JPPT | Single Center Retrospective Study

Evaluation of the Closure of Patent Ductus Arteriosus With Ibuprofen Compared to Indomethacin

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OBJECTIVE Limited data exist comparing indomethacin and ibuprofen for the treatment of patent ductus arteriosus (PDA). The objective was to compare the safety and efficacy of indomethacin and ibuprofen for treatment of PDA closure.

METHODS This single-center, pre-test/post-test quasi-experiment included preterm infants admitted to the neonatal intensive care unit who received indomethacin (July 1, 2013–September 30, 2015) or ibuprofen (December 1, 2015–July 31, 2019) for PDA. Patients were excluded if they were thrombocytopenic, had existing kidney injury, unresolved intraventricular hemorrhage (IVH) or necrotizing enterocolitis (NEC) at treatment initiation. Data were obtained from the electronic health record. Study outcomes were complete PDA closure, degree of PDA closure, resolution of symptoms, and new-onset acute kidney injury (AKI), IVH, or NEC.

RESULTS A total of 114 patients were included: 44 (39%) received indomethacin and 70 (61%) received ibuprofen. Twenty-one (21%) patients experienced successful PDA closure within 1 week: 13 (32%) indomethacin patients and 8 (13%) ibuprofen patients ($p = 0.023$). PDA size reduction occurred in 43 (46%) patients with 29 (25%) experiencing complete symptom resolution. Significantly more indomethacin patients compared with ibuprofen patients experienced new-onset AKI (48% vs 17%; $p < 0.001$) and received concomitant nephrotoxins (68% vs 39%; $p = 0.002$). There were no significant differences in new-onset IVH or NEC.

CONCLUSIONS Indomethacin administration successfully closed the PDA in more neonates than ibuprofen but resulted in higher rates of AKI. However, this was confounded by more frequent administration of concomitant nephrotoxins. Larger trials are needed to help elucidate the optimal drug for closure of the PDA in neonates.

ABBREVIATIONS AKI, acute kidney injury; BW, birth weight; CGA, corrected gestational age; DA, ductus arteriosus; ELBW, extremely low birth weight; GA, gestational age; GI, gastrointestinal; hs-PDA, hemodynamically significant patent ductus arteriosus; IV, intravenous; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NSAIDs, non-steroidal anti-inflammatory drugs; PDA, patent ductus arteriosus; PO, oral; pRIFLE, pediatric risk, injury, failure, loss, end stage renal disease; RDS, respiratory distress syndrome; VLBW, very low birth weight

KEYWORDS necrotizing enterocolitis; newborn; nonsteroidal anti-inflammatory drugs; patent ductus arteriosus; renal insufficiency; thrombocytopenia

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Introduction

The ductus arteriosus (DA) is a blood vessel that connects the pulmonary artery to the aorta in fetal circulation. This blood vessel allows fetal blood to bypass the underdeveloped lungs. When a full-term infant is born, the DA normally constricts and becomes functionally closed around 72 hours of age.[1] Closure of the DA, however, is often delayed in preterm infants. Commonly preterm neonates are classified into the following categories based on gestational age (GA): moderate-to-late preterm (GA 32 to <37 weeks), very preterm (GA 28 to <32 weeks), and extremely preterm (GA <28 weeks).[2] Additionally, neonates are commonly classified based on birth weight: low birth weight (LBW, <2500 grams), very low birth weight (VLBW, <1500 grams), and extremely low birth weight (ELBW, <1000 grams).[2] It is also important to note a neonate's postnatal age, which is defined as days after birth and corrected gestational age (CGA), which adds the birth GA and postnatal age together.[2]

The literature indicates the DA can remain open at 4 days of life in approximately 10% of neonates born at 30 to 37 weeks' gestation, 80% of neonates born at 25 through 28 weeks' gestation, and 90% of those

born at 24 weeks' gestation.[1] By day 7 after birth, those rates decline to approximately 2%, 65%, and 87%, respectively.[1,3]

If the DA remains open and functional, it is termed a patent ductus arteriosus (PDA).[4] It is known that circulation and production of prostaglandins is a contributing factor of PDA.[4] There are several variables associated with affecting prostaglandin synthesis and function that also can contribute to a persistent PDA including maternal factors (e.g., preeclampsia, diabetes mellitus) and patient-specific factors (e.g., race, GA, postnatal age, infection, and respiratory distress severity).[4] The PDA in preterm neonates can result in excess blood flow through the pulmonary circulation and hypoperfusion of the systemic circulation via left-to-right shunting of blood from the aorta to pulmonary arteries. This can lead to complications such as respiratory distress syndrome (RDS), pulmonary hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis (NEC), renal insufficiency, prolonged assisted ventilation, intraventricular hemorrhage (IVH), periventricular leukomalacia, cerebral palsy, or death.[1,3,5]

