Comparison of Ketorolac and Indomethacin for the Closure of Patent Ductus Arteriosus among Preterm Infants Born at the Philippine General Hospital: A Randomized Controlled Crossover Design

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ABSTRACT

Background. Indomethacin has been the gold standard for the closure of patent ductus arteriosus (PDA). Still, the availability of the intravenous (IV) form has been a big issue precluding its use in the Philippines. IV ketorolac is another non-steroidal anti-inflammatory drug (NSAID) that is cheaper and more available in our country and used for post-cardiac surgery pain management among neonates.

Objectives. To compare the efficacy of ketorolac versus indomethacin in the closure of patent ductus arteriosus among preterm infants.

Methods. We conducted a randomized controlled, double-blind, crossover design, non-inferiority trial on the use of indomethacin versus ketorolac among preterm infants with PDA. We enrolled preterm infants at 5-12 days postnatal life, diagnosed with PDA by echocardiography at the Philippine General Hospital (PGH). We excluded infants with upper gastrointestinal bleeding, renal failure, birthweight < 500 grams, septic shock, and lethal anomalies. Patients were randomly allocated between two treatment groups (indomethacin versus ketorolac). The primary outcome measure was PDA closure measured after the treatment course. Adverse events like oliguria and bleeding were recorded.

Results. A total of 27 preterm infants were randomly assigned to the indomethacin (0.2 mg/kg/dose) and ketorolac (0.6 mg/kg/dose) group. Ketorolac has a 60% success rate for PDA closure (9/15) compared to indomethacin 41.67% (5/12) (p=0.154). No renal insufficiency and bleeding diathesis were noted. Five patients died in the study, four in the group initially allocated in ketorolac and one in indomethacin. Causes of death were late-onset sepsis, bronchopulmonary dysplasia, and congenital adrenal hyperplasia.

Conclusion. The success rate of PDA closure between IV ketorolac and IV indomethacin was not significantly different. There was neither oliguria nor bleeding observed in both groups.

Keywords: patent ductus arteriosus, ketorolac, indomethacin

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INTRODUCTION

Patent ductus arteriosus (PDA) remains a significant cause of cardiovascular morbidity during the newborn period. The incidences among low birth weight (<1500 grams) and extremely low birth weight (<1000 grams) infants are 33% and 65%, respectively.[1]

There have been emerging PDA closure treatment options for the past decade - from tolerance, conservative

management (fluid restriction), medical management, surgical ligation to transcatheter closure.[1] All these came about with the lack of improvement in long-term outcomes in any treatment options.[2] Still, the most commonly used approach is early symptomatic pharmacologic therapy which avoids prolonged exposure to pulmonary over-circulation.[3] Persistent left to right shunting increases the hydrostatic fluid filtration into the lung interstitium leading to impairment of lung mechanics and longer mechanical ventilation.[4]

Intravenous indomethacin has been the 'gold standard' of pharmacologic treatment of PDA over the past 40 years. It has a high closure rate and decreases the risk of severe IVH (intraventricular hemorrhage) and pulmonary hemorrhage.[5] Newer NSAIDs have been investigated since indomethacin is associated with increase in serum creatinine (azotemia).[5] Ibuprofen, another NSAID has been found to be as effective as indomethacin with less risk of NEC and transient renal insufficiency, although it does not reduce IVH and increases hyperbilirubinemia.[5,6] Paracetamol is also an effective alternative but is associated with transient liver enzyme elevation.[7] Still, for moderate to large PDAs, indomethacin has the highest rate of PDA closure, followed by ibuprofen and then paracetamol.[8]

Intravenous forms are needed for infants who cannot tolerate or are still unstable for enteral feedings. At present, only IV paracetamol is available in our country, which still requires further studies due to the sub-optimal quality of studies and the limited number of infants treated so far to be recommended as standard of care for PDA.[3,9]

