MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2019; 25: 3668-3675
DOI: 10.12659/MSM.914181

Received: 2018.11.19
Accepted: 2019.01.28
Published: 2019.05.17

Effectiveness and Renal Functions Safety of Treatments Used for Neonates with Patent Ductus Arteriosus: A Prospective Cohort Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Source of support: Medical Research Projects of Wuhan Municipal Health Planning Commission (No: WX18Z22)

Background: Neutrophil gelatinase-associated lipocalin plays an important role in renal dysfunctions. The objective of this study was to test the hypothesis that indomethacin used in treating patent ductus arteriosus protects infants from renal dysfunction.

Material/Methods: This prospective cohort study assessed data on urine prostaglandin metabolites, urinary neutrophil gelatinase-associated lipocalin, and the renal functions of preterm infants with confirmed patent ductus arteriosus who had been injected with indomethacin (n=144, ID group) or acetaminophen (n=144, AP group).

Results: A reduction of neutrophil gelatinase-associated lipocalin in urine samples was found in the ID group (993±48 μG/L *vs.* 103±5 μG/L, $p<0.0001$). The reduction in prostaglandin (673±32 pg/mL *vs.* 139±7 pg/mL, $p<0.0001$) and the closure of ductus (2.64±0.89 mm *vs.* 2.31±0.81 mm, $p=0.001$) were found in the ID group after the first dose of indomethacin, but the closure of ductus (2.47±0.54 mm *vs.* 2.32±0.55 mm, $p=0.02$) and prostaglandin reduction (667±31 pg/mL *vs.* 129±7 pg/mL, $p<0.0001$) were found after the second dose of acetaminophen. Indomethacin had greater effect in reducing the risk of acute kidney injury than did acetaminophen ($p=0.042$).

Conclusions: Indomethacin treatment used in treating patent ductus arteriosus protects infants from renal dysfunction.

MeSH Keywords: **Acetaminophen • Arbaprostil • Ductus Arteriosus, Patent • Indomethacin • Intensive Care, Neonatal • Neutrophils**

Abbreviations: **PDA** – patent ductus arteriosus; **NGAL** – neutrophil gelatinase-associated lipocalin; **STROBE** – Strengthening The Reporting of Observational studies in Epidemiology

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/914181

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Background

Patent ductus arteriosus (PDA) is a congenital heart disorder in neonates that is associated with high morbidity and mortality [1,2]. About 50% of neonates born prior to 32 weeks of gestation have an increased risk of PDA, and it is the second most common heart disease in neonates [3,4].

In normal neonates, the ductus arteriosus closes at birth, but in PDA, this blood vessel remains open, which results in uneven diffusion of blood to the aorta and pulmonary artery, finally resulting in pulmonary hypertension and heart failure if untreated [5]. Several factors contribute to the occurrence of PDA.

First, prostaglandin E2 plays a role in keeping the ductus arteriosus open. In the fetus, the production of prostaglandin is very high because of the placenta and there is a decline in fetal lung metabolism [6]. At birth, prostaglandin levels fall due to proper functioning of the lungs and removal of the placenta. The muscles of the ducts contract, which results in shortening, and within 24–48 h the ductus arteriosus closes completely [7,8]. However, if the level of prostaglandin is abnormal, it results in PDA, most commonly in preterm neonates. Failure of the ductus arteriosus to close can result in hemorrhage, bronchopulmonary dysplasia, enterocolitis, and death [9,10].

Second, neutrophil gelatinase-associated lipocalin (NGAL) plays an important role in renal development, but during inflammation or ischemic conditions, NGAL expression becomes abnormal [11–13]. In premature newborns with PDA, the level of NGAL becomes elevated and this is associated with acute kidney infection [14–16]. This might be due to the critical cardiac circulation and uneven distribution of blood, which leads to renal perfusion and finally results in kidney failure [17]. Hence, it is necessary to treat this patency. The standard treatment of PDA is indomethacin. Indomethacin and acetaminophen inhibit the production of prostaglandin by acting on the enzyme cyclooxygenases [1,18,19]. Other drugs, such as ibuprofen, are also used in treating PDA, with fewer adverse effects, but their efficacy is lower than that of indomethacin [20].