Numerous studies have been reported in the literature evaluating different treatment approaches for the closure of PDA. However, there are still challenges on ideal management of PDA in premature infants. These challenges include determining a more uniform definition of a hemodynamically significant PDA (hs-PDA) that leads to adverse events and determining how to balance the safety and efficacy of inherent risks associated with medical therapy and surgical ligation.[6] Historically, PDA has been treated medically with non-steroidal anti-inflammatory drugs (NSAIDs), such as indomethacin and ibuprofen, or more invasively with surgical measures such as ligation.[3,6,7] Studies have shown ibuprofen is as effective in closing the PDA compared with indomethacin, but reduces the risk of NSAID-associated renal dysfunction and the development of NEC.[6] Due to a potential safety benefit in utilizing ibuprofen to close the PDA, our institution changed from using indomethacin to ibuprofen. The purpose of this study was to evaluate the efficacy and safety of indomethacin as compared with ibuprofen in preterm neonates with symptomatic PDA post-formulary change.

Materials and Methods

Data collected from the electronic health record (EHR; Epic) through manual chart review of objective data, as well as provider notes, included baseline demographics (sex, treatment weight collected within 24 hours prior to treatment initiation or within 24 hours after the first dose of treatment, birth weight collected within 24 hours after birth, birth weight classification, GA, gestational classification, postnatal age defined as the age of life after birth up to the time of treatment initiation, corrected GA calculated as GA + postnatal age, height, baseline serum creatinine, baseline urine output, baseline platelet count, baseline respiratory support, baseline echocardiogram obtained, baseline size of PDA reported in either mm or size category per the EHR), clinical treatment characteristics (first dosing regimen in mg/kg/day for the total daily dose of the study drug, duration of therapy of the first dosing regimen, secondary course needed followed with the dose and duration, concomitant nephrotoxic medications administered, concomitant normal saline boluses given), and clinical outcomes (increased respiratory support, successful PDA closure defined as suspected per EHR documentation or documented per echocardiogram, final degree of PDA closure reported in either mm or size category for unsuccessful closures, PDA symptom resolution as documented in the EHR, thrombocytopenia, need for platelet transfusion, suspected or documented NEC as identified by imaging and/or in the EHR, suspected or documented IVH as identified by imaging and/or in the EHR, new-onset acute kidney injury (AKI) defined by the RIFLE risk category,[8] highest serum creatinine collected, and lowest urine output recorded). Of note, the specific baseline demographic parameters collected (i.e., height, serum creatinine, urine output, platelet, and respiratory support) were within 24 hours prior to treatment initiation or within 24 hours after the first dose of treatment. Furthermore, the clinical outcomes collected (i.e., respiratory support, PDA closure, symptom resolution, thrombocytopenia/platelet transfusion, NEC, IVH, renal function/AKI) were within 24 hours after beginning treatment up to 1 week after the last treatment dose. Information pertaining to ibuprofen and indomethacin regimens was collected, as well as concomitant medication use that could influence renal function. Besides nephrotoxic agents, data on use of dopamine and supplemental fluid were also collected as they are known to be possible nephroprotective factors.

This was a single center, pre-test/post-test quasi-experiment that was conducted at a level IV neonatal intensive care unit (NICU) at a tertiary care academic medical center. Included neonates were required to have been born alive before 37 weeks' gestation, admitted to the NICU, and received at least 1 dose of either indomethacin or ibuprofen for suspected (per physician discretion based on clinical presentation since at the time of the study there was no institutional protocol in place) or documented (via echocardiogram) PDA. These patients were subsequently divided into 2 groups: the pre-group received intravenous (IV) indomethacin between July 1, 2013 through September 30, 2015, and the post-group received IV ibuprofen between December 1, 2015 through July 1, 2019. The initial standard dose at our institution for intravenous indomethacin was 0.2 mg/kg given intravenously over approximately 20 to 30 minutes. Then followed 12 to 24 hours later with 2 additional doses based off of postnatal age (0.1 mg/kg/dose if < 48 hours old, 0.2 mg/kg/dose if > 48 hours old

but ≤ 7 days old, or 0.25 mg/kg/dose if > 7 days old) with each additional dose being separated by 12 to 24 hours. The standard dosing at our institution for intravenous ibuprofen for PDA closure is a loading dose of 10 mg/kg given intravenously over 15 minutes, followed 24 hours later by 2 maintenance doses of 5 mg/kg with each maintenance dose also being separated by 24 hours. Patients were excluded if they were thrombocytopenic (platelets <50,000 TH/cmm), had a urine output <1 mL/kg/hr, serum creatinine >1.5 mg/dL, or unresolved IVH or NEC at the time of treatment initiation.

