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Comparison of the Efficacy and Complications of Oral versus Intravenous Ibuprofen in Low-birth-weight Neonates with Patent Ductus Arteriosus: A Retrospective Cohort Study

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ABSTRACT

Background: Patent ductus arteriosus (PDA) is associated with morbidity in preterm neonates. This study aimed to compare the efficacy of oral versus intravenous Ibuprofen in preterm neonates with PDA.

Methods: 80 low birth weight neonates (gestational age <37 weeks) with PDA were enrolled in this retrospective cohort study. Both groups received an equal dose of 10mg/kg followed by 5 mg/kg for 2 days. In the first group, ibuprofen was administered intravenously and in the second group, it was administered via the oral route. PDA was initially confirmed by echocardiography.

Results: Gestational age in the two groups ranged from 29 to 36 weeks. PDA remained open in 3 patients in the IV group (7.5%) and 1 patient in the oral ibuprofen group (2.5%). Although complications' were on average lower in neonates treated with IV ibuprofen, this difference was not significant. Similarly, the PDA closure rate did not differ significantly between the groups. However, in the oral group, the PDA closure rate was 39 (97.5%) after the third treatment course (95% CI: 86.8%–99.9%) while in the IV group, the PDA closure rate was 37(92.5%, 95% CI: 79.6%–98.4%). Compared to infants treated with intravenous ibuprofen, the rate ratio and rate difference of PDA closure were estimated at 0.94 (95% CI: 0.85, 1.04) and -0.05 (95% CI: -0.14, 0.04), in orally treated patients, respectively.

Conclusion: This study suggested that oral ibuprofen is as effective as intravenous ibuprofen for the management of PDA in pregnant women with gestational age <37 weeks. In fact, oral ibuprofen is an alternative to intravenous ibuprofen with lower side effects for the treatment of preterm neonates with PDA.

Keywords: Echocardiography, Ibuprofen, Neonate, Patent ductus arteriosus

Introduction

Patent ductus arteriosus (PDA) is associated with respiratory complications and severe hemodynamic diseases, particularly in preterm newborns. Other morbidities linked to ductal patency include pulmonary hemorrhage, bronchopulmonary dysplasia (BPD), severe respiratory distress syndrome (RDS), prolonged assisted ventilation, necrotizing enterocolitis (NEC), renal dysfunction, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), cerebral palsy, and death (1, 2).

Literature has demonstrated an inverse relationship between the onset of PDA and the gestational age of neonates at the time of delivery. The arterial duct remains patent up to 4 days in 10% of neonates born at 30–37 gestation weeks, 80% of neonates born between 25-28 weeks, and 90% of neonates born earlier than 24 weeks of gestation (3, 4).

The treatment of choice for PDA is

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cyclooxygenase inhibitors such as indomethacin and ibuprofen (5). A study showed that ibuprofen can close ductal patency in 70 to 85% of patients (6). However, cyclooxygenase inhibitors are not 100% safe for patients and adverse effects such as decreased platelet aggregation, peripheral vasoconstriction, hyperbilirubinemia, gastrointestinal bleeding and perforation, and renal failure are expected (7).

Pharmacokinetically, the oral intake of ibuprofen contributes to its rapid absorption with its concentration peaking after 1-2 h in premature infants and those over 3 months of age. Besides, oral ibuprofen is cheaper and more accessible than the IV form though slight variations are observed in the pharmacokinetics of the oral form among different individuals. Despite the high success rate of oral Ibuprofen in the closure of PDA, its administration via the oral route is associated with a high incidence of adverse effects (8). As opposed to the oral form, the intravenous administration of ibuprofen does not reduce its concentration in renal, mesenteric, or cerebral blood flow (9). Hence, one may wonder whether the intravenous form may yield more effective results. To date, there is no assurance and solid evidence indicating that oral Ibuprofen is more efficient than IV Ibuprofen in the closure of PDA.

