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ORIGINAL ARTICLE

Comparative study of the efficacy and safety of paracetamol, ibuprofen, and indomethacin in closure of patent ductus arteriosus in preterm neonates

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Abstract In this prospective study, we compared the efficacy and side effects of indomethacin, ibuprofen, and paracetamol in patent ductus arteriosus (PDA) closure in preterm neonates. Three hundred preterm neonates with hemodynamically significant PDA (hs-PDA) admitted at our neonatal intensive care unit were enrolled in the study. They were randomized into three groups. Group I (paracetamol group) received 15 mg/kg/6 h IV paracetamol infusion for 3 days. Group II (ibuprofen group) received 10 mg/kg IV ibuprofen infusion followed by 5 mg/kg/day for 2 days. Group III (indomethacin group) received 0.2 mg/kg/12 h indomethacin IV infusion for three doses. Laboratory investigations such as renal function test, liver function test, complete blood count, and blood gases were conducted in addition to echocardiographic examinations. All investigations were done before and 3 days after treatment. There was no significant difference between all groups regarding efficacy of PDA closure ($P = 0.868$). There was a significant increase in serum creatinine levels and serum blood urea nitrogen (BUN) in the ibuprofen and indomethacin groups ($P < 0.001$). There was a significant reduction in platelet count and urine output (UOP) in both ibuprofen and indomethacin groups ($P < 0.001$). There was a significant increase in bilirubin levels in only the ibuprofen group ($P = 0.003$). No significant difference of hemoglobin (HB) level or liver enzymes in all groups ($P > 0.05$). Ventilatory settings improved significantly in patients with successful closure of PDA than those with failed PDA closure ($P < 0.001$).

Conclusion: Paracetamol is as effective as indomethacin and ibuprofen in closure of PDA in preterm neonates and has less side effects mainly on renal function, platelet count, and GIT bleeding.

What is Known:
- *Hemodynamically significant patent ductus arteriosus has many complications for preterm and low birth weight neonates and better to be closed. Many drugs were used for medical closure of PDA* e.g. *indomethacin, ibuprofen and recently paracetamol. Many studies compare safety and efficacy of paracetamol with either indomethacin or ibuprofen.*

What is New:
- *It is the first large study that compares the efficacy and side effects of the three drugs in one study.*

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Keywords PDA closure · Preterm neonate · Paracetamol · Ibuprofen · Indomethacin

Abbreviations

BUN	Blood urea nitrogen
COX	Cyclooxygenase
GIT	Gastrointestinal tract
HB	Hemoglobin

Hs-PDA	Hemodynamically significant patent ductus arteriosus
IV	Intravenous
IVH	Intraventricular hemorrhage
MV	Mechanical ventilation
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
NSAID	Nonsteroidal anti-inflammatory drugs
PDA	Patent ductus arteriosus
PG	Prostaglandin
PIP	Positive intermittent pressure
ROP	Retinopathy of prematurity
SGOT	Serum glutamate-oxaloacetic transaminase
SGPT	Serum glutamate-pyruvate transaminase
UOP	Urinary output

Introduction

Patent ductus arteriosus (PDA) is a common complication in preterm neonates with incidence of 30–67% in extremely preterm neonates (gestational age <26 weeks) [10]. The left-to-right shunt caused by the PDA results in increased pulmonary blood flow and increased incidence of further comorbidities such as chronic lung disease, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and retinopathy. Therefore, closure of the PDA is essential to prevent these complications and to improve both cardiorespiratory status and survival rate [11, 13, 27].

Prostaglandins (PG) play a major role in patency of PDA. So, cyclooxygenase inhibitors are conventionally used to induce its closure such as indomethacin and ibuprofen which are nonselective cyclooxygenase inhibitors. Both indomethacin and ibuprofen were recorded to be successful in ductal closure in 70% of cases. Indomethacin and ibuprofen compete with the arachidonic acid substrate for the active cyclooxygenase site. Therefore, the potency of these drugs is influenced by endogenous arachidonic acid levels. Nevertheless, they can cause weakened platelet aggregation, hyperbilirubinemia, peripheral vasoconstriction, and decreased organ blood flow with subsequent renal dysfunction and gastrointestinal perforations [25].