The primary outcome of this study was to assess the efficacy of ibuprofen compared with indomethacin for complete PDA closure within 1 week following completion of treatment via percentage of patients achieving this endpoint. Secondary efficacy outcomes included degree of PDA closure, need for a second course of PDA medication treatment or surgical ligation post-treatment, and clinical symptom resolution of PDA. Symptom resolution was measured by documented PDA resolution (see definition above), decrease in oxygen requirements, absence of invasive oxygen support, and/or resolution of renal dysfunction associated with the PDA (serum creatinine was ≤1.5 mg/dL).[7] Findings related to these data points were collected from medical charts for 1 week after the patient completed the course of treatment. Secondary safety outcomes included new-onset renal injury utilizing the pRIFLE criteria to assess change in serum creatinine and urine output, thrombocytopenia (platelets < 50,000 TH/cmm), suspected or confirmed NEC and IVH, or gastrointestinal (GI) bleeding.[8] These safety outcomes were collected from medical charts for 1 week after patient received the last dose of treatment.

Study endpoints were examined using descriptive and inferential statistics. Statistical analysis was performed using SPSS software version 26.0 (IBM). Categorical data were analyzed using χ^2 or Fisher exact test, and continuous data were analyzed using Student *t* test or Mann-Whitney *U* test, as appropriate. We conducted a convenience sample to ensure we obtained as many patients as possible for inclusion. This study was approved by the institutional review board, and written, informed consent was waived.

Results

Overall, 195 patients were screened, with 44 patients included in the indomethacin group and 70 patients in the ibuprofen group. Most patients excluded were due to NEC or IVH at time of treatment initiation. A total of 53 (46.5%) patients were male, and the median birth weight (BW) was 760 grams (IQR, 630–950) with a median treatment weight of 850 grams (687.5–1012.5). Ninety-three (81.6%) patients were classified as ELBW, with 20 (17.5%) classified as VLBW. Additionally, 96 (84.2%) patients were deemed to be extremely preterm neonates, with 17 (14.9%) very preterm, and 1 (0.9%) moderate-to-late preterm. The overall demographic and baseline characteristics of the patients are displayed in Table 1.

There were some significant differences in baseline characteristics between groups, namely for CGA, renal function, and respiratory support. The median CGA at the time of treatment initiation was 26.9 weeks (25.6–28.7) in the indomethacin group compared with 28 weeks (26.8–30) in the ibuprofen group (p = 0.015). Additionally, baseline serum creatinine for the indomethacin patients was significantly higher than for the ibuprofen patients (0.75 mg/dL vs 0.62 mg/dL; p = 0.009). Although the clinical status of baseline PDA size category was similar between groups, there was a significant difference with the patients' respiratory support. Thirty-eight (86.4%) indomethacin patients compared with 43 (61.4%) ibuprofen patients had invasive respiratory support with mechanical ventilation (p = 0.004). A breakdown of concomitant medications with the potential to impact renal function can be seen in Table 2. The number of concomitant nephrotoxic medications used was higher for the indomethacin group compared with the ibuprofen group (68.2% vs 38.6%; p = 0.002).

Primary and Secondary Efficacy Outcomes. The primary efficacy outcome of complete closure of the PDA within 1 week following the end of treatment was able to be assessed in 41 of the 44 indomethacin patients and 61 of the 70 ibuprofen patients. Some patients were unable to be assessed due to incomplete charting or pertinent patient information being unavailable. Complete closure occurred in 21 (20.6%) total patients including 13 patients (31.7%) in the indomethacin group and 8 patients (13.1%) in the ibuprofen group (p = 0.023) (Table 3). There was no difference in the size of the PDA post-treatment between groups, however, 27 of the 78 (34.6%) patients still had a large PDA despite therapy. The secondary efficacy outcomes were not significantly different between groups regarding symptom resolution, increased respiratory support, and the need for a second course of treatment. Eighteen (40.9%) patients in the indomethacin group and 25 (35.7%) patients in the ibuprofen group received a second course of treatment (p = 0.577).

Secondary Safety Outcomes. Secondary safety results were similar between groups for most of the endpoints assessed. However, 9 (20.5%) patients in the indomethacin group and 5 (7.1%) patients in the ibuprofen group received platelet transfusions (p = 0.035) (Table 4). Additionally, there was a statistically significant difference in the incidence of new-onset acute renal injury. Twenty-one (47.7%) patients in the indomethacin group developed renal injury as compared with 12 (17.1%) patients in the ibuprofen group (p < 0.001). Additionally, there was no statistically significant difference between the groups in terms of development of NEC or IVH post-treatment (p = 0.561 and p = 1.000, respectively).