Ketorolac is another NSAID candidate for pharmacologic closure of PDA among preterm infants. In a systematic review, ketorolac is safe with minimal adverse effects when used among term neonates and infants without renal dysfunction.[10] Its analgesic properties result from decreased prostaglandin synthesis through non-selective competitive inhibition of cyclooxygenase (COX)-1 and -2. Due to the platelet inhibition in the arachidonic acid pathway,[11] ketorolac has been associated with mild, non-fatal bleeding episodes.[12,13] There are still limited studies on ketorolac, and RCTs are lacking.[12] All ketorolac studies were on term infants except for a local study by Abat-Senen, who investigated the effect of ketorolac as prophylaxis for intraventricular hemorrhage among preterm infants ≤32 weeks and <1500 grams.[14]

Significance

Due to the unavailability of intravenous indomethacin in our country, other drugs such as IV ketorolac may be an alternative drug for the closure of patent ductus arteriosus among preterm infants.

General objective

To compare the efficacy of IV ketorolac versus IV indomethacin in the closure of patent ductus arteriosus among preterm infants.

MATERIALS AND METHODS

Setting and population

We enrolled preterm infants <37 weeks of gestation at 5-12 days postnatal life, diagnosed with PDA by echocardiography at the Philippine General Hospital (PGH). We excluded infants with upper gastrointestinal bleeding, renal failure, birthweight < 500 grams, septic shock, and lethal anomalies. The conduct of enrollment of subjects was summarized in Figure 1.

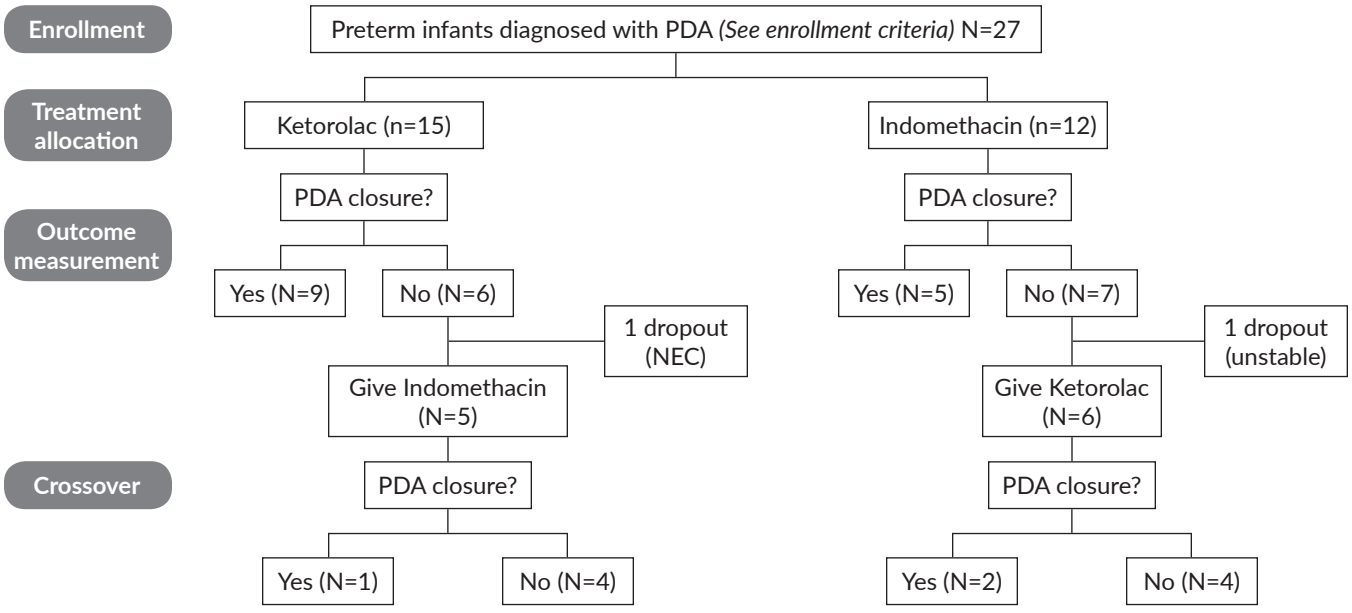

Figure 1. Flowchart on enrollment of subjects.

