%) babies were male and 19(42.2%) babies were female. Demographics and clinical characteristics of the study population (n= 45) are reported in Table 1. The mean birth weight of preterm babies with hs-PDA receiving Inj. Paracetamol was 1789±63 gms and mean gestational age was 33±2.75 weeks. Similarly, mean Silverman's score for assessment of respiratory distress was 6.67 ± 1.16 and the Inj. Paracetamol was started as a treatment for Hs-PDA at 3.67± 1.67 days of life. Main problems of Hs-PDA babies were tachypnea and grunting with requiring various forms of respiratory support for maintaining oxygen staturation ≥ 90% via Mechanical ventilation, ventilator continous positive airway pressure (CPAP) etc. By 2D Echo measurement, mean Hs-PDA size noted was 2.15± 0.48 mm and mean LA: Aorta ratio was 1.79± 0.32. During treatment of Hs-PDA, a total of 13.33±5.13 doses of Inj.Paracetamol were given over the mean period of 81.42± 32.41 hrs duration. After the treatement with Inj. Paracetamol, the mean duration of preterm babies with hs-PDA kept under ventilator CPAP was 60.18 ± 40.71hrs whereas mean durationof preterm babies under mechanical ventilation was 43.07 ± 58.98hrs.

Table 1. Demographics and clinical parameters of babies with hs-PDA (n = 45)

S.No.	Variables	Mean	Range
1.	Birth weight	1789.31± 63gms	(800 – 3500) gms
2.	Gestational age (yrs)	33 ± 2.75wks	(27- 36)wks
3.	Silverman's score for assessment of respiratory distress	6.67±1.16	(3- 10)
4.	Maternal Age	28.47± 4.39 yrs	(19-40) yrs.
5.	Hs-PDA size	2.15± 0.48 mm	(1.5-3.8) mm
6.	Left Atrium: Aorta ratio	1.79± 0.32	(1.5-3.4)
7.	Age of starting Inj. Paracetamol	3.67± 1.67 days of life	(2-8) days of life
8.	Total doses of Inj. Paracetamol given	13.33± 5.13 doses	(3-24) doses
9.	Total duration of Inj, Paracetamol given	81.42± 32.41 hrs.	(8-144) hrs.
10.	Total duration of Mechanical Ventilation	43.07± 58.98 hrs	(0-240) hrs.
11.	Total duration of Ventilator CPAP	60.18± 40.71 hrs	(0-220) hrs.
12.	Total duration of oxgen requirement	9.07± 5.07 days	(4-28) days
13.	Total duration of hospital stay	12.71± 6.26 days	(4-32) days

While analyzing the outcome of 45 preterm babies with hs-PDA under Inj. Paracetamol therapy, 38 (84.4%) babies'hs-PDA was closed whereas 7 (15.6%) babies hs-PDA was not closed.(Fig.1). Among 45 babies, 36 (80%) babies were discharged after PDA closure and 9 (20%) babies expired during treatment process. (Fig.2).