It has been shown that preterm infants suffering from PDA are at higher risk of mortality and morbidity. On the other hand, the pharmacological response is strongly dependent on a patient's gestational age. In light of the above, this retrospective cohort was conducted to compare the efficacy of oral versus intravenous ibuprofen for the closure of PDA and shed light on its positive and negative dimensions in high-risk preterm infants.

Methods

This retrospective cohort study was approved by the Ethics Committee of the University of Medical Sciences (IR.ARAKMU.REC.1400.212). Informed consent was obtained from all guardians of neonates.

In this study, participants consisted of all premature infants with a gestational age <37 weeks, who were referred to the neonatal intensive care unit (NICU) at Talaghani Hospital ARAK. After obtaining parental consent, the neonates born between July 2016 and November 2019 were enrolled in the study. The sample size was calculated according to the previous research, with a first-type error of 5%, a test power of 80%, and an effect size of 0.64 between the two study groups. Using G * Power software, a sample size of n=40 patients was estimated for each group (10, 11). In many of the moderate-late preterm infants, PDA would close spontaneously within a few days to a week after birth. Therefore, infants whose PDA remained open during the first week were deemed eligible for the study.

The inclusion criteria consisted of newborns with a gestational age of <37 weeks, postnatal age ≤ 10 days, a definitive PDA diagnosis by echocardiography, parental consent, and birth weight ≤2500 g.

The sampling method of the study is shown in Figure 1.

Patients with congenital life- threatening chromosome anomalies, other congenital heart diseases, a history of asphyxia at birth, sepsis, severe coagulopathy or liver dysfunction, platelet count < 50000/mm3, necrotizing enterocolitis, interventricular hemorrhage (IVH), signs of bleeding (blood in the endotracheal or stools, or oozing from the puncture site), serum creatinine > 1/6 mg/dl, and urine output <1 mL/kg/hour were excluded from the study.

Intravenous ibuprofen was administrated to 40 neonates in group II (a single dose of 10mg/kg IV stat, followed by 5 mg/kg for 2 days) by a syringe pump over 15 min. To prevent medicine loss, line flushing with the isotonic normal saline was performed.

Group I consisted of 40 neonates receiving oral ibuprofen. The oral route consisted of a syrup of Pruvil, and 120 mL/5 mL oral suspension containing 100 mg, 312 mOsmol/L, which was stabilized with propylparaben, methylparaben, and sodium benzoate. By the same token, infants in Group I received suspensions equal to 10mg/kg, followed by 5 mg/kg for 3 days through an orogastric tube. In other words, infants received ibuprofen either orally or intravenously at the dose of 10, 5, 5 mg/kg every 24 h for 3 days. The OG tube was flushed with 1 ml of sterile water after each oral administration. Infants had an enteral feeding regiment from the first day of study.

In the course of treatment, all infants were reassessed by a pediatric cardiologist based on echocardiography with a 5-7 MH2 transducer (model: mylab 70) to determine whether further intervention is warranted.

Regarding the infants' diet, the fluid-based diet was started at 70 to 80 ml/kg per day for all neonates with a daily increase rate of 10 to 20 ml/kg to reach a maximum of 150 ml/kg per day. Infants with severe respiratory distress were supported by mechanical ventilation or

nasal CPAP (continuous positive airway pressure).

Additionally, the participants' renal function was investigated by measuring the serum creatinine, BUN, and urine output before and after the intervention. A closed PDA after the treatment course, as proven by echocardiographic studies, was deemed as proof of treatment success.