The objective of this prospective cohort study was to test the hypothesis that indomethacin used to treat PDA protects infants from renal dysfunction at the level I of evidence.

Material and Methods

Drugs and reagents

Injectable indomethacin (INDOCIN®) was purchased from Iroko Pharmaceuticals LCC (Philadelphia, PA, USA) and injectable acetaminophen (Mol) was purchased from Gufic Biosciences. Clean tubes, carbonate buffer, phosphate buffer, mouse monoclonal anti-rabbit IgG, wash buffer, Ellman's reagent, and ELISA buffer were purchased from Cayman Chemical, USA. Microwells were purchased from Sigma-Aldrich (St. Louis, MO, USA).

Ethical consideration and consent to participate

This study was registered in the Research Registry (*www.researchregistry.com*), UID No.: researchregistry4523 dated 29 December 2014. The protocol (HUM/CL/5/15 dated 1 January 2015) of the study was approved by the Taihe Hospital review board. The study adhered to the laws of China, the strengthening the reporting of observational studies in epidemiology (STROBE) statement, and the Declaration of Helsinki (V2008). An informed consent form was signed by parents of the infants, who were informed regarding interventions, pathology, and publication of the work-up in all formats irrespective of time and language.

Inclusion criteria

Preterm infants with confirmed PDA were included in the study. Echocardiograms with the neonatal probe (Acuson X 300, Siemens Medical Solutions, Erlangen, Germany) were taken by pediatricians (with at least 3 years of experience) at the institutes for confirmation of PDA.

Exclusion criteria

We excluded neonates with congenital chromosomal abnormalities, malformations in heart, and pulmonary hypertension.

Cohorts

The ID group (n=144) consisted of neonates who had been injected with 0.2 mg/kg indomethacin intravenously, followed by a second and third dose of 0.1 mg/kg indomethacin after 24 and 48 h, respectively. The AP group (n=144) consisted of neonates who had been injected with 10 mg/kg acetaminophen intravenously followed by a second and third dose of 5 mg/kg acetaminophen after 24 and 48 h, respectively.

Echocardiographic measurements

To assess patent ductus arteriosus, echocardiograms with a neonatal probe of all the infants were taken on days 1, 3, and 7 after the start of treatment.

Urine sample collection

After each dose, a urine sample was collected by the nursing staff of the institute. Urine samples were collected from the infants by placing a cotton ball (Suzhou Sunmed Co., Beijing, China) at

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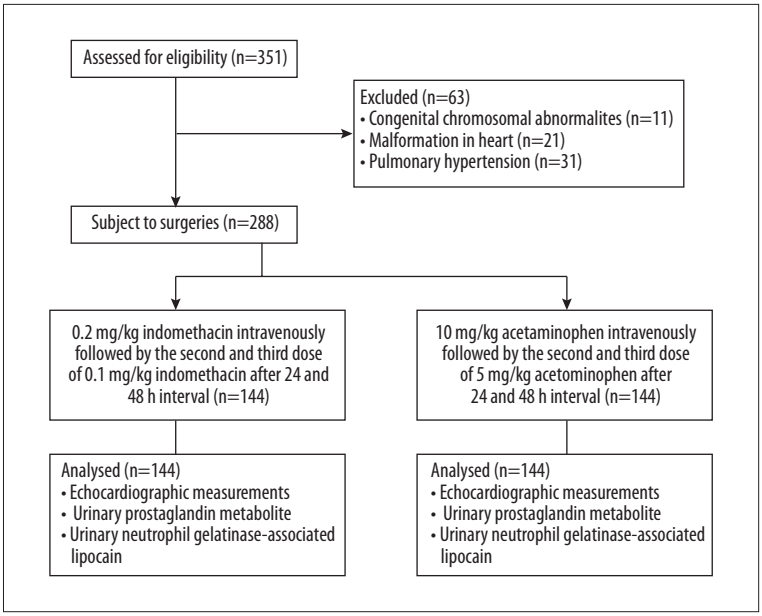

Figure 1. Flow diagram of the work-up.

the perineum or by using a bladder catheter (Roche Diagnostics, Suzhou, Beijing, China). The disposable diapers (Huggies®, Kimberly-Clark, Beijing, China) were checked every 3 h and the cotton balls were stored in a refrigerator (Lead-lined, Lemer Pax, Paris, France). The cotton balls were centrifuged (Clinical centrifuge, DT5-6A (2), Thermo Fisher Scientific, Beijing, China) and collected urine was stored at –80°C (LN2 liquid nitrogen tank, Huanghua Baihengda Xiangtong Machinery Co., Beijing, China) for later analysis of prostaglandin metabolite and NGAL levels.