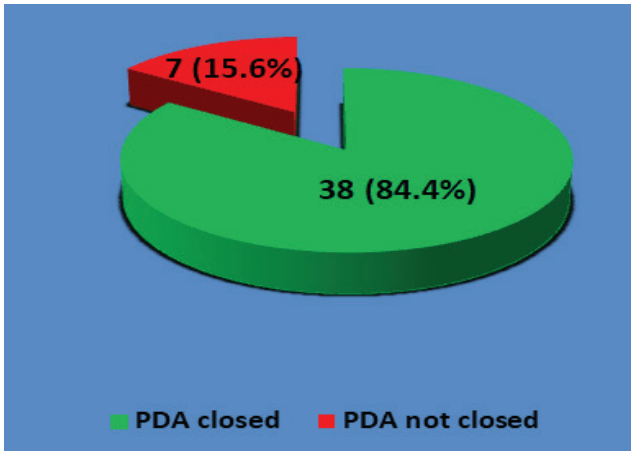


Fig 1. Result of PDA closure with Inj. Paracetamol

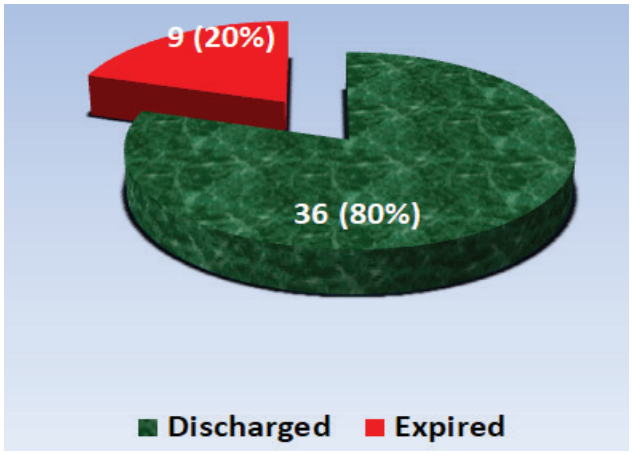
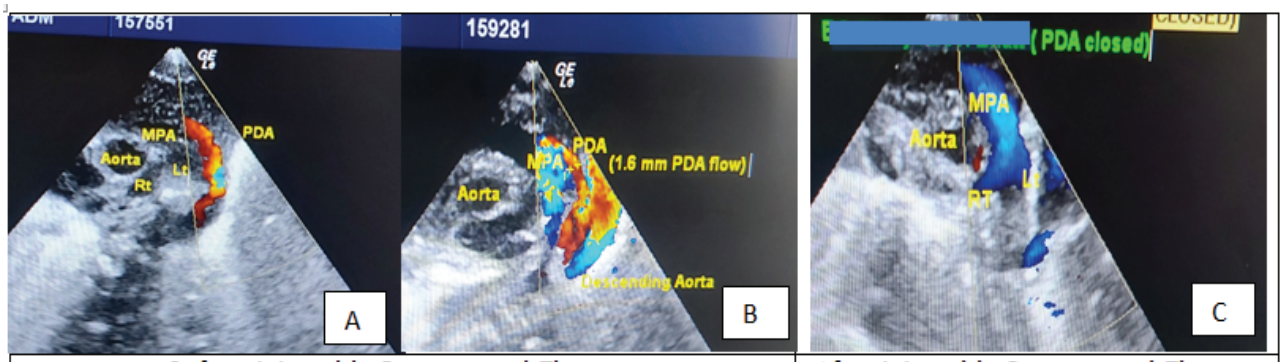


Fig 2. Out come of hs-PDA babies after Treatment

Glipmse of 2D Echo photographs demonstrating hs-PDA before and after the Injetable paracetamol treatment Fig. 3 (A) (B) (C).



Before Injectable Paracetamol Therapy

Fig 3 (A) (B). 2D Echo Ductal view in color doppler showing hs-PDA flow (red flow). Flow is seen in Main Pulmonary artery (MPA) also. (blue flow)

After Injectable Paracetamol Therapy

Fig 3 (C). 2D Echo ductal view in color doppler showing no flow in ductus arteriousus, Flow is only seen in Main Pulmonary artery (blue flow) suggestive of hs-PDA closure.

Table 2. Cross tabulation showing association between PDA closure status with respect to various neonatal charecteristics(n = 45 babies)

S.N.	Variables		Response to Inj. Paracetamol (PDA closed =38)		No response to Inj. Paracetamol (PDA not closed=7)		p value
			n	%	n	%	
1.	Gender	Male	16	(42.1)	3	(42.8)	0.00
		Female	22	(57.9)	4	(57.2)	
		Total	38	(100)	7	(100)	
2.	Gestational Age	26-28 wks	3	(7.9)	2	(28.5)	0.03
		29-33 wks	10	(26.3)	4	(57.2)	
		34-36 wks	25	(65.8)	1	(14.3)	
		Total	38	(100)	7	(100)	
3.	Birth weight	800-1000 gms	5	(13.2)	1	(14.2)	0.66
		1001-1500 gms	9	(23.6)	3	(43.0)	
		1501-2000 gms	11	(28.9)	2	(28.6)	
		2001-3500 gms	13	(34.3)	1	(14.2)	
		Total	38	(100)	7	(100)	
4.	PDA size	1.5 - 2 mm	23	(60.5)	1	(14.3)	0.05
		2.1 - 3 mm	14	(36.8)	5	(71.4)	
		3.1- 4 mm	1	(5.2)	1	(14.3)	
		Total	38	(100)	7	(100)	
5.	LA: Aorta ratio	1.4 -2	36	(94.7)	4	(57.1)	0.31
		2.1-2.5	2	(5.3)	1	(14.3)	
		Total	38	(100)	5	(100)	

6.	Age of treatment	2 - 5 days of life	32	(84.2)	6	(85.7)	0.70
		6 -10 days of life	6	(15.8)	1	(14.3)	
		Total	38	(100)	7	(100)	
7.	Other problems in baby including hs-PDA	Yes	13	(34.2)	5	(71.4)	0.09
		No	25	(65.8)	2	(28.6)	
		Total	38	(100)	7	(100)	

Table 2 analysed the association between PDA closure stautus with respect to various neonatal charecteritics. In this study showed PDA closure was seen more in female babies 57.9% (22) as compared to male 42.1% (16) ; p value 0.000. Similalry,Inj. Paracetamol responded well to close PDA among 65.8% (25) babies with gestational age 34-36 wks, 34.3%(13) babies with birth weight 2001-3500 gms category, in 2 D Echo findings 94.7% (36) babies had LA:Aorta ratio1.4- 2 and 60.5% (23) babies had PDA size 1.5-2 mm.In most of the babies, treatment was started between 2nd -5th days of lifewho responded with inj. Paracetamol treatment .Out of 38 babies, 65.8% (25) who responded to injection paracetamol treatment did not have any other morbid illnesses whereas 5 of the 7 babies who did not respond to injection paracetamol treatment had morbid illness such as septicemia, pulmonary artery hypertension, pneumonia etc. in addition to hs-PDA.

DISCUSSION

This studyhighlighted theefficacy of inj. paracetamol in closing hs-PDA.Terrin et al had published a case series of neonates with hs-PDA treated with paracetamol because of contraindication to ibuprofen or indomethacin and ductal closure was noted in 70% of neonates with no adverse reactions likewise in our study also ductal closure was noted in 84.4 % preterm neonates with inj. Paracetamolwith only one baby having raised liver enzyme.[12]

A retrospective study done by Dhungana D et al in Kathmandu, Nepal highlighted 91.67%closure of hs-PDAby inj. Paracetamol among preterm babies and 75% babies were discharged from the hospital.[13] Similarly in our study also, PDA was closed in 84.4% babies and 80% babies were discharged from the hospital as two babies were expired due to fulminant sepsis despite of PDA closure

A double-blind, parallel, randomized, placebo-controlled trial study done by Schindler T et al in Syndey, Australia.[14] In that study, ≤ 29weeks , 58 preterm babies with a ductus arteriosus size >0.9 mm at 6 h of life were randomized to 29 babies with intravenous paracetamol (15 mg/kg initially and then 7.5 mg/kg every 6 h) and 29 babies with intravenous dextrose (placebo) for 5 days. The study found closure of hs-PDA is more in intervention group, 59% (17) babies vs .21% (6) babies in control (p = 0.003, relative risk reduction 0.35 (95% CI 0.16–0.77).[14] In our study also mean duration of staring Injectable Paracetamol for PDA closure in preterm babies is 3.67± 1.6 days of life and 84.4% (38) babies hs-PDA is closed highlighting the role of Injectable Parcetamol in ductus closure.

CONCLUSION

Probably, this is the first prosepective analytical study done in Nepal so far , highlighting efficacy of injectable paracetamol as one of the alternative treatment in the closure of PDA in preterm infants. As it is easily available with very less side effects and especially useful in preterm infants with feeding intolerance or when oral therapy is contraindicated.

LIMITATION OF THE STUDY

Since this is a study of a single institution with convenient sampling, the outcome cannot be generalized.

ACKNOWLEDGEMENTS

Our sincere hearty thanks and acknowledgment to Pediatric Department faculties, DM Neonatology residents, MD Paediatrics residents and nursing staff for their tireless effort on better neonatal care during management of hs-PDA closure to make this study successful. At last but not the least, our sincere gratitude and thanks to all the neonates and their parents, without them this research would not be possible.