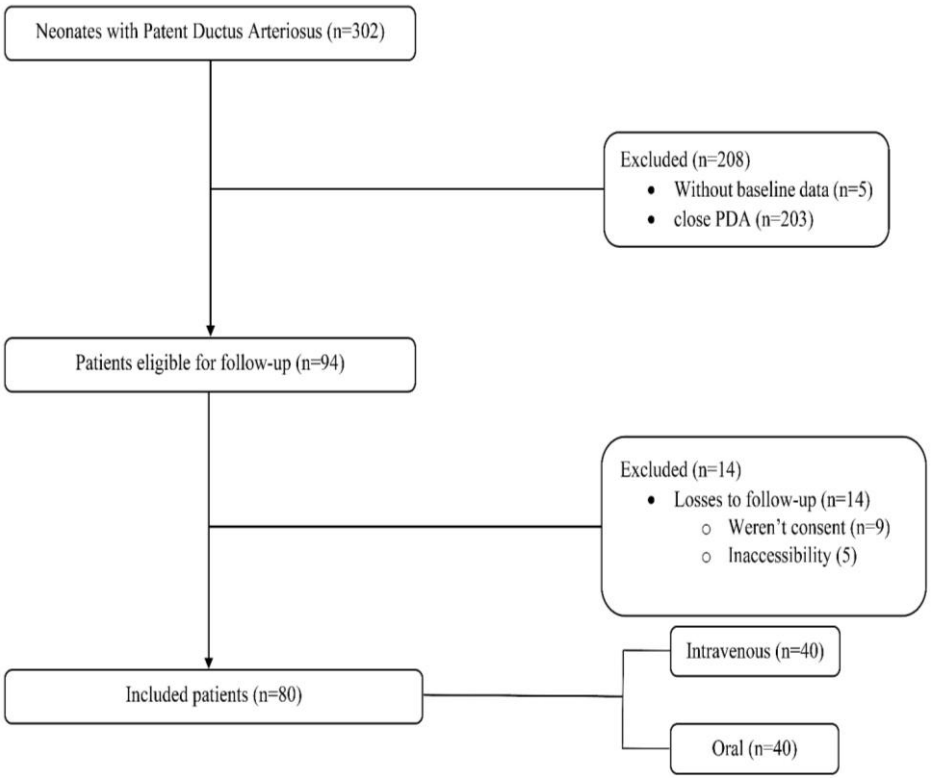

Figure 1. Flow diagram of patients' recruitment

Statistical analysis

After ensuring randomization and blinding, data analysis was performed using the IBM SPSS19 (IBM SPSS Inc, Chicago, IL, USA). A P-value <0.05 was considered significant. Descriptive and inferential statistics were used for data analysis. In descriptive analyses, quantitative and categorical data were presented as mean ± standard deviation (minimum-maximum) and frequency (percentage). As for quantitative variables, intra-group and inter-group comparisons were made using paired samples t-test, and independent samples t-test, respectively. As regards categorical variables, an inter-group comparison was drawn using the Chi-square test (or Fisher's exact test). The risk ratio (RR) and risk difference (RD) were calculated for PDA closure.

Results

In this study, infants had a gestational age of 29 to 36 weeks. The minimum and maximum weight measures were 750 and 2500 gr, respectively. Both groups did not exhibit any complications such as gastrointestinal bleeding (GIB), necrotizing enterocolitis (NEC), and sepsis during the intervention. During of course of the study, one patient in the intravenous group and two patients from the oral group expired. All three cases died of RDS. Cranial sonography did not show intraventricular hemorrhage in infants. PDA remained open in 3 patients in the IV group (7.5%) and 1 patient in the oral ibuprofen group (2.5%) after the first treatment course. Nasal continuous positive airway pressure (CPAP) and mechanical ventilation support with intermittent positive pressure ventilation (NIPPV, SIMV, AC) were observed in both groups with the same mean duration. However, complications were reported 12 neonates who had received oral ibuprofen. Nonetheless, there has been no significant difference between the groups.

The clinical characteristics of the preterm infants are listed in Table 1. As can be seen, there was no significant difference between the two groups in terms of baseline features. Generally,

the complication rate was numerically lower in neonates treated with IV ibuprofen; however, there was no significant difference between intravenous and oral ibuprofen groups.

Table 2 outlines the results of laboratory tests run for all patients before and after the intervention.