Table 1. Patient Demographics and Baseline Characteristics

Variable	N (%) or Median [IQR]			
	Total (N = 114)	Indomethacin (n = 44)	Ibuprofen (n = 70)	p value
General demographic information				
Sex, male	53 (46.5)	22 (50)	31 (44.3)	0.552
Birth weight, grams	760 [630–950], n = 113	733 [635–990], n = 43	765 [625–925], n = 70	0.489
Birth weight classification				
Low birth weight*	1 (0.9)	0 (0)	1 (1.4)	1.000
Very low birth weight†	20 (17.5)	10 (22.7)	10 (14.3)	0.249
Extremely low birth weight‡	93 (81.6)	34 (77.3)	59 (84.3)	0.347
Gestational age, wk	25.86 [24.43–27.43]	25 [23.89–28]	26 [24.54–27.43]	0.547
Gestational age classification				
Moderate-to-late preterm§	1 (0.9)	1 (2.3)	0 (0)	0.386
Very preterm¶	17 (14.9)	10 (22.7)	7 (10)	0.063
Extremely preterm#	96 (84.2)	33 (75)	63 (90)	0.033
Baseline information at treatment initiation				
Weight, grams	850 [687.5–1012.5]	810 [672–982.5]	865 [714.5–1042.5]	0.225
Height, cm	33.75 [31.5–36], n = 113	34 [32–35.5], n = 43	33.3 [31.4–36.05]	0.952
Postnatal age, wk	1.29 [0.86–2.29]	1 [0.57–1.57]	1.64 [1.14–3.18]	<0.001
Corrected gestational age, wk	27.71 [26–29.14]	26.93 [25.57–28.68]	28 [26.82–29.96]	0.015
Serum creatinine, mg/dL	0.69 [0.5–0.86], n = 113	0.75 [0.61–0.89], n = 43	0.62 [0.43–0.85], n = 70	0.009
Urine output, mL/kg/hr	3.7 [2.9–4.6]	3.9 [2.8–4.7]	3.7 [2.9–4.3]	0.183
Platelet count, TH/cmm	205 [134–273.5], n = 101	186 [128–266], n = 39	211.5 [156–282.5], n = 62	0.236
Respiratory support				
Invasive	81 (71.1)	38 (86.4)	43 (61.4)	0.004
Non-invasive	33 (28.9)	6 (13.6)	27 (38.6)	1.000
Size category of PDA				
Small	2 (1.8)	0 (0)	2 (2.9)	0.522
Small to moderate	5 (4.4)	2 (4.5)	3 (4.3)	1.000
Moderate	13 (11.4)	3 (6.8)	10 (14.3)	0.222
Moderate to large	11 (9.6)	2 (4.5)	9 (12.9)	0.199
Large	83 (72.8)	37 (84.1)	46 (65.7)	0.032

PDA, patent ductus arteriosus; for size determination please see Methods

* Low birth weight defined as <2500 grams.
† Very low birth weight defined as <1500 grams.
‡ Extremely low birth weight defined as <1000 grams.
§ Moderate-to-late preterm defined as gestational age of 32 to <37 wk.
¶ Very preterm defined as gestational age of 28 to <32 wk.
# Extremely preterm defined as gestational age of <28 wk.

Discussion

Similar to this study, Chan et al[9] reported findings of a study comparing the effectiveness and complications associated with NSAIDs for the treatment of PDA after switching from indomethacin to ibuprofen at their institution. The study was conducted at a level III NICU in a tertiary center in Hong Kong and the indomethacin cohort included 52 patients, and the ibuprofen cohort 43. Patients in the indomethacin cohort were given either 0.2 mg/kg/dose intravenously every 24 hours for a total of 3 doses or 0.1 mg/kg/dose intravenously every 24 hours for a total of 6 doses. Patients in the

Table 2. Concomitant Medications

Variable	N (%)			
	Total (N = 114)	Indomethacin (N = 44)	Ibuprofen (N = 70)	p value
Nephrotoxic medications	57 (50)	30 (68.2)	27 (38.6)	0.002
Vancomycin	28 (24.6)	17 (38.6)	11 (15.7)	0.006
Amikacin	25 (21.9)	14 (31.8)	11 (15.7)	0.043
Gentamicin	15 (13.2)	10 (22.7)	5 (7.1)	0.017
Furosemide	17 (14.9)	10 (22.7)	7 (10)	0.063
Normal saline boluses	12 (10.5)	5 (11.4)	7 (10)	1.000
Dopamine	20 (17.5)	11 (25)	9 (12.9)	0.097