Urinary prostaglandin metabolite analysis

The urine samples from the neonates with PDA were analyzed for prostaglandin synthesis. The Prostaglandin E Metabolite ELISA Kit (Cayman Chemical, San, Diego, CA, USA) was used for analyzing prostaglandin in the urine samples. The urine samples were derivatized according to the manufacturer's guidelines; 500-µL samples of urine were aliquoted into a clean tube, to which this 150 µL of carbonate buffer was added. The samples were incubated overnight at 37°C (Yorko, San, Diego, CA, USA). About 200 µL of phosphate buffer and 150 µL of ELISA buffer were added to the samples. From the derivatized samples, 100 µL was loaded into each well. The wells were precoated with mouse monoclonal anti-rabbit IgG and blocked with proprietary formulations of proteins. The samples were incubated (Yorko, San, Diego, CA, USA) for 1 h, followed by washing using a washing buffer to remove the unbound reagents. Then, the wells were developed using Ellman's reagent. The color developed was absorbed at 412 nm (colorimetric analysis, Colorimeter, Shimadzu Co., Tokyo, Japan) [9,10]. Pathologists (with at least 3 years of experience, blind to interventions) at the pathological laboratories of the institutes performed the analysis.

NGAL analysis

The presence of NGAL in urine was analyzed using an NGAL ELISA kit (Sigma-Aldrich, St. Louis, MO, USA). About 100 µL of each sample was loaded into the microwells, followed by incubation at room temperature for 1 h and washing using a washing buffer. Then, the wells were incubated with biotinylated NGAL antibody (Sigma-Aldrich, St. Louis, MO, USA) and HRP-streptavidin (Sigma-Aldrich, St. Louis, MO, USA) for 1 h as per the manufacturer's protocol. The concentration of NGAL was measured at 450 nm (colorimetric analysis, Colorimeter, Shimadzu, Tokyo, Japan) [14–16]. Pathologists of pathological laboratories of the institutes performed the analysis.

Renal functions evaluations

Serum creatinine, urinary albumin, fractional excretion of sodium, and urine output were also evaluated at the time of enrollment and after the third dose of the interventions. Serum creatinine value above 75 µM/L with urine output less than 0.5 mL/kg/h was considered as acute kidney injury (institutional guideline of pediatrics) [21].

Statistical analysis

For statistical analysis, we used 2-tailed paired *t* tests for continuous variables and the chi-square independent-samples test for constant variables. The results were considered significant at a 95% level of confidence. The software used for the statistical analyses was SPSS for Windows 11.0 version (SPSS, Inc., Chicago, IL, USA).

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Table 1. Clinical characteristic features of the preterm infants.

Clinical characteristics		Groups		Comparisons between groups
		ID	AP	
Intervention		Indomethacin	Acetaminophen	
Neonates enrolled in the study (sample size)		144	144	*p*-Value
Gestational age (week)	Minimum	24	24	0.135
	Maximum	31	31	
	Mean ±SD	29.42±2.51	29.01±2.12	
Birth weight (g)	Minimum	989	980	0.895
	Maximum	2111	2210	
	Mean ±SD	1367.53±334.51	1362.35±331.49	
Sex	Male	99 (69)	87 (60)	0.175
	Female	45 (31)	57 (40)	
Nature of delivery	Normal	25 (17)	21 (15)	0.629
	Caesarean	119 (83)	123 (85)	
Diameter of ductal arteriosus (mm)**		2.64±0.89	2.47±0.54	0.051
Urinary prostaglandin (pg/mL)#		673±32	667±31	0.107
Urinary neutrophil gelatinase-associated lipocalin (μG/L)##		993±48	989±47	0.476
Sepsis*		22 (15)	27 (19)	0.531
Serum creatinine (μM/L)		77.86±6.52	76.76±5.92	0.135
Urinary albumin (mg/L)		63.36±8.13	64.01±8.89	0.518
Fractional excretion of sodium		3.71±1.05%	3.67±1.01%	0.742
Acute kidney injury###		9 (6)	10 (7)	0.812
Urine output (mL/kg/h)		1.01±0.11	1.02±0.12	0.462