Study conduct

This was a randomized controlled, double-blind, crossover trial. All patients admitted to NICU with an echocardiographic finding of patent ductus arteriosus were eligible for enrollment. The investigators obtained informed consent from the parents and guardians of patients who satisfied the enrollment criteria. Afterward, they were randomly allocated to two treatment groups (ketorolac and indomethacin groups) using a computer-generated random sequence enclosed in an opaque envelope. Parents and caregivers, residents, fellows in training, attending physicians, and pediatric cardiologists were all blinded to the treatment allocation. Outcomes were then measured after completing the drug regimen. If PDA failed to close, the subject was re-allocated to the other group after 24 hours of washout (Figure 1). After a single dose of ketorolac (0.5 mg/kg) and indomethacin (0.2 mg/kg), the half-lives were 236 minutes among infants and 11-25 hours among preterm infants.[15,16] As success rates of pharmacologic closure of PDA decrease after the first week, the 24-hour washout period was chosen to provide the crossover drug before the end of the second week.[7]

Intervention

A code was used to conceal the drug's identity administered to the patient. Ketorolac (Toradol®, Hoffman-La Roche, Switzerland), assigned Drug A, was given at 0.6 mg/kg/dose every 12 hours for three doses and Indomethacin (Indocin®, Teva Pharmaceuticals, USA), assigned Drug B, was given at 0.2 mg/kg/dose every 12 hours also for three doses. A research assistant prepared the drug, administered it to the study participants, and recorded it in data collection form and medical chart for documentation.

Outcome measures

The primary outcome of interest was PDA closure determined via a 2D echocardiogram. A pediatric cardiologist, not involved in the study and blinded to the allocation, performed the echocardiogram upon enrollment and after completing a full course of the drug. Urine output and bleeding events were monitored along the course of the study.

Statistical analysis

Data entry and analysis were done using SPSS®. Code was only broken after data cleaning and data analysis. Means and frequencies were computed for baseline characteristics. The Chi-square test or student's t-test compared clinical characteristics and treatment outcomes between groups. An intention-to-treat analysis was also done.

Ethical consideration and safety

The Research Implementation Development Office of the University of the Philippines College of Medicine approved the research proposal before the study was conducted. Safety outcomes were also included to ensure patient safety. Reports were submitted to the hospital ethics board for cases of severe adverse and life-threatening events. Any patient with severe adverse events would be dropped from the study, and treatment allocation revealed.

RESULTS

A total of 27 preterm infants were recruited in the study. Baseline characteristics are shown in Table 1. There were no differences in age of gestation (30.7 vs. 31.5 weeks), birthweight (1215 vs. 1254 g), age drug was administered (6.8 vs. 5.8 days), and PDA size (1.78 vs. 1.64 mm). Baseline platelet count (185,933 vs 200,254 mm^3), creatinine (59.85 vs 55.92 µmol/ml) and total fluid intake (131 vs 131.2 ml/kg/day) between the ketorolac and control group, respectively.

There was a higher PDA closure after giving ketorolac (9/15; 60%) compared with indomethacin (5/12; 41.67%), but this did not reach statistical significance (p=0.343) (see Table 2). Among the seven patients whose ductus remained open after an initial course of indomethacin, one patient was withdrawn due to suspected necrotizing enterocolitis. The remaining six infants were crossed over to ketorolac with a resultant two additional PDA closures. For those who received ketorolac originally but with the persistence of PDA (n=6), one was dropped due to instability. Only five patients were crossed over to receive indomethacin leading to only 1 PDA closing.