Table 1. Baseline and Clinical Characteristics

Variables	Intravenous Ibuprofen (N=40)	Oral Ibuprofen (N=40)	P-value*
Gender (F/M), No. (%)	13/17	15/15	0.605
Gestational age, week	32.12±2.95	32.45±2.11	0.567
Age at the start of treatment (d)	5.11±2.13	5.26±3.18	0.805
Birthweight, Kg	2.14±0.25	2.17±0.14	0.510
Mean arterial pressure (mmHg)	29.86 ± 6.73	28.94±7.61	0.568
Pulse pressure (mmHg)	13.32±9.68	14.75±8.49	0.485
Normal vaginal delivery (NVD), No.	26	28	0.633
RDS, n (%)	36	38	0.675
Surfactant, No. (%)	39	36	0.359
Total Complications (n)	9	13	0.446
NEC (n)	1	3	0.615
Sepsis (n)	3	5	0.712
IVH (n)	5	1	0.201
Gastrointestinal bleeding (after total dose)	0	4	0.116
Pulmonary hypertension	32	35	0.051
Mechanical ventilation(n)	24	27	0.244
BUN, mmol/L (pre-treatment)	4.10±2.62	4.03±2.48	0.903
BUN, mmol/L (post- treatment)	4.68±2.54	4.11±1.14	0.201
Cr (pre- treatment) (mg/dL)	1.01±0.33	1.02±0.47	0.913
Cr (post- treatment) (mg/dL)	1.02±0.62	1.03±0.74	0.806
Urine amount (ml/kg/ h) (before treatment)	2.31±0.29	2.27±0.13	0.429
Urine amount (ml/kg/ h) (after treatment)	2.47±0.72	2.83±0.96	0.793
Bil (post treatment) (mg/dL)	5.62± 3.01	5.79± 3.47	0.815
Bil (pre- treatment) (mg/dL)	7.35 ± 2.61	7.42 ± 2.83	0.909
PH (post- treatment)	22.13±9.47	23.23±8.62	0.588
PH (pre- treatment)	29.46±4.85	30.98±2.71	0.089

***** P-Value was calculated by paired t test at 95% of CI

BUN; Blood urea nitrogen: / CR; creatinine: / OB : occult blood; / NEC :necrotizing enterocolitis / IVH : interventricular hemorrhagic / PH : pulmonary hypertension / Bil : Hyperbilirubinemia

Compared to the baseline lab results, the mean serum levels of BUN and Cr as well as the urine output were significantly higher after treatment. However, the mean levels of bilirubin and PH were significantly higher before the treatment.

The echocardiography findings of low birthweight neonates before treatment are summarized in Table 3. No significant difference was between the two groups in the mean and standard deviation of ductus arteriosus before the treatment.

According to Table 4, the closure success rate did not vary significantly between the infants treated with oral and IV ibuprofen after the first course of treatment. Nevertheless, the infants receiving ibuprofen via the oral route exhibited a PDA closure rate of 97.5% (39 cases) after the third course of treatment (95% CI: 86.8%–99.9%). On the other hand, infants in the IV ibuprofen group demonstrated a closure rate of 92.5% (37 cases)

Table 2. Laboratory markers

	Intravenous Ibuprofen		P-value	Oral Ibuprofen		P-value
	Before	After		Before	After	
BUN, mmol/L	4.10±2.62	4.68±2.54	<0.001*	4.03±2.48	4.11±1.14	<0.001*
Cr (mg/dL)	1.01±0.33	1.02±0.62	<0.001*	1.02±0.47	1.03±0.74	<0.001*
Urine amount (ml/kg/ h)	2.31±0.29	2.47±0.72	<0.001*	2.27±0.13	2.83±0.96	<0.001*
Bil (mg/dL)	7.35 ± 2.61	5.62± 3.01	<0.001*	7.42 ± 2.83	5.79± 3.47	<0.001*
PH(mmHg)	29.46±4.85	22.13±9.47	<0.001*	30.98±2.71	23.23±8.62	<0.001*