Continuous variables were represented as mean ±SD and constant variables were represented as number (percentage). The Chi-square Independence was used for constant variables and the two-tailed paired *t*-test was used for continuous variables. A $p<0.05$ was considered as significant. * On antibiotics treatment. Pathologists (three years of experience, blind regarding interventions) of pathological laboratories of the institutes were involved in the analysis; # According to Prostaglandin E Metabolite ELISA Kit; ## According to NGAL ELISA kit; ** According to echocardiograms with the neonatal probe; ### Serum creatinine value >75 μM/L with urine out <0.5 mL/kg/h was considered as acute kidney injury (institutional guideline of pediatrics).

Results

Clinical characteristic features of the preterm infants

Preterm infants, gestational age below 32 weeks with confirmed PDA admitted at the Department of the Neonatal Intensive Care units of the Taihe Hospital, China and Wuhan Maternal and Child Healthcare Hospital, China from 3 January 2015 to 5 July 2018 were included in the analysis. Preterm infants who had congenital chromosomal abnormalities (n=11), heart malformations (n=21), or pulmonary hypertension (n=31) were excluded from analysis. The final analysis was carried out in 288 preterm neonates. With no specific order, the infants were equally divided into 2 groups (ID group and AP group) with 144 preterm infants in each group. A flow diagram of the work-up is presented in Figure 1.

The mean birth weight of the neonates was less than 1500 g. The gestational age and the mean birth weight of the infants in the indomethacin treatment (ID group) were 29.42±2.51 weeks and 1367.53±334.51 g, respectively, and 29.01±2.12 weeks and 1362.3±331.49 g, respectively, in the acetaminophen (AP group). NGAL, analyzed in the urine of infants before treatment, showed a remarkable increase in the urine samples after treatment (Table 1).

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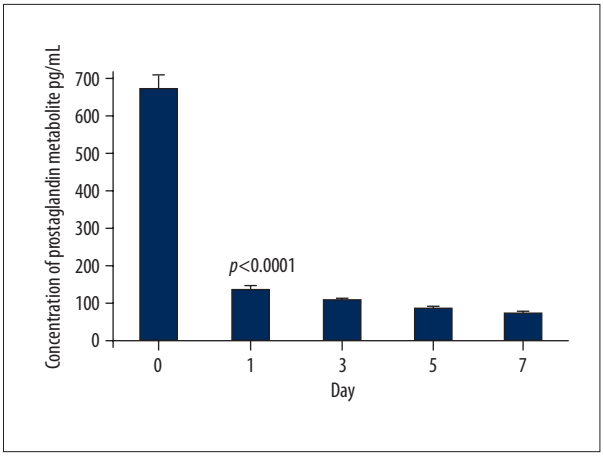

Figure 2. Expression of urinary prostaglandin in preterm infants after treatment with indomethacin. 0: Before treatment. The experiments were performed 3 times and the results are expressed as means and standard deviation of the mean. There were 144 neonates enrolled in each group. A 2-tailed paired *t* test was used for statistical analysis. $p<0.05$ was considered significant. Pathologists (with at least 3 years of experience, blind to interventions) of pathological laboratories of the institutes were involved in the analysis. According to Prostaglandin E Metabolite ELISA Kit.

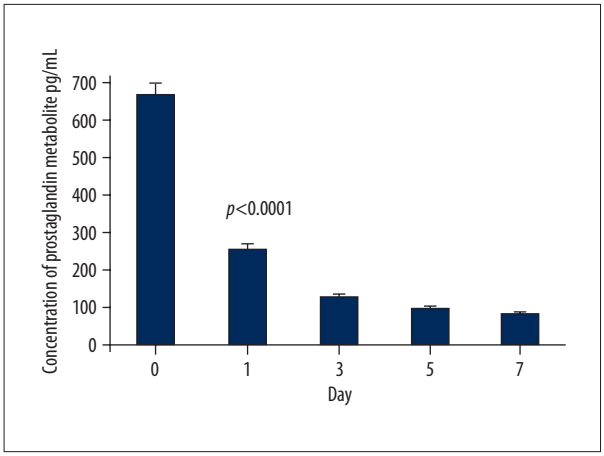

Figure 4. Expression of urinary prostaglandin in preterm infants after treatment with acetaminophen. 0: Before treatment. The experiments were performed 3 times and the results are expressed as means and standard deviation of the mean. There were 144 neonates enrolled in each group. A 2-tailed paired *t* test was used for statistical analysis. A $p<0.05$ was considered significant. Pathologists (with at least 3 years of experience, blind to interventions) at pathological laboratories of the institutes were involved in the analysis. According to Prostaglandin E Metabolite ELISA Kit.

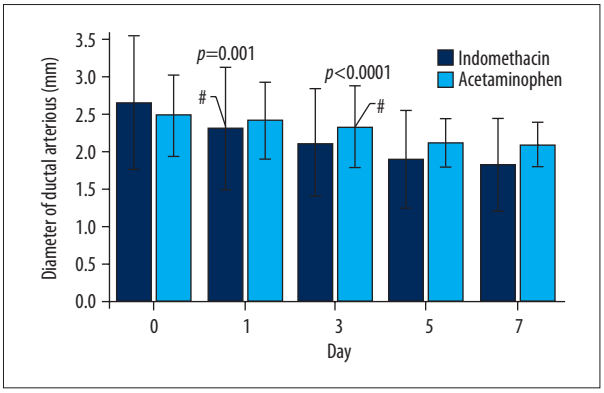

Figure 3. Echocardiographic measurements. The experiments were performed 3 times and the results are expressed as means and standard deviation of the mean. There were 144 neonates enrolled in each group. A 2-tailed paired *t* test was used for statistical analysis. A $p<0.05$ was considered significant. Pediatricians (with at least 3 years of experience, blind to interventions) at the institutes were involved in the analysis. According to echocardiograms with the neonatal probe. # The closure of ductal reported the first time.

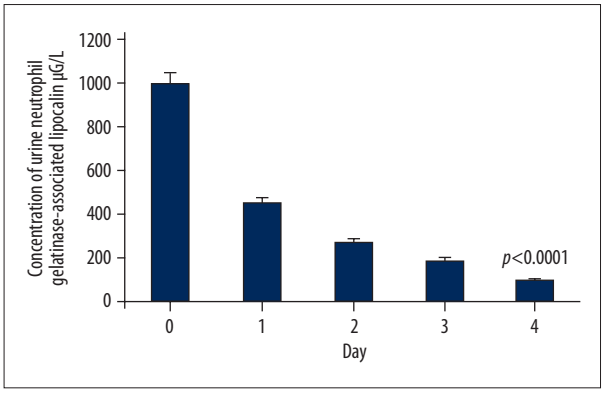

Figure 5. Expression of a urinary neutrophil gelatinase-associated lipocalin in preterm infants after treatment with indomethacin. 0: Before treatment. The experiments were performed 3 times and the results are expressed as means and standard deviation of the mean. There were 144 neonates enrolled in each group. A 2-tailed paired *t* test was used for statistical analysis. $p<0.05$ was considered significant. Pathologists (with at least 3 years of experience, blind to interventions) at pathological laboratories of the institutes were involved in the analysis. According to NGAL ELISA kit.

NGAL and urinary prostaglandin metabolite analysis

Infants in the ID group had showed a significant decrease in prostaglandin (673±32 pg/mL *vs.* 139±7 pg/mL, $p<0.0001$, Figure 2) and ductal closure (2.64±0.89 mm *vs.* 2.31±0.81 mm, $p=0.001$, Figure 3) after the first dose of indomethacin. After the second and the third doses (0.1 mg/kg) of indomethacin (at 24 and 48 h), no ductal reopening of was observed and the

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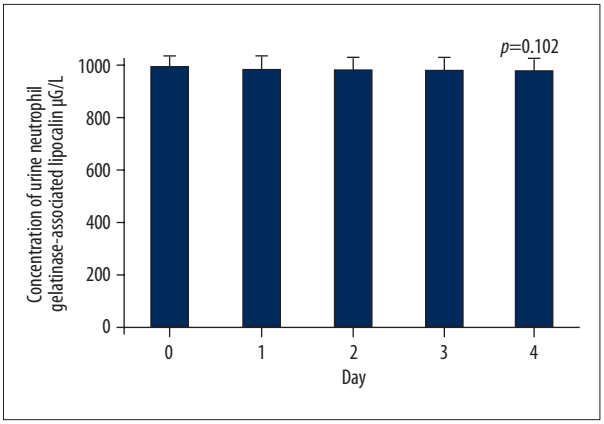

Figure 6. Expression of a urinary neutrophil gelatinase-associated lipocalin in preterm infants after treatment with acetaminophen. 0: Before treatment. The experiments were performed 3 times and the results are expressed as means and standard deviation of the mean. There were 144 neonates enrolled in each group. A 2-tailed paired t test was used for statistical analysis. $p<0.05$ was considered significant. Pathologists (with at least 3 years of experience, blind to interventions) at pathological laboratories of the institutes were involved in the analysis. According to NGAL ELISA kit.

level of prostaglandin in urine was significantly reduced ($p\leq0.05$ for both). After the first dose of acetaminophen, infants of the AP group showed a slight reduction in prostaglandin synthesis (667±31 pg/mL *vs.* 257±13 pg/mL, $p<0.0001$, Figure 4) but no change in ductal closure (2.47±0.54 mm *vs.* 2.41±0.51 mm, $p=0.333$). Reduced prostaglandin levels and ductal closure were observed after the second dose of acetaminophen (667±31 pg/mL *vs.* 129±7 pg/mL, $p<0.0001$ for urinary prostaglandin; 2.47±0.54 mm *vs.* 2.32±0.55 mm, $p=0.02$ for ductal closure) and after the third dose (667±31 pg/mL *vs.* 96±5 pg/mL, $p<0.0001$ for urinary prostaglandin; 2.47±0.54 mm *vs.* 2.11±0.31 mm, $p<0.0001$ for ductal closure).

After treatment with indomethacin, the NGAL was significantly reduced, and there was a further, but very slight reduction after the third dose (993±48 μG/L *vs.* 103±5 μG/L, $p<0.0001$, Figure 5). In contrast, no such reduction in NGAL was observed after the third dose of acetaminophen (989±47 μG/L *vs.* 980±46 μG/L, $p=0.102$, Figure 6).

Renal function evaluation

After the third dose of indomethacin, we found lower urinary albumin ($p=0.0006$), less fractional excretion of sodium ($p<0.0001$), and less acute kidney injury ($p=0.042$). Indomethacin treatment improved urine output ($p=0.017$) in the preterm neonates with PDA, but no such change was observed with acetaminophen (Table 2).

Discussion

In the present analysis, the efficacy and the role of indomethacin and acetaminophen were analyzed in the urine samples of preterm neonates with PDA. Prostaglandin has a role in failure

Table 2. Renal functions evaluations.

Parameters	Groups						Comparisons between groups
	ID			AP			
Intervention	Indomethacin			Acetaminophen			
Level	BL	EL	SA	BL	EL	SA	
Neonates enrolled in the study (sample size)	144	144	*p*	144	144	*p*	*p*-Value
Urine output (mL/kg/h)	1.01±0.11	1.11±0.12*	<0.0001	1.02±0.12	1.08±0.09	<0.0001	0.017
Serum creatinine (μM/L)	77.86±6.52	74.95±5.13	<0.0001	76.76±5.92	75.81±4.01	0.112	0.114
Urinary albumin (mg/L)	63.36±8.13	59.11±7.42*	<0.0001	64.01±8.89	62.12±7.21	0.049	0.0006
Fractional excretion of sodium	3.71±1.05%	2.11±0.81%*	<0.0001	3.67±1.01%	3.01±0.99%	<0.0001	<0.0001
Acute kidney injury##	9 (6)	1 (1)*	0.024	10 (7)	8 (6)	0.808	0.042

BL – at the time of enrollment; EL – after the third dose of intervention; SA – statistical analysis between BL and EL. Continuous variables were represented as mean ±SD and constant variables were represented as number (percentage). The Chi-square Independence was used for constant variables and the two-tailed paired *t*-test was used for continuous variables. A $p<0.05$ was considered as significant. * Significant effect of indomethacin treatment than acetaminophen treatment. ## Serum creatinine value >75 μM/L with urine out <0.5 mL/kg/h was considered as acute kidney injury (institutional guideline of pediatrics).