Table 1. Comparison of the baseline characteristics between infants who received ketorolac versus indomethacin for the closure of the patent ductus arteriosus (PDA) among preterm infants

Variables	Ketorolac (n=15)		Indomethacin (n=12)		p-value*
	Mean	SD	Mean	SD	
Age of gestation, *(weeks)*	30.70	2.55	31.50	1.760	0.346
Birthweight, *(g)*	1215.93	348.469	1254.17	200.520	0.739
Age of life study drug given *(day)*	6.80	2.426	5.80	2.426	0.574
Baseline PDA size *(mm)*	1.76	0.502	1.64	0.469	0.196
Baseline platelet count	185,933	82,014	200,254	67,008	0.630
Baseline Creatinine *(s.i.)*	59.85	30.859	55.92	34.081	0.756
TFI *(ml/kg/day)*	131.00	24.52	132.30	22.210	0.898

**Chi-square test*

Table 2. Comparison of the status of PDA between preterm infants who received ketorolac versus indomethacin for PDA closure

Status of the PDA	Study Drug		P-value
Initial Drug	Ketorolac (n=15)	Indomethacin (n=12)	0.343*
Closed	9	5	
Remained patent	6	7	
Percentage	60%	41.7%	
Crossover	Indomethacin (n=5)***	Ketorolac (n= 6)***	1.000**
Closed	1	2	
Remained patent	4	4	
Percentage	20%	33%	

**Pearson Chi-Square; **Fisher's Exact Text; ***One patient each were dropped from the study due to instability*

Table 3. Comparison of selected safety outcomes between preterm infants who received ketorolac versus indomethacin for PDA closure

Parameter	Ketorolac (n=15)	Indomethacin (n=12)	p value
Mean size of DA remained patent after study drug administration	1.125 ± 0.42720	1.400 ± 0.51640	0.392
Bleeding events, n	0	0	-
Urine Output	3.81 ± 1.328	3.39 ± 1.128	0.419
Deaths	5/15 (33%)	1/12 (8.3%)	0.182*

**Fischer Exact Test, the rest by independent t-test*

There were neither bleeding diatheses nor oligurias observed among the neonates. The persistent PDA among those who initially received ketorolac was smaller than those initially given indomethacin (1.12 vs. 1.4 mm), but this did not reach a statistical difference. Four patients in the ketorolac group and one in the indomethacin group died (p=0.25). Of the four deaths In the ketorolac group, the causes were late-onset sepsis (2), pulmonary interstitial emphysema (1), and one due to a possible adrenal crisis from congenital adrenal hyperplasia. In the indomethacin group, the patient died due to late-onset sepsis (Table 3).

DISCUSSION

Non-steroidal anti-inflammatory drugs (NSAIDs) are a group of chemically diverse molecules sharing a similar site of action in the arachidonic acid pathway. Indomethacin, ibuprofen, and ketorolac inhibit prostaglandin synthesis with the inhibition of the cyclooxygenase (COX). Prostaglandin E1 (PGE1) is the prostanoid that maintains the patency of the ductus arteriosus. Cyclooxygenase inhibition leads to ductal constriction and closure. Paracetamol is also a prostaglandin synthesis inhibitor, but its site of action is downstream in the arachidonic pathway with the inhibition of peroxidase, again leading to prostaglandin synthesis inhibition.[17]

Ketorolac is a good candidate for PDA closure as its site of action is the same as indomethacin and ibuprofen, both considered standards of care for ductal closure. Ketorolac has been mainly used in neonates and infants for postoperative pain management for cardiac and abdominal surgeries.[10,12] As mentioned, the only RCT (randomized controlled trial) involving the use of ketorolac on preterm and very low birth weight infants was a local study by Abat-Senen, which showed no increase in the adverse events.[14]

In the literature review, there has been no previous study on the use of ketorolac in the closure of the PDA among preterm infants. This study showed a higher success rate in PDA closure among the preterm infants initially given IV ketorolac than IV indomethacin, but this did not reach statistical significance. Based on the literature, the usual closure rate of indomethacin was 80% among infants 1000-1750 grams, but the success rate was only 45% in this study.[7] A possible explanation for the lower success rates of both indomethacin and ketorolac could be the later treatment age.[7] In this study, the average ages of drug administration were 5.8 and 6.8 days for indomethacin and ketorolac, respectively. Some studies advocated early asymptomatic therapy for high-risk infants for higher success rates.[7] Unfortunately, there has been no consensus on the criteria to define hemodynamically significant PDA to identify high-risk infants adequately.[1,2] As mentioned, symptomatic therapy (cardiac murmur, tachycardia, wide pulse pressure) has still been widely advocated to avoid unnecessary exposure to adverse effects of medical and surgical interventions.[3]

Among those who received an initial course of ketorolac but with persistent PDA, there was a smaller ductal diameter at 1.125 mm compared with 1.4 mm among those who received the initial indomethacin course. This could indicate higher chances of closure spontaneously or after the second course of NSAID. Furthermore, ketorolac therapy did not lead to oliguria or bleeding. Deaths occurred

remote from the treatment period for both groups, with most deaths due to late-onset sepsis and respiratory failure due to chronic lung disease.

This study shows that IV ketorolac is a potential alternative to IV indomethacin and IV ibuprofen, both unavailable in the Philippines, in the closure of PDA. Another NSAID, IV paracetamol is now commonly used for PDA closure among preterm infants who cannot tolerate oral medications. Further studies on paracetamol are still needed to gain FDA approval for its indication for PDA closure.[3] Similarly, ketorolac, widely used as postoperative analgesia in infants and neonates alike, deserves further studies to explore the rational and appropriate guidelines based on pharmacologic and pharmacokinetic studies.[17]

A significant limitation in this study is the availability of IV Indomethacin. The drug became unavailable in the Philippines during the recruitment phase of the study. Efforts to import the IV indomethacin were not successful due to the shortage of the IV form during the study period. The prolonged unavailability of this drug has led to the premature termination of this study. The study team then decided to break the code and analyze the data.

CONCLUSION

The PDA closure rates after ketorolac therapy do not significantly differ from IV indomethacin. Further studies need to be done for a more robust conclusion with larger sample size.

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Statement of Authorship

All authors contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising and approved the final version submitted.

Author Disclosure

All authors declared no conflicts of interest.