Moreover, non steroidal anti-inflammatory drugs (NSAIDs) are contraindicated in many conditions such as renal failure, intracerebral hemorrhage, gastrointestinal problems, and thrombocytopenia. If NSAIDs were contraindicated, the only available solution was surgical ligation with its risks of cardiothoracic surgery and impaired neurological outcome [25, 27]. Therefore, alternative pharmacological drugs were needed, so paracetamol has gained attention as an alternative drug for PDA closure after several studies [5, 7, 22].

Paracetamol also inhibits prostaglandin synthetase activity through acting at the peroxidase segment of the enzyme leading to reduction of PG synthesis [16]. Paracetamol has a therapeutic advantage over other NSAID as it has no peripheral vasoconstrictive effect. Therefore, paracetamol was tried as a line of treatment in closure of PDA with observed fewer side effects compared to other cyclooxygenase inhibitors, e.g., ibuprofen or indomethacin in many studies [5, 7, 22].

The aim of this work was to compare the efficacy and side effects of paracetamol, indomethacin, and ibuprofen in the closure of hemodynamically significant PDA (hs-PDA) in preterm neonates mainly on renal and liver function, platelet count, and hemoglobin level.

Patients and methods

This randomized prospective study was conducted in the neonatal intensive care unit (NICU) of Tanta university hospital on 300 preterm neonates with a gestational age less than 28 weeks during the period from January 2012 to December 2015.

Inclusion criteria

Preterm neonates with gestational age less than 28 weeks or birth weight less than 1500 g in the first 2 weeks of life with hs-PDA diagnosed with echocardiography and clinical examination.

Exclusion criteria

Preterm neonates with major congenital anomalies, life threatening sepsis, NEC, IVH, UOP <1 ml/kg/h in the last 24 h, serum creatinine concentration >1.5 mg/dl, platelet count <100,000/ml, complex congenital heart, or duct-dependent lesions.

Written informed consent was obtained from the parents of all subjects of the study before enrollment. The study was approved by the local Ethics Committee of Faculty of Medicine of our University. The study has complied with the World Medical Association Declaration of Helsinki. All preterm neonates in our neonatal unit were assessed in the first 48 h by clinical and echocardiographic examination to detect hs-PDA.

All neonates meeting the inclusion criteria were randomized into one of the three groups. Random allocation software was used for random sequence generation. The random number list was generated by QuickCalc GraphPad Software Inc., La Jolla, CA, USA. Allocation concealment was done by sequentially numbered sealed opaque envelopes. Once the written consent was signed, the sealed opaque envelope was opened and the neonate was enrolled into the respective group by the doctor on duty who was not blinded and not a part of the study. All other treating staff and outcome assessors were blinded to the treatment group.

The study included 300 preterm neonates with hs-PDA. Neonates were divided into three groups:

Group I (paracetamol group): 100 neonates received 15 mg/kg IV infusion paracetamol over 30 min followed by 15 mg/kg/6 h IV infusion for 3 days. Dilution of paracetamol was required in neonates that weighed less than 1000 g using glucose 5% or sodium chloride. Nine percent to achieve concentration of 2 mg/ml.
Group II (Ibuprofen group): 100 neonates received 10 mg/kg IV infusion ibuprofen followed by 5 mg/kg/day for 2 days.
Group III (Indomethacin group): 100 neonates received 0.2 mg/kg indomethacin IV infusion over 30 min for three doses 12 h apart.

Echocardiographic criteria of hs-PDA are the following: left atrial dilatation (left atrial: aortic root >1.6), diastolic turbulence (backflow) on Doppler in the pulmonary artery, internal diameter of duct >1.5 mm, and reverse end diastolic flow in the descending aorta/mesenteric artery [18].

Clinical criteria of hs-PDA are the following: tachycardia, bounding pulse with wide pulse pressure, hyperdynamic precordium with continuous murmur on auscultation, hepatomegaly, edema, unexplained metabolic acidosis, failure of respiratory distress syndrome to improve at 2–7 days, and unexplained CO_2 retention in mechanically ventilated neonates [1].

All neonates in our study were subjected to the following:

- Full history taking (prenatal, natal, and family history).
- Clinical examination (to identify signs of circulatory compromise, this includes evaluation of capillary filling time, lethargy, oliguria (defined as urine output of less than 1 ml/kg/h), and measurement of vital signs).
- Laboratory assessment (hemoglobin level, arterial blood gas, renal function tests, serum bilirubin, SGPT level, SGOT level, and platelets count).
- Cranial ultrasound scanning was done before and after treatment to detect IVH.
- Echocardiographic examination performed by a pediatric cardiologist who was blinded to the study and treatment groups (to evaluate PDA diameter, left atrial/aortic root ratio, and pressure across PDA) using S7 transducer of ultrasound machine (Vivid 7, GE Healthcare, Horten, Norway). Echocardiography was done before and 3 days after initiation of treatment to assess the closure of PDA and the need for a second course of medical treatment. Closure of hs-PDA was defined as no flow could be detected through the duct by echocardiography. If PDA failed to close after first course of treatment, a second course of treatment of the same drug was given. No cross-over of drugs was allowed.

All laboratory investigations were done before and 3 days after initiation of medications. Specific outcomes and complications occurred after the use of the three drugs of the study such as retinopathy of prematurity (ROP), gastrointestinal (GI) bleeding, NEC, pulmonary hemorrhage, IVH, and sepsis were recorded. Ventilation was used for cases of severe respiratory distress in the form of continuous positive airway pressure or mechanical ventilation. Parameters and duration of mechanical ventilation were recorded.

The primary outcome was to compare the efficacy of each drug used in the study in closing hs-PDA in preterm neonate after the first and second course of treatment. The secondary outcome was to compare side effects and complications occurred after the use of paracetamol, ibuprofen, and indomethacin in these preterm neonates.

Statistics

In order to detect a difference of 21% in the closure rate of PDA between paracetamol, indomethacin, and ibuprofen groups with a type I error of 0.05 and statistical power of

Table 1 Baseline characteristics and echocardiographic data of preterm infants in all studied groups

	Group I (paracetamol) $N = 100$	Group II (ibuprofen) $N = 100$	Group III (indomethacin) $N = 100$	(ANOVA) P value
Gestational age(weeks)	26 ± 1.9	25 ± 2.1	26 ± 2.1	0.969
Sex (male:female)	60:40	80:20	60:40	0.532
Weight (Kg)	1.1 ± 0.13	1 ± 0.12	1.1 ± 0.14	0.682
Age at start medication (in days)	2.7 ± 4.4	3.2 ± 4.2	3.1 ± 5.1	0.968
Diameter of PDA (mm)	2.7 ± 0.6	2.8 ± 0.6	2.7 ± 0.7	0.907
Pressure across PDA (mmHg)	37 ± 7	36 ± 8	32 ± 7	0.335
Left atrial/aortic root ratio	2.1 ± 0.4	2.2 ± 0.5	2.2 ± 0.5	0.822

P value is significant if <0.05

90%, 97 patients were required in each group. Statistical analysis of the present study was conducted, using the mean, standard deviation, paired *t* test, analysis of variance (ANOVA) tests by SPSS V 17. $P < 0.05$ is considered significant.

Results

Demographic and echocardiographic parameters between all groups before treatment were not statistically different (Table 1). Similarly, in Table 2, there was no significant difference found in all studied groups before treatment with regard to serum creatinine level, BUN, bilirubin, SGPT, SGOT, platelet, hemoglobin level, and UOP as *P* values >0.05.

In addition, the results of Table 2 showed that there was significant difference in all studied groups after treatment regarding serum creatinine, serum BUN, serum bilirubin level, serum platelet level, and urine output (*P* value <0.05), while there was no significant difference between all groups after treatment regarding SGPT, SGOT, and serum hemoglobin.

Serum creatinine and BUN were found to be significantly increased in group II and group III after treatment. However, they showed to be higher in the indomethacin group than the ibuprofen group (*P* value <0.001). Also, Table 2 showed that serum bilirubin level was significantly increased in ibuprofen group after treatment (*P* value >0.05). Both platelet count and UOP were significantly decreased in group II and group III after treatment and the reduction was higher in the indomethacin group compared to the ibuprofen group.

There was a significant reduction in positive intermittent pressure (PIP), FiO_2, oxygenation index, and duration of mechanical ventilation in closed PDA compared to non-closed PDA patients in all ventilated cases (P = <0.001) (Table 3).

Table 4 shows no significant difference between the three groups with regard to rate of PDA closure and failure ($P > 0.05$). The rate of closure after the first treatment course was 80% in paracetamol therapy, 77% in the ibuprofen group, and 81% in the indomethacin group. The cumulative closure rate was increased after the second treatment course to be 88% in paracetamol group, 83% in ibuprofen group, and 87% in indomethacin group with no statistically significant difference between the three groups. Number of neonates who underwent ductal ligation was nearly the same in the three groups. There was no significant difference between all groups for secondary outcomes except GIT bleeding which was more observed in indomethacin and ibuprofen groups than paracetamol group ($P < 0.05$).

Discussion

Hemodynamically significant PDA in preterm infants is better to be closed to decrease complications of PDA, through

Table 2 Serum creatinine, BUN, bilirubin, SGPT, platelet, hemoglobin level, and UOP before medical closure of PDA in all the studied groups

	Group I (paracetamol) Mean ± SD			Group II (ibuprofen) Mean ± SD			Group III (indomethacin) Mean ± SD			ANOVA
	Before	After	P^a	Before	After	P^a	Before	After	P^a	$P1^b$ value
Serum creatinine	0.56 ± 0.07	0.55 ± 0.05	0.726	0.55 ± 0.07	0.69 ± 0.16	0.029*	0.52 ± 0.06	0.90 ± 0.19	0.001*	<0.001*
Serum BUN	20 ± 2.71	20.60 ± 2.80	0.460	19.50 ± 2.51	22.10 ± 3.04	0.05*	21.60 ± 3.47	32 ± 3.62	<0.001*	0.000*
Serum bilirubin level	1.21 ± 0.20	1.26 ± 0.19	0.521	1.22 ± 0.28	1.94 ± 0.78	0.012*	1.20 ± 0.19	1.20 ± 0.19	1.00	0.003*
Serum SGPT Level	24.70 ± 3.97	26 ± 3.50	0.094	24.90 ± 4.01	25.70 ± 4.17	0.343	25.50 ± 3.98	25.40 ± 4.09	0.798	0.779
Serum SGOT Level	36.5 ± 11.8	37.4 ± 14.3	0.152	37 ± 11.5	37.9 ± 11.9	0.654	36.9 ± 11.9	37.4 ± 12.8	0.736	0.471
Platelet count	238 ± 40.77	246 ± 36.58	0.537	237.7 ± 61.86	206 ± 65.52	0.004*	235 ± 39.51	134 ± 27.57	<0.001*	<0.001*
Serum HB level	11.50 ± 0.94	11.30 ± 0.72	0.522	11.55 ± 1.01	11.10 ± 0.84	0.302	11.65 ± 0.75	11 ± 0.82	0.109	0.694
Daily UOP	2.25 ± 0.41	2.24 ± 0.37	0.811	2.16 ± 0.44	1.69 ± 0.60	0.006*	2.28 ± 0.36	1.10 ± 0.37	<0.001*	<0.001*

[a] Comparison between value before and after treatment in each group (paired *t* test)

[b] Comparison between three groups after treatment

*P value is significant if <0.05

Table 3 Some ventilatory settings and duration of mechanical ventilation in patients with and without PDA medical closure

	Patients with failed PDA closure $N = 42$	Patients with PDA closure $N = 258$	P
PIP	21 ± 1.6	17 ± 0.9	<0.001*
FIO_2	37 ± 4.8	22 ± 1.7	<0.001*
Oxygenation index	4.8 ± 0.6	2.2 ± 0.2	<0.001*
Duration of MV (days)	12.7 ± 4.5	6.5 ± 0.9	<0.001*

PIP positive intermittent pressure, *MV* mechanical ventilation

*P value is significant if <0.05

pharmacotherapy, surgical, or catheter closure [15, 22]. Pharmacotherapy seems to be the therapy of choice because of its safety and effectiveness in treatment of hs-PDA in preterm infants [12, 28].

Drugs like cyclooxygenase (COX) inhibitors, e.g., indomethacin and ibuprofen, were used in closure of PDA [12, 28]. Paracetamol is an alternative therapeutic approach for ductal closure through inhibition of prostaglandin synthetase activity. Although its efficacy in PDA closure has been approved, studying its side effects relative to indomethacin and ibuprofen simultaneously has not been investigated before. To the best of our knowledge, it is the first study comparing the efficacy and side effects of paracetamol, ibuprofen, and indomethacin in closure of PDA in preterm neonate at the same time.

Our study showed that paracetamol is as effective as indomethacin and ibuprofen in promoting ductal closure of PDA in preterm infants. The rate of closure in paracetamol therapy (80%) was more or less similar to that after ibuprofen (77%) and indomethacin (81%) therapy. This was in agreement with other studies [5, 8, 21, 22]; however, a higher rate of PDA closure (>95%) was reported by other investigators [7]. This could be related to higher mean of gestational age in their study (31.6 weeks) with better response to pharmacological treatment. PDA is known to be less responsive to cyclooxygenase inhibition in young preterms due to higher expression of prostaglandin receptors in their PDA walls. On the other hand, Roofthooft et al. [26] had disappointing results with PDA closure after IV paracetamol treatment with a low success rate of only 17%. This could be due to a late start of paracetamol administration in their study (median of 14 days).

Comparing side effect of the three drugs showed that in the risk of elevation of serum creatinine, BUN level accompanied by oliguria was greatest in the indomethacin group compared to a lower risk in the ibuprofen group while the renal function was unaffected in the paracetamol group. This could be explained by the fact that ibuprofen has less vasoconstrictive effects and consequently less decreased organ blood flow adverse effects than indomethacin-treated patients [6, 12, 30].

Table 4 Outcome of neonates according to treatment group

	Group I (paracetamol) $N = 100$	Group II (ibuprofen) $N = 100$	Group III (indomethacin) $N = 100$	P value (ANOVA)
Primary outcome:				
No. of PDA closed after the first course of treatment	80	77	81	0.868
No. of PDA closed after the second course of treatment	8	6	6	0.781
No. of surgical ligations	12	17	13	0.674
Secondary outcome (complications):				
ROP	7	10	15	0.07
GIT bleeding	1	7	10	0.007*
NEC	3	6	9	0.074
Pulmonary hemorrhage	2	5	7	0.09
IVH	5	7	10	0.176
Sepsis	15	19	14	0.848

PDA patent ductus arteriosus, *ROP* retinopathy of prematurity, *NEC* necrotizing enterocolitis, *IVH* intraventricular hemorrhage

*P value is significant if <0.05

There are two types of cyclooxygenase isoenzymes known as COX-1 and COX-2; COX-1 is primarily involved in basal physiologic processes in the kidney. Although both isoenzymes are inhibited by ibuprofen and indomethacin, indomethacin is more potent against COX-1. In addition, some experimental evidence suggests that there may be another mechanism that partly explains the differences in the effects of both drugs on regional circulations [31].

In addition, increased creatinine level after indomethacin therapy could be explained by the nonselective vasoconstrictive effect of the drug causing reduction of blood flow through various organs [32]. Hammerman et al. reported that paracetamol could offer important therapeutic advantages over NSAID (e.g., indomethacin and ibuprofen) as paracetamol has no peripheral vasoconstrictive effect, so it can be given to infants with clinical contraindications to NSAIDs [8]. Our results were in disagreement with other investigators who studied effect of high dose of ibuprofen in closure of PDA in preterm neonates and found that neither significant oliguria nor elevated creatinine levels were found. According to their data, these renal reversible side effects seem not to be strictly dose dependent [19, 24].

We found a significant increase in serum bilirubin level in only the ibuprofen group after treatment. This went with the results of other investigators [25, 34]. The increase in total bilirubin concentration could be due to inhibition of hepatic glucuronidation of bilirubin by ibuprofen. In addition, ibuprofen has a very high albumin binding affinity, competing with bilirubin leading to potentially increased risk of bilirubin encephalopathy [25, 34]. Considering the previous data with recent reports of low bilirubin kernicterus threshold in preterm neonates, we have to be cautious about giving ibuprofen to small preterm neonates with hyperbilirubinemia [20].

Regarding the caution of hepatotoxicity of paracetamol in neonates, we found that there was no significant change in SGPT or SGOT serum levels in all groups after treatment including the paracetamol group. This result was in agreement with Jacqz-Aigrain et al. [9] who reported that neonates tend to suffer less from the hepatotoxic effects of paracetamol than do older children. This can be explained by the metabolism of paracetamol that changes with age. In adults, the majority of paracetamol is conjugated with glucuronic acid and, to a lesser extent, with sulfate. Hepatic glucuronidation is relatively immature at birth. The sulfate conjugate predominates in preterm infants, newborns, and young infants [17]. With maturation, these clearance pathways for paracetamol change. The usual adult ratio of 2:1 glucuronide to sulfