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Efficacy of Oral Paracetamol in Closure of Hemodynamically Significant Patent Ductus Arteriosus in Preterm Infants

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Abstract

Background: Ductus arteriosus is a vascular connection between the pulmonary artery and descending aorta. Which closes after birth, whereas if it remains patent it is called as patent ductus arteriosus (PDA). The incidence of PDA is inversely related to birth weight and gestational age (GA). In preterm infants it varies between 40% and 60% on the third day of life. This study shows paracetamol may be used as an alternative to other nonsteroidal anti-inflammatory drugs and is effective in ductal closure with minimal side effects.

Aim and Objective: Our study is aimed to determine the efficacy of oral paracetamol in closing hemodynamically significant patent ductus arteriosus in preterm infants.

Material and Methods: 25 preterm infants with hemodynamically significant PDA (hs-PDA) were treated with Paracetamol oral suspension, administered through an orogastric tube at 15 mg/kg per dose in 6 hourly intervals for 3 consecutive days. Transthoracic echocardiography will be done 24 hrs after the completion of course. PDA closure will be confirmed when there is no demonstrable open ductus or no flow on color Doppler. Those babies in whom hsPDA remained open or reopened, will receive a second course of the study drug. If the ductus remains open even after second course, is considered as failed.

Results: The effectiveness of the closure of the ductus arteriosus with paracetamol reported in our study was 88% (n = 22). Out of 22 cases of PDA closure, 14 cases (56%) had a positive response after one treatment course and 8 cases (32%) had a positive response after two treatment courses and 3 cases (12%) treatment failure.

Conclusion: Our results highlight that paracetamol could become not only an alternative treatment in closing PDA but also the treatment of choice in several scenarios. The use of oral paracetamol for ductus arteriosus closure could be effective and economical. Our data on the effectiveness of paracetamol in the treatment of PDA merits for conduction of further well designed and robust randomized control trials, to confirm the usefulness of paracetamol as first choice agent in management of PDA due to its lesser side effect profile.

Keywords: *Oral Paracetamol; Pre-term; Transthoracic Echocardiography; Colour Doppler; Hemodynamically Significant Patent Ductus Arteriosus*

Abbreviations

hs-PDA: Hemodynamically Significant Patent Ductus Arteriosus; GA: Gestational Age

Introduction

In preterm infants, failure or delay in spontaneous closure of Ductus Arteriosus (DA), results in the condition of Patent Ductus Arteriosus (PDA), represents a significant issue [2]. A prolonged situation of PDA can be associated with several short- and long-term complications. Despite years of researches and clinical experience on PDA management, unresolved questions about the treatment and heterogeneity of clinical practices in different centers still remain, in particular regarding timing and modality of intervention. Nowadays, the most reasonable strategy seems to be reserving the treatment only to hemodynamically significant PDA. The first-line therapy is medical, and ibuprofen is the drug of choice, which causes nephrotoxicity [3]. Administration of oral paracetamol recently gained attention, appearing as effective as traditional nonsteroidal anti-inflammatory drugs (NSAIDs) in PDA closure, with lower toxicity. The results of the studies analyzed in this review mostly support paracetamol efficacy in closure of patent ductus arteriosus.

Materials and Methods

We conducted a prospective case series study of 25 preterm infants of < 37 weeks of gestational age (GA) with clinical and echocardiographic features of hemodynamically significant PDA (hsPDA) recruited from the NICU unit Hanagal Shri Kumareshwar Hospital from January 2021 to October 2022.

Paracetamol oral suspension will be administered through an orogastric tube at 15 mg/kg per dose in 6 hourly intervals for 3 consecutive days. Transthoracic echocardiography will be done 24 hrs after the completion of course. PDA closure will be confirmed when there is no demonstrable open ductus or no flow on color Doppler.

Those babies in whom hsPDA remained open or reopened, will receive a second course of the study drug.

If the ductus remains open even after second course, is considered as failed.

Echocardiography criteria: Transductal diameter ≥ 1.5 mm with one of the following:

- Left atrium: Aorta root diameter ratio > 1.5:1
- Ductal velocity < 20 cm/sec
- Mitral inflow velocity E/A ratio > 1
- Absent or reversed diastolic flow in descending thoracic aorta.

Results

Between January 2021 and October 2022, there were a total of 25 preterm infants who had significant PDA. All received paracetamol suspension. In 14/25 PDA closure (56%) happened after 1st course, and in 8/25 (32%) after 2nd course and failure in remaining 3 (12%). Results among the 25 patients who underwent paracetamol were as follows: mean GA was 33 weeks ranging from 29 to 36 weeks and mean birth weight was 1,350g ranging from 790 to 1,860g. 21 preterm were male and remaining female. Table 1 describes main clinical findings among infants who received paracetamol. Complete closure was observed in 22/25 (88%). Fourteen babies were treated for 3 days, and 8 babies for 6 days i.e. requiring 2nd course, and not closed in 3 babies even after 2 courses of treatment (Table 2 and 3).

Parameters		Count	Percentage
Gender	Male	21	84
	Female	5	16
GA in weeks	< 32	3	12
	32 - 35	17	68
	> 35 - 36+6	5	20
Mode of delivery	NVD	18	72
	LSCS	7	28
Surfactant requirement	Yes	22	88
	No	3	12
Ventilation requirement	Yes	5	20
	No	20	80
Birth weight in grams	< 1000	1	4
	1000 - 1500	6	24
	> 1500	18	72

Table 1

Assessment	Number	Transductal Diameter		Paired t test		Left Atrium:Aorta Ratio		Paired t Test	
		Mean	SD	P- Value	Significance	Mean	SD	P-Value	Significance
Before	25	1.99	0.34	< 0.001	Significant	1.7:1	0.3	< 0.001	Significant
After	25	0.52	0.51			1.15:1	0.5		

Table 2: *Echocardiographic parameters.*

Outcome	Count	Percentage
Improved after 1st course	14	56
Improved after 2nd course	8	32
Failure	3	12
Death	No	0

Table 3

Discussion

Hammerman., *et al*. reported for the first time several case reports on premature infants who received paracetamol achieving ductal closure [1]. 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. Indomethacin and ibuprofen inhibit cyclooxygenase (COX3) in a non- selective manner. Paracetamol acts by inhibiting prostaglandin synthetase [5]. Alternatively, paracetamol has been proposed to selectively inhibit a central isoform of COX3, but the existence of a functional human COX3 has been questioned [6]. Oncel., *et al*. used paracetamol in 10 premature infants under than 30 weeks of GA with a 100% of effectiveness [6].

Among 13 observational studies published, paracetamol was orally given [4-8] (112 premature infants), and in 12 observational studies, paracetamol was given iv (150 premature infants) with a closing average up to a 72.2% in oral route versus 66% with iv paracetamol. In our study closure rate is 88% slightly higher compared to some previous studies, probably due to early starting of oral paracetamol. The mean gestational age in our study in which PDA got closed after 1st course of treatment was 33 weeks, whereas for those requiring 2nd course of treatment for PDA closure was 30 weeks and mean gestational age was 29 weeks in treatment failure babies.

Conclusion

This study results highlight that paracetamol could become not only an alternative treatment in closing PDA but also the treatment of choice in several scenarios.

The use of oral paracetamol for ductus arteriosus closure could be effective and economical.

This data merits for conduction of further well designed and robust randomized control trials, to confirm the usefulness of paracetamol as first choice agent in management of PDA due to its lesser side effect profile.

Conflict of Interest

None.

Bibliography

1. Hammerman C., *et al*. "Ductal clorure with paracetamol: a surprising new approach to patent ductus arteriosus treatment". *Pediatrics* 128 (2011): e1618-e1621.

2. Dani C., *et al*. "Efficacy and safety of intravenous paracetamol in comparison to ibuprofen for the treatment of patent ductus arteriosus in preterm infants: study protocol for a randomized control trial". *Trials* 17 (2016): 182.

3. El-Khuffash A., *et al*. "Efficacy of paracetamol on patent ductus arteriosus closure may be dose dependent: evidence from human and murine studies". *Pediatric Research* 76 (2014): 238-244.

4. Dang D., *et al*. "Comparison of oral paracetamol versus ibuprofen in premature infants with patent ductus arteriosus: a randomized controlled trial". *PLoS One* 8 (2013): e77888.

5. Jasani B., *et al*. "Oral paracetamol in treatment of closure of patent ductus arteriosus in preterm neonates". *Journal of Postgraduate Medicine* 59 (2013): 312-314.

6. Oncel MY., *et al*. "Oral paracetamol versus oral ibuprofen in the management of patent ductus arteriosus in preterm infants: a randomized controlled trial". *The Journal of Pediatrics* 164 (2014): 510-4. e1.

7. Yang B., *et al*. "Oral paracetamol vs. oral ibuprofen in the treatment of symptomatic patent ductus arteriosus in premature infants: a randomized controlled trial". *Experimental and Therapeutic Medicine* 12 (2016): 2531-2536.

8. Bagheri MM., *et al*. "Comparison of oral acetaminophen versus ibuprofen in premature infants with patent ductus arteriosus". *Iranian Journal of Pediatrics* 26 (2016): e3975.

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