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REFERENCES

1. Prescott S, Keim-Malpass J. Patent Ductus Arteriosus in the Preterm Infant: Diagnostic and Treatment Options. Adv Neonatal Care. 2017 Feb;17(1):10-18. doi: 10.1097/ANC.0000000000000340. PMID: 27740976.
2. Benitz WE; Committee on Fetus and Newborn, American Academy of Pediatrics. Patent Ductus Arteriosus in Preterm Infants. Pediatrics. 2016 Jan;137(1). doi: 10.1542/peds.2015-3730. Epub 2015 Dec 15. PMID: 26672023.
3. Conrad C, Newberry D. Understanding the Pathophysiology, Implications, and Treatment Options of Patent Ductus Arteriosus in the Neonatal Population. Adv Neonatal Care. 2019 Jun;19(3): 179-87. doi: 10.1097/ANC.0000000000000590. PMID: 30720481.
4. Clyman RI. Patent Ductus Arteriosus, its Treatments, and the Risks of Pulmonary Morbidity. Semin Perinatol. 2018 Jun;42(4):235-42. doi: 10.1053/j.semperi.2018.05.006. Epub 2018 May 10. PMID: 29958703.
5. Ferguson JM. Pharmacotherapy for Patent Ductus Arteriosus Closure. Congenit Heart Dis. 2019 Jan;14(1):52-6. doi: 10.1111/chd.12715. Epub 2018 Dec 11. PMID: 30536827.
6. Ohlsson A, Walia R, Shah SS. Ibuprofen for the Treatment of Patent Ductus Arteriosus in Preterm or Low Birth Weight (or both) Infants. Cochrane Database Syst Rev. 2020 Feb 11;2(2):CD003481. doi: 10.1002/14651858.CD003481.pub8. PMID: 32045960; PMCID: PMC7012639.
7. Su BH, Lin HY, Chiu HY, Tsai ML, Chen YT, Lu IC. Therapeutic Strategy of Patent Ductus Arteriosus in Extremely Preterm Infants. Pediatr Neonatol. 2020 Apr;61(2):133-41. doi: 10.1016/j.pedneo.2019.10.002. Epub 2019 Oct 29. PMID: 31740267.
8. Liebowitz M, Kaempf J, Erdeve O, Bulbul A, Håkansson S, Lindqvist J, et al. Comparative Effectiveness of Drugs Used to Constrict the Patent Ductus Arteriosus: A Secondary Analysis of the PDA-TOLERATE Trial (NCT01958320). J Perinatol. 2019 May;39(5):599-607. doi: 10.1038/s41372-019-0347-4. Epub 2019 Mar 8. PMID: 30850756; PMCID: PMC6561645.
9. Terrin G, Conte F, Oncel MY, Scipione A, McNamara PJ, Simons S, et al. Paracetamol for the Treatment of Patent Ductus Arteriosus in Preterm Neonates: A Systematic Review and Meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2016 Mar;101(2): F127-36. doi: 10.1136/archdischild-2014-307312. Epub 2015 Aug 17. PMID: 26283668.
10. Stone SB. Ketorolac in Postoperative Neonates and Infants: A Systematic Review. J Pediatr Pharmacol Ther. 2021;26(3):240-7. doi: 10.5863/1551-6776-26.3.240. Epub 2021 Mar 31. PMID: 33833624; PMCID: PMC8021237.
11. Kim JS, Kaufman J, Patel SS, Manco-Johnson M, Di Paola J, da Cruz EM. Antiplatelet Effect of Ketorolac in Children After Congenital Cardiac Surgery. World J Pediatr Congenit Heart Surg. 2018 Nov;9(6):651-658. doi: 10.1177/2150135118799041. PMID: 30322371.
12. Moffett BS, Wann TI, Carberry KE, Mott AR. Safety of Ketorolac in Neonates and Infants after Cardiac Surgery. Paediatr Anaesth. 2006 Apr;16(4):424-8. doi: 10.1111/j.1460-9592.2005.01806.x. PMID: 16618297.
13. Aldrink JH, Ma M, Wang W, Caniano DA, Wispe J, Puthoff T. Safety of Ketorolac in Surgical Neonates and Infants 0 to 3 Months Old. J Pediatr Surg. 2011 Jun;46(6):1081-5. doi: 10.1016/j.jpedsurg.2011.03.031. PMID: 21683202.
14. Abat-Senen K, Calotes-Castillo L, Mantaring JM. Prophylactic Intravenous Ketorolac for Prevention of Intraventricular Hemorrhage in Preterm Infants ≤1500 Grams: A Double-Blind Randomized, Placebo-Controlled Trial. Acta Med Philipp. 2016; 50(2):70-74.
15. Cohen MN, Christians U, Henthorn T, Vu Tran Z, Moll V, Zuk J, et al. Pharmacokinetics of Single-dose Intravenous Ketorolac in Infants Aged 2-11 Months. Anesth Analg. 2011 Mar;112(3):655-60. doi: 10.1213/ANE.0b013e3182075d04. Epub 2011 Jan 13. PMID: 21233498.
16. Pacifici GM. Clinical Pharmacology of Indomethacin in Preterm Infants: Implications in Patent Ductus Arteriosus Closure. Paediatr Drugs. 2013 Oct;15(5):363-76. doi: 10.1007/s40272-013-0031-7. PMID: 23754139.
17. Aranda JV, Salomone F, Valencia GB, Beharry KD. Non-steroidal Anti-inflammatory Drugs in Newborns and Infants. Pediatr Clin North Am. 2017 Dec;64(6):1327-1340. doi: 10.1016/j.pcl.2017.08.009. PMID: 29173788.