Table 3. Clinical Efficacy Outcomes

Variable	N (%)			
	Total (N = 114)	Indomethacin (N = 44)	Ibuprofen (N = 70)	p value
Successful PDA closure	21 (20.6), n = 102	13 (31.7), n = 41	8 (13.1), n = 61	0.023
Birth weight classification				
Low birth weight*	1 (100), n = 1	—	1 (100), n = 1	—
Very low birth weight†	6 (30), n = 20	4 (40), n = 10	2 (20), n = 10	0.628
Extremely low birth weight‡	15 (18.3), n = 82	9 (29), n = 31	6 (11.8), n = 51	0.050
Prematurity classification				
Moderate-to-late preterm§	0 (0), n = 1	0 (0), n = 1	—	—
Very preterm¶	8 (57.1), n = 14	5 (55.6), n = 9	3 (60), n = 5	1.000
Extremely preterm#	13 (14.9), n = 87	8 (25.8), n = 31	5 (8.9), n = 56	0.057
Size category of PDA	n = 78	n = 26	n = 52	
Small	20 (25.6)	10 (38.5)	10 (19.2)	0.067
Small to moderate	10 (12.8)	2 (7.7)	8 (15.4)	0.482
Moderate	11 (14.1)	2 (7.7)	9 (17.3)	0.319
Moderate to large	10 (12.8)	2 (7.7)	8 (15.4)	0.482
Large	27 (34.6)	10 (38.5)	17 (32.7)	0.614
Symptom resolution	29 (25.4)	15 (34.1)	14 (20)	0.093
Birth weight classification				
Low birth weight	1 (100), n = 1	—	1 (100), n = 1	—
Very low birth weight	8 (40), n = 20	4 (40), n = 10	4 (40), n = 10	1.000
Extremely low birth weight	20 (21.5), n = 93	11 (32.4), n = 34	9 (15.3), n = 59	0.053
Prematurity classification				
Moderate-to-late preterm	0 (0), n = 1	0 (0), n = 1	—	—
Very preterm	8 (47.1), n = 17	6 (60), n = 10	2 (28.6), n = 7	0.335
Extremely preterm	21 (21.9), n = 96	9 (27.3), n = 33	12 (19), n = 63	0.354
Increased respiratory support	59 (51.8)	21 (47.7)	38 (54.3)	0.495
Birth weight classification				
Low birth weight	0 (0), n = 1	—	0 (0), n = 1	—
Very low birth weight	9 (45), n = 20	5 (50), n = 10	4 (40), n = 10	1.000
Extremely low birth weight	50 (53.8), n = 93	16 (47.1), n = 34	34 (57.6), n = 59	0.325
Prematurity classification				
Moderate-to-late preterm	1 (100), n = 1	1 (100), n = 1	—	—
Very preterm	8 (47.1), n = 17	3 (30), n = 10	5 (71.4), n = 7	0.153
Extremely preterm	50 (52.1), n = 96	17 (51.5), n = 33	33 (52.4), n = 63	0.936

PDA, patent ductus arteriosus

* Low birth weight defined as <2500 grams.
† Very low birth weight defined as <1500 grams.
‡ Extremely low birth weight defined as <1000 grams.
§ Moderate-to-late preterm defined as gestational age of 32 to <37 wk.
¶ Very preterm defined as gestational age of 28 to <32 wk.
# Extremely preterm defined as gestational age of <28 wk.

Table 4. Clinical Safety Outcomes

Variable	N (%) or Median [IQR]			
	Total (N = 114)	Indomethacin (N = 44)	Ibuprofen (N = 70)	p value
Platelet transfusion	14 (12.3)	9 (20.5)	5 (7.1)	0.035
Birth weight classification				
Low birth weight*	0 (0), n = 1	—	0 (0), n = 1	—
Very low birth weight†	3 (15), n = 20	2 (20), n = 10	1 (10), n = 10	1.000
Extremely low birth weight‡	11 (11.8), n = 93	7 (20.6), n = 34	4 (6.8), n = 59	0.091
Prematurity classification				
Moderate-to-late preterm§	1 (100), n = 1	1 (100), n = 1	—	—
Very preterm¶	3 (17.6), n = 17	2 (20), n = 10	1 (14.3), n = 7	1.000
Extremely preterm#	10 (10.4), n = 96	6 (18.2), n = 33	4 (6.3), n = 63	0.087
Post-treatment platelets, TH/cmm	157 [92.5–236.5], n = 105	171 [114–244.5], n = 41	138.5 [84.25–222.5], n = 64	0.257
Necrotizing enterocolitis	7 (6.2), n = 113	2 (4.5), n = 44	5 (7.2), n = 69	0.561
Birth weight classification				
Low birth weight	0 (0), n = 1	—	0 (0), n = 1	—
Very low birth weight	0 (0), n = 20	—	—	—
Extremely low birth weight	7 (7.6), n = 92	2 (5.9), n = 34	5 (8.6), n = 58	1.000
Prematurity classification				
Moderate-to-late preterm	0 (0), n = 1	0 (0), n = 1	—	—
Very preterm	1 (5.9), n = 17	0 (0), n = 10	1 (14.3), n = 7	0.412
Extremely preterm	6 (6.3), n = 95	2 (6.1), n = 33	4 (6.5), n = 62	1.000
Intraventricular hemorrhage	15 (13.2)	6 (13.6)	9 (12.9)	1.000
Birth weight classification				
Low birth weight	0 (0), n = 1	—	0 (0), n = 1	—
Very low birth weight	5 (25), n = 20	3 (30), n = 10	2 (20), n = 10	1.000
Extremely low birth weight	10 (10.8), n = 93	3 (8.8), n = 34	7 (11.9), n = 59	0.741
Prematurity classification				
Moderate-to-late preterm	0 (0), n = 1	0 (0), n = 1	—	—
Very preterm	3 (17.6), n = 17	2 (20), n = 10	1 (14.3), n = 7	1.000
Extremely preterm	12 (12.4), n = 97	4 (12.1), n = 33	8 (12.5), n = 64	1.000
New-onset acute renal injury	33 (28.9)	21 (47.7)	12 (17.1)	<0.001
Birth weight classification				
Low birth weight	0 (0), n = 1	—	0 (0), n = 1	—
Very low birth weight	7 (35), n = 20	5 (50), n = 10	2 (20), n = 10	0.350
Extremely low birth weight	27 (29), n = 93	16 (47.1), n = 34	11 (18.6), n = 59	0.005
Prematurity classification				
Moderate-to-late preterm	1 (100), n = 1	1 (100), n = 1	—	—
Very preterm	3 (17.6), n = 17	3 (30), n = 10	0 (0), n = 7	0.228
Extremely preterm	29 (30.2), n = 96	17 (51.5), n = 33	12 (19), n = 63	<0.001
Degree of new-onset acute renal injury				
Risk	22 (66.7)	14 (66.7)	8 (66.7)	1.000
Injury	9 (27.3)	6 (28.6)	3 (25)	1.000
Failure	2 (6.1)	1 (4.8)	1 (8.3)	1.000

* Low birth weight defined as <2500 grams.
† Very low birth weight defined as <1500 grams.
‡ Extremely low birth weight defined as <1000 grams.
§ Moderate-to-late preterm defined as gestational age of 32 to <37 wk.
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ibuprofen cohort were given a loading dose of 10 mg/kg/dose followed by 2 maintenance doses of 5 mg/kg/dose with each dose being separated by 24 hours. The majority of patients (52%) in the indomethacin cohort compared with 44% in the ibuprofen cohort had a birth weight ≤ 1000 grams. Fifty-two percent of patients in the indomethacin cohort compared with 47% in the ibuprofen cohort were extremely preterm (GA < 28 weeks).

The postnatal age when treatment was first initiated ranged from 1.6 to 20.2 and 3.7 to 11.7 days in the indomethacin and ibuprofen cohort, respectively. After the first course of treatment, ductal closure was observed in 62% of patients in the indomethacin cohort compared with 58% in the ibuprofen cohort. The percentage of patients who required additional course(s) of treatment was 35% vs 30% in the indomethacin and ibuprofen cohort, respectively. Incidence of GI effects such as NEC and GI bleeding were higher in the ibuprofen cohort compared with the indomethacin cohort. During the treatment course, there was an increase in serum creatinine and decrease in urine output, but no statistically significant difference between treatment groups.

When comparing the results in the study conducted by Chan et al[9] to this study, there were some noteworthy differences. While the rate of closure in both studies was higher in the indomethacin group compared with the ibuprofen group, the rate of successful PDA closure in both the indomethacin and ibuprofen groups was considerably lower in this study, comparatively. Although it is difficult to determine the exact reasons for this difference, it is important to note that there was a higher percentage of patients who were ELBW and extremely preterm in both groups of this study compared with the cohorts in the study conducted by Chan et al,[9] which could be contributing factors. In this study, although not statistically significant the closure rate of the PDA in ELBW infants was 29% in the indomethacin group compared with 12% in the ibuprofen group. Additionally, in this study the closure rate of extremely preterm infants was 26% vs 9% in the indomethacin group compared with the ibuprofen group even though not statistically significant.

Baseline Characteristics. Prematurity is a risk factor for PDA, and it is thought GA at birth influences the rate of spontaneous closure. It has been noted previously that the PDA in patients with a birth GA ≥ 28 weeks is likely to close spontaneously; however, the PDA often does not close on its own in extremely preterm patients, especially those with RDS.[3,5] It has also been reported that GA could affect the closure of the PDA when utilizing medication intervention with indomethacin.[4] The median (IQR) birth GA in our study for the entire study population was 25.86 weeks (24.43–27.43) with the majority of patients in the study population (84.2%) classified as extremely preterm. This is important to note since based on the GA/level of prematurity observed in this study, patients included would likely require intervention due to decreased likelihood of spontaneous closure of the PDA. The GA could also affect the success of closure observed with utilization of medication. In this study, the PDA closure rate in the extremely preterm groups were lower compared with the other levels of prematurity.

In addition to considering a patient's GA for risk of PDA, it is also important to consider the patient's postnatal age when determining appropriateness of treatment. It is known that indomethacin has been used as prophylaxis within 24 hours of birth and also for treatment once patients show signs and symptoms of PDA.[10] It is thought that early treatment compared with late treatment may be beneficial in lower birth weight patients presenting with a murmur due to the risk of a larger PDA developing weeks later.[11] However, the exact timeframe for when treatment should be initiated for patients with PDA is not definitive. It was previously thought that patients with a postnatal age outside of 10 to 14 days will be less likely to experience closure of the ductus with medical intervention, but it has also been suggested that a more appropriate criterion to look at for success of ductal closure may be the CGA rather than the postnatal age.[3,12] Specifically, one study found that patients with a CGA of ≤ 33 weeks demonstrated complete closure of the PDA after indomethacin, while patients > 33 weeks did not demonstrate complete closure of the PDA but did show some improvement.[12] In our study at the time of treatment with either indomethacin or ibuprofen, the median (IQR) of the postnatal age for the entire study population was 1.29 weeks (0.86–2.29) and the CGA was 27.71 weeks (26–29.14). It is important to note that the median CGA would still be classified as extremely preterm, and the IQR falls well below the 33-week cutoff. Based on this information, the patients would fall in the window where closure with medication intervention would still be expected, but it is unclear if closure rates would have varied if treatment was initiated later for some of the patients.

It in addition to GA, BW is thought to influence the spontaneous closure of the PDA. It has been noted that in patients > 1000 grams the PDA should close on its own; however, the PDA often does not close spontaneously in patients with an ELBW.[5,13] The median (IQR) of the birth weight in our study for the entire study population was 760 grams (630–950), with the majority of patients in the study population classified as ELBW. This is noteworthy since based on the BW results observed in our study, patients included were at risk for not experiencing spontaneous closure of the PDA and should require intervention. In this study, the PDA closure rate in the extremely low birth weight groups were lower compared with the other birth weight categories.

Efficacy Outcomes. In a 2020 Cochrane Review examining ibuprofen for the treatment of PDA, there were 24 studies included comparing oral (PO)/(IV) ibuprofen to PO/IV indomethacin.[14] Overall, there were no significant differences found regarding PDA closure rates. In this study, there were more complete closures of the PDA with patients receiving indomethacin compared with ibuprofen. Although complete closure statistically significantly favored indomethacin, only 46% of the overall patient population experienced some size reduction. Even though not statistically significant, the closure rate in the extremely preterm

infants who received indomethacin was higher compared with the ibuprofen group in this study.

In a meta-analysis conducted by Mitra et al,[6] 68 randomized clinical trials were included, and in these studies, there were varying treatment regimens used with a total of 4802 infants included. The overall closure rate in this meta-analysis was 67.4%. Of note, high dose PO ibuprofen was found to be the best medication option for PDA closure and had a higher odds ratio of PDA closure compared with the standard dose IV ibuprofen in this meta-analysis. Of note, the closure rate in the meta-analysis was significantly higher compared with the closure rate in this study. Additionally, only standard dose IV ibuprofen was used in this study.

It is important to note that in recent years, some institutions have implemented the use of acetaminophen as a treatment option for the closure of the PDA in addition to NSAIDs. Acetaminophen has literature to support comparable efficacy to indomethacin and ibuprofen.[6,15,16] There have been a couple of randomized controlled trials comparing the efficacy and safety of indomethacin, ibuprofen, and acetaminophen for the closure of PDA. El-Mashad et al[17] included 100 patients in each treatment group and found that the PDA was closed after the first treatment course in 81% of patients in the indomethacin group vs 77% in the ibuprofen group vs 80% in the acetaminophen group. Overall, this result was not deemed statistically significant, and the authors stated there was no significant difference in efficacy between groups. Of note, the baseline demographics were similar between all 3 groups regarding GA, with all patients being extremely preterm. The postnatal age at the start of treatment was similar between groups as well, with all patients being < 10 days of life. Weight was similar between groups and ranged from 0.88 to 1.24 kg for the entire study population. Overall, the study conducted by El-Mashad et al[17] reported a higher rate of closure in both the indomethacin and ibuprofen group compared with this study and did not find a statistically significant difference. Of note, there were differences in postnatal age and weight between studies, which could be contributing factors to the difference in closure rate. The TOLERATE Trial was a multicenter trial that explored early treatment vs a conservative approach of the PDA in patients who were extremely preterm at birth.[18] As part of a secondary analysis, efficacy of medications was evaluated, and agents patients received varied by center.[19] Treatments included were indomethacin, ibuprofen, and acetaminophen. The greatest constriction of the PDA was found with indomethacin compared with ibuprofen and acetaminophen. While the treatment approach/study design was different in this secondary analysis, the finding of indomethacin being more effective than ibuprofen was similar to our study.

In addition to evaluating closure of the PDA, it is important to explore respiratory support requirements. In the TOLERATE trial it was reported that 48% of patients received continuous positive airway pressure or nasal ventilation, while 49% of patients were intubated.[18] An overall higher percentage of patients at baseline in our study required invasive respiratory support. In our study, only 25% of all patients experienced complete clinical symptom resolution. Further analysis was conducted to examine symptom resolution in both groups. Although there was a statistically significant higher proportion of patients in the indomethacin group who required mechanical ventilation at baseline vs the ibuprofen group, there was no difference identified in terms of PDA symptom resolution post-treatment between groups.