REFERENCES

1. Mitra S, Florez ID, Tamayo ME, Aune D, Mbuagbaw L, Veroniki AA, Thabane L. Effectiveness and safety of treatments used for the management of patent ductus arteriosus (PDA) in preterm infants: a protocol for a systematic review and network meta-analysis. BMJ Open. 2016 Jul 25;6(7):e011271. DOI: 10.1136/bmjopen-2016-011271.

2. Allegaert K, Anderson B, Simons S, van Overmeire B. Paracetamol to induce ductus arteriosus closure: is it valid? Arch Dis Child 2013;98:462–6. DOI: 10.1136/archdischild-2013-303688

3. Koch J, Hensley G, Roy L, Brown S, Ramaciotti C, Rosenfeld CR. Prevalence of spontaneous closure of the ductus arteriosus in neonates at a birth weight of 1000 gram or less. Pediatrics. Apr 2006;117(4):1113-21. DOI: 10.1542/peds.2005-1528

4. Evans N. Preterm patent ductus arteriosus: should we treat it? J Paediatr Child Health. Sept 2012 ;48(9):753-8. DOI: 10.1111/j.1440-1754.2012.02542.x

5. Singh Y, Fraisse A, Erdeve O and Atasay B. Echocardiographic Diagnosis and Hemodynamic

Evaluation of Patent Ductus Arteriosus in Extremely Low Gestational Age Newborn (ELGAN) Infants. Nov 2020. Front. Pediatr. 8:573627.
DOI: 10.3389/fped.2020.573627

6. Brunner B, Hoeck M, Schermer E, Streif W, Kiechl -Kohlendorfer U. Patent ductus arteriosus low platelets. Cyclooxygenase inhibitors and intraventricular hemorrhage in very low birth weight preterm infants. J Pediatr.2013;163:23–8.
DOI: 10.1016/j.jpeds.2012.12.035

7. Weisz DE, More K, McNamara PJ, Shah PS. PDA ligation and health outcomes: a meta-analysis. Pediatrics. 2014;133(4):e1024–46.
DOI: 10.1542/peds.2013-3431.

8. Arlettaz R. Echocardiographic evaluation of patent ductus arteriosus in preterm infants. Front. Pediatr. June 2017; 5(147).
DOI.org/10.3389/fped.2017.00147.

9. Sunil B, Patel S, Girish N. IV Paracetamol for closure of patent ductus arteriosus in preterm neonates admitted to a tertiary care centre. Int J Contemp Pediatr. 2018;5:294-8.
DOI:https://doi.org/10.18203/2349-3291.ijcp20180022

10. El Hajjar M, Vaksmann G, Rakza T, Kongolo G, Storme L. Severity of the ductal shunt: a comparison of different markers. Arch Dis Child Fetal Neonatal Ed. (2005) 90:F419–22.
DOI: 10.1136/adc.2003.027698

11. Tschuppert S, Doell C, Arlettaz-Mieth R, Baenziger O, Rousson V, Balmer C et al. The effect of ductal diameter on surgical and medical closure of patent ductus arteriosus in preterm neonates: size matters. J ThoracCardiovasc Surg. (2008) 135:78–82.
DOI:: 10.1016/j.jtcvs.2007.07.027.

12. Terrin G, Conte F, ScipioneA, Bacchio E, Conti MG, Ferro R et al. Efficacy of paracetamol for the treatment of patent ductus arteriosus in preterm neonates. Ital J Pediatr. 2014;40(1):21.
DOI: 10.1186/1824-7288-40-21

13. Dhungana D, Shrestha M, Joshi S. An observational study on use of intravenous paracetamol for closure of patent ductus arteriosus in Newborns. NMMJ.2021; (2)1:18-20.
DOI: https://doi.org/10.3126/nmmj.v2i1.37216

14. Schindler T, Smyth J, Bolisetty S, Michalowski J, Lui K.Earlyparacetamol (EPAR) trial: Arandomized controlled trial of earlyparacetamol to promote closureof the ductus arteriosus inpreterm infants. Neonatology (2021);118(3): 274–81.
DOI: https://doi.org/10.1159/000515415