P-value was calculated by the paired t test at CI=95%, PH: pulmonary hypertension

Table 3. Echocardiography findings at the Baseline

	Intravenous Ibuprofen (N=40)	Oral Ibuprofen (N=40)	P-value
Diameter (mm)	1.87 ± 0. 52	1.62 ± 0.94	0.146
Qp: Qs ratio shunt	1.32±0.48	1.48±0.62	0.201
Systolic PAP (mm Hg)	32.13±4.19	31.61±5.98	0.654

Diastolic PAP (mm Hg)	10.49 ±6.42	11.29±5.73	0.558
PDA mean velocity in systolic phase (m/ s)	1.5 ± 0.83	1.6±0.79	0.583
LA/Ao ratio	2.1±0.96	2.2±0.58	0.575

PAP: pulmonary arterial pressure. LA/Ao ratio: Left atrium/aorta root diameter

Table 4. Outcomes of Each Treatment

	Intravenous Ibuprofen (N=40)	Oral Ibuprofen (N=40)	P-value	RR (95% CI)	RD (95% CI)
PDA closure rate after the first dose					
No	8 (20.0)	9 (22.5)	0.785$	0.96 (0.77, 1.21)	-0.025 (-0.20, 0.15)
Yes	32 (80.0)	31 (77.5)			
PDA closure rate after the second dose					
No	3 (7.5)	1 (2.5)	0.615*	0.94 (0.85, 1.04)	-0.05 (-0.14, 0.04)
Yes	37 (92.5)	39 (97.5)			
PDA closure rate after the third dose					
No	3 (7.5)	1 (2.5)	0.615*	0.94 (0.85, 1.04)	-0.05 (-0.14, 0.04)
Yes	37 (92.5)	39 (97.5)			

$ P-value was calculated by Chi-square

* P-value was calculated by Fisher's exact test

after the third course (95% CI: 79.6%–98.4%). According to the inter-group comparisons, RR and RD estimates of PDA closure rate were 0.94 (95% CI: 0.85, 1.04) and -0.05 (95% CI: -0.14, 0.04) after the third treatment course, respectively in patients treated via the oral route.

Discussion

PDA is a common cardiac disease among premature infants. An open vascular channel between the lungs and the heart, this arterial duct remains patent after birth due to the immature development, which could be life-threatening for newborns. The treatment of choice is indomethacin, a medicine that can successfully close PDA in the majority of infants. However, indomethacin may induce serious side effects such as low blood flow and hypoperfusion in several organs. Hence, ibuprofen has been introduced as an alternative medicine. As effective as indomethacin in PDA closure, Ibuprofen reduces the risk of NEC and transient renal insufficiency. As such, ibuprofen appears to be a safer drug of choice. A recent review shed further light on the effectiveness of ibuprofen versus paracetamol. Oro-gastric administration of ibuprofen is as effective as IV administration. There is, nevertheless, a paucity of research on evaluating the effect of ibuprofen on longer-term outcomes in infants with PDA (12).

It has been shown that ibuprofen absorption is slower via the oral route with a longer half-life, which may provoke better responses (8). However, determining the bioavailability of IV and oral Ibuprofen warrants further studies.

The use of IV ibuprofen may be associated with unfavorable outcomes due to limited accessibility and higher prices as opposed to its oral form. Should scientists prove that the oral form is as effective as the IV form without serious complications, prescribing ibuprofen via the oral route will be more convenient. In this study, participants consisted of 80 low birth weight (LBW) preterm infants with a definitive diagnosis of PDA. The baseline echocardiographic findings did not differ significantly between the groups. The model presented in this study could effectively evaluate the efficacy of oral and IV ibuprofen in the closure of PDA. The results showed that oral ibuprofen slightly outperformed the IV form following one course of treatment [IV= 37(92.5), Oral= 39 (97.5%), P= 0.615], but this difference was not statistically significant. A randomized study by Fakhraee et al. (13) suggested that the patent duct was successfully closed in all 18 preterm neonates (GA=34 weeks) treated with oral ibuprofen, but in only 15 out 18 patients treated with oral indomethacin (P=0.05), the patent duct was closed. In their open-trial study, Heyman et al. reported PDA closure in 20 out of 21 (95.2%) infants treated with an incomplete course of oral ibuprofen (14).

Another randomized pilot study (15) revealed that 7 out of 9 patients treated with oral ibuprofen and 10 out of 12 those treated with intravenous indomethacin had successful closure of PDA closure (p=0.75). Aly et al. explored the effect of oral ibuprofen in neonates with PDA, reporting 83% success in the treatment of their patients and PDA closure after the treatment course (15). Applying a similar protocol for ibuprofen administration in our patients, we found a similar rate of PDA closure after two courses of treatment with ibuprofen (97% closure).

In addition, Heyman et al. registered a PDA

closure rate of 95.5% (14), which is somehow akin to our study. Contrary to our results, Cherif et al. reported a PDA-closure rate of 70% in preterm infants after the administration of oral ibuprofen, which was lower than our study (14). Hence, the success rate varies mildly between studies with regard to the assessment of the oral administration of ibuprofen.

In another meta-analysis, a high dose of oral ibuprofen was found to be associated with a higher closure chance of symptomatic PDA as opposed to the standard doses of IV ibuprofen or IV indomethacin (16).

In line with our results, other evidence indicates that intravenous administration of ibuprofen is more likely to fail in the closure of the duct than the oral form (10, 14). However, those studies investigated preterm infants with very low birth weight and treated their patients immediately after birth, which is distinct from our study sample.

The findings of the present study suggested that oral ibuprofen yielded better outcomes than IV ibuprofen. Nevertheless, treatment efficacy was almost identical in both groups. The results of a study demonstrated the relationship between postnatal age, clearance of the drug and the level of blood drug. It found that serum ibuprofen concentration rose four days after birth (17). Sharma et al (6) showed IV ibuprofen has a higher peak plasma concentration, a prolonged time to peak plasma concentration, and a lower area under the curve (AUC). Compared to intravenous ibuprofen, the oral administration of ibuprofen has a lower peak plasma concentration, but even the first dose of oral drugs induces therapeutic effects (18). This implies that even a lower plasma drug level might be sufficient for the closure of PDA with fewer adverse effects. In the same vein, Barzilay et al.,(19) proved that AUC0-24 is higher in the oral form of ibuprofen than in the IV form, leading to a higher rate of ductus arteriosus closure. Heyman et al. (20) reported that responses can be observed within a single dose of the drug. It should be borne in mind that the medicine's half-life, time-plasma concentration curve, and plasma levels of drug vary remarkably when prescribed to preterm infants. As reported in another study, ibuprofen, if used at older postnatal ages, is more likely to be ineffective in closing the ductus arteriosus in preterm neonates, , even at higher dosages. They further claimed that the optimal window for the pharmacological treatment of PDA in preterm neonates is the first days of life (21).

However, an association has been found between the plasma concentration of the drug and its effect on the closure of ductus. The pharmacokinetic features of oral ibuprofen are still subject to debate. Therefore, an appropriate dose has yet to be determined.

Nevertheless, the loading dose is a crucial strategy for infants with PDA. Literature shows that a high dose of ibuprofen for PDA closure is more effective than a normal dose (22). In the present study, a dose of 10 mg/kg was administrated on the first day, followed by 5 mg/kg on the next two days in both groups. This dosage has already been approved for the closure of PDA. However, Some studies have demonstrated that more effective results can be achieved in infants treated with higher doses of ibuprofen. Moreover, no difference was observed in the side effects of high or low doses of ibuprofen. Thus, it can be concluded that higher doses of ibuprofen are sufficiently safe with greater efficacy (17). However, in this study, attempts were made to use the lowest dosage of ibuprofen to minimize the potential side effects.

As far as safety is concerned, IV form has been shown to trigger complications such as NEC, pulmonary hypertension, GI bleeding or perforation, renal tolerance and intraventricular hemorrhage. The results of a meta-analysis suggested that both oral and IV can contribute to the prevention of NEC. They reported less gastrointestinal bleeding following treatment with oral ibuprofen (23). The present study, however, did not show any significant difference in GI bleeding and NEC in both groups. Given the inconsistent results reported in the literature, further research is warranted to draw inclusive conclusions about the GI safety of oral ibuprofen in LBW neonates with open PDA, especially those with low gestational age. Hence, higher gastrointestinal complications with oral intake of hyperosmolar ibuprofen suspensions in preterm infants are reasonably expected (10, 11).

We found that 9(22.5%) and 12(30%) of cases experienced complications with IV and oral ibuprofen administrations, respectively. Except for IVH (12.5%), other complications such as sepsis (12.5%), GIB (10%) and NEC (7.5%) were less common in infants treated with IV form. However, the risk of IVH cannot be ruled out at any cost. Intraventricular hemorrhage (IVH) (odds ratio [OR]: 5 P: 0.04) and BW were found to increase mortality (OR: 0.87 P: 0.034). Alsafadi et al. reported that conservative treatment (OR:

1.4, P = 0.38), paracetamol (OR: 0.87, P = 0.22), and ibuprofen (OR 1.2, P = 0.12) had no effect on mortality (24).

In the present study, gastrointestinal bleeding was observed in 4 neonates treated with oral ibuprofen, but no GI bleeding was reported in the IV group. This finding is aligned with those reported by Cherif et al. Further, NEC was observed in 2.7% of subjects in the IV group and 7.5% of subjects in the oral group. Cherif et al reported NEC only in one (3.1%) neonate in the IV group (14). in another study on neonates treated with oral ibuprofen,19 patients (12.6%) reported GI bleeding (13, 20, 25)

In their report, osmolality and PH were 312 mOsmol/L and 5.8, respectively. This suggests that GI bleeding could be dependent on the manner of oral administration.

Infants have renal insufficiency, which is triggered by physiological reasons at this age. This can be attributed to two reasons: 1- vascular resistance is high in infant kidneys 2- Infants receive only a small fraction of the cardiac output (26). The elevated renal flow and vasodilation of vessels are highly associated with the functions of prostaglandins in the body, which can be affected by ibuprofen and indomethacin. However, renal side effects are also evident due to the limitation of metabolizing enzymes. To evaluate renal complications, we measured three variables of Cr, BUN, and urine output. According to the results, there were no significant differences between the two groups.

Tiker et al., (27) and Erdeve et al (26) treated very low birthweight infants with oral ibuprofen recovered from renal complications. Also, Cherif et al (14, 19) reported that 3 (9.3%) neonates in the IV group of their study presented renal failure, while none of the subjects in the oral group reported renal impairment. Previous studies showed that the level of creatinine is low in the oral group (28). In addition, Gokmen et al., (19) suggested that cystatin C, as a marker of glomerular filtration rate, is high in the oral group. Therefore, cystatin-C can be a better predictor of possible renal failure after taking oral ibuprofen (26).

In light of the above evidence, preterm infants with PDA can benefit from both oral and IV ibuprofen as acceptable alternatives to the PDA treatment. Overall, the findings of this study favor the oral ibuprofen over IV ibuprofen.

One limitation of this study was its limited sample size. Further multicentral studies are required to achieve more reliable results. Hence, the measurement of PGE2 in plasma and urine is recommended to r predict the possibility of renal failure and GI complications in neonates with PDA. Another limitation of the current study was that ibuprofen plasma levels and serum cystatin-C levels were not measured.

Conclusion

This study showed that oral ibuprofen is as effective as IV ibuprofen for the treatment of PDA. Indeed, oral ibuprofen is an alternative to IV ibuprofen with lower complications. The complications reported in the oral group were identical to those treated with IV ibuprofen.

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Conflicts of interest

The authors have no conflict of interest to report

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