Safety Outcomes. There are a number of potential side effects that are important to monitor while patients are receiving NSAIDs for the closure of the PDA including NEC, IVH, and nephrotoxicity.[14] Due to these potential side effects from medical treatment, these diagnoses were excluded from our study.

The 2020 Cochrane review regarding ibuprofen found that the risk of NEC was reduced in patients receiving ibuprofen compared with indomethacin.[14] However, in the meta-analysis by Mitra et al,[6] it was found there was no significant difference in the odds of the occurrence of NEC in patients with hs-PDA given indomethacin, ibuprofen, acetaminophen, or placebo. In the study conducted by El-Mashad et al,[17] 18 patients (6%) overall developed NEC with the majority being in the indomethacin group (n = 9) vs 6 patients in the ibuprofen group vs 3 in the acetaminophen group. However, this finding was not statistically significant. In our study, a total of 7 patients were diagnosed with NEC within 24 hours of treatment initiation and up to a week after medication completion. Although the percentage of patients with NEC in the ibuprofen group was slightly higher compared with the indomethacin group, this was not considered statistically significant.

In the meta-analysis by Mitra et al,[6] there was no significant difference in the odds of the occurrence of IVH. A total of 22 patients (7%) in the study conducted by El-Mashad et al[17] developed IVH. The most patients with IVH were in the indomethacin group (n = 10) compared with 5 in the acetaminophen group and 7 in the ibuprofen group; however, this was not statistically significant. In our study, a total of 15 patients (13%) developed IVH. There was a slightly higher percentage of patients in the indomethacin group with IVH, but this was not statistically significant.

In the 2020 Cochrane Review regarding ibuprofen, the serum creatinine concentrations were lower 3 days after treatment with ibuprofen compared with indomethacin.[14] Fanos et al[20] conducted a retrospective analysis in patients ≤ 30 weeks GA who received treatment for PDA and found that NSAIDs can affect renal function in this patient population. Specifically, the authors reported that indomethacin could be more nephrotoxic compared with ibuprofen since it took the

serum creatinine longer to normalize with indomethacin, although the difference was not significant. In our study, there was a higher incidence of statistically significant renal injury in the indomethacin group; however, these patients also received a statistically significant higher number of concomitant nephrotoxic agents compared with the ibuprofen group. This difference was primarily driven by higher usage of vancomycin and aminoglycosides in the indomethacin group compared with the ibuprofen group. Nephrotoxic agents such as vancomycin and aminoglycosides can have residual effects on renal function shortly after the medications have been stopped. Therefore, this should be considered when evaluating renal injury in patients being treated for PDA with concomitant nephrotoxic medications.

Limitations. There are a number of limitations associated with this study. This study took place at a single center during a specified timeframe, so there is a limited sample size, and there were fewer patients included in the indomethacin group. However, since this study took place at a level IV NICU, some baseline demographic information may be comparable to other level IV NICUs. This study was retrospective in nature, therefore confounders exist that were difficult to control for, such as concomitant medications. One medication class that could have specifically influenced the results of PDA closure was the concomitant administration of diuretics, such as furosemide. Often patients receive furosemide in between aliquots of blood transfusions or for respiratory related issues; however, this could be counterproductive when a patient has a PDA as furosemide stimulates prostaglandin E_2 production.[21] While concomitant use of furosemide could have influenced the rate of closure, only a small portion of patients (15%) received this medication while being treated for a PDA. Although we excluded patients with certain conditions at baseline (e.g., NEC, IVH), it is hard to confirm if the intervention was the only reason the complication occurred as the study population is at risk for these complications independent of PDA treatment. Additionally, it is difficult to determine if the respiratory support required at baseline/after treatment was due to the PDA or if there were additional contributing factors, such as prematurity. In addition to neonatal factors, there are also maternal factors that could influence the PDA. These were not explored in this study and could be unidentified confounders influencing the results. Since this study was retrospective in nature, there could have been other confounders that impacted the results such as potential changes in providers or provider preference or other changes in practices at the institution during the study period.

Conclusion

Overall, indomethacin administration successfully closed the PDA of more neonates compared with ibuprofen, although the overall percentage of PDA closure was low compared with other studies. While indomethacin may have been associated with more PDA closures, in general, ibuprofen had a greater safety profile than indomethacin. These findings should be interpreted with caution due to the limited sample size of the study. Patients who received ibuprofen also had a younger GA and received less concomitant nephrotoxins, both of which could have impacted the safety and efficacy of the drug. In the future, larger studies are needed to provide more guidance on appropriate medication selection, timing of medication administration, and neonatal and maternal factors that could contribute to successful closure of the PDA in very preterm and extremely preterm neonates.

Article Information

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