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of the ductus arteriosus to close. Indomethacin, ibuprofen, and acetaminophen have the ability to inhibit prostaglandin by acting on the enzyme cyclooxygenase [1,18], and ibuprofen is associated with some renal effects, pulmonary hypertension, and hyperbilirubinemia [22]. Therefore, it is important to be careful when selecting drugs for use in treating PDA in neonates.

In this analysis, we found a significant reduction of prostaglandin and improved closure of the ductal arteriosus in the neonates with PDA even after the first dose of indomethacin treatment. These findings agree the findings of Pezzati et al., who observed ductal arteriosus closure even after the first dose [23]. Another study found 66.7% ductal closure after injecting indomethacin [24]. In addition to indomethacin, acetaminophen also effectively reduces prostaglandin levels after the second dose, and 46% PDA closure was observed after acetaminophen treatment [24]. Many reports have shown the effectiveness of indomethacin in PDA treatment, and this can be considered as a standard drug of choice for PDA treatment [1,25]. However, because indomethacin can have adverse effects, drugs such as acetaminophen and ibuprofen have been used. However, these 2 drugs also have adverse effects, and their efficacy is lower when compared to indomethacin [26]. The present analysis explains the effectiveness of indomethacin in PDA treatment.

We found that indomethacin not only inhibits prostaglandin, but also reduces the level of NGAL in urine samples. NGAL is a molecular protein with 25kDa, which belongs to the lipocalin family and is highly expressed in injured nephrons [27]. NGAL is present in low concentration in the respiratory, gastrointestinal, and urinary tracts, and its expression is very high during inflammation or ischemic conditions [11–13]. NGAL is considered to be a specific marker for detecting severe renal problems [28]. NGAL is also one of the reasons why PDA, if untreated, results in acute kidney infection and finally leads to renal failure [16]. Due to the opening of ductus arteriosus in preterm neonates with PDA, there is an abnormal level of cardiac circulation and renal perfusion, which in turn elevate the intensity of NGAL [17]. It has also been reported that the diameter of the PDA is an indicator of high NGAL production and is associated with high mortality [3,29,30]. Some other reports found low levels of NGAL in urine in neonates who have higher gestational age and birth weight, since they have the capacity to metabolize renal metabolites [14,15,31]. In addition, ibuprofen, indomethacin, and acetaminophen can alter renal function [10,32]. Our findings show that indomethacin significantly reduced the level of NGAL in the urine of infants with PDA. Although this reduction was not observed with acetaminophen administration, acetaminophen does reduce prostaglandin levels and can help close the ductus arteriosus, as well as having an effect on renal dysfunction. In contrast, indomethacin not only reduces prostaglandin levels, but also reduces the NGAL level, which means it plays a vital role in ductus arteriosus closure, even after the first dose, in contrast to acetaminophen.

The main reason behind such results is that indomethacin reduces the NGAL level and lowers the risk of renal failure; hence, the neonates can metabolize it and there is proper perfusion of circulation and renal functioning. Therefore, the risk factor related to PDA overcome within a short period of time and the morbidity and mortality rate also decreased.

The limitations of the present study include, lack of randomization and the fact that pathologists from only 2 pathology laboratories were involved in the analysis. Further studies should be carried out to investigate the molecular mechanism by which indomethacin affects NGAL, and such research may lead to discovery of new methods for preventing PDA without any adverse effects.

Conclusions

Intravenous injection of indomethacin and acetaminophen significantly reduces the synthesis of prostaglandin. However, the efficacy of indomethacin has been shown to be due to the capability of reducing urinary neutrophil gelatinase-associated lipocalin in the urine of neonates with patent ductus arteriosus. Hence, this analysis shows the superior safety and effectiveness of indomethacin in reducing the risk of patent ductus arteriosus compared to acetaminophen. These findings may improve management and promote new paradigms in treating neonates with patent ductus arteriosus.

Acknowledgments

The authors are thankful to all medical and non-medical staff of Taihe Hospital, Hubei University of Medicine, Shiyan, China and Wuhan Maternal and Child Healthcare Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

Conflict of interest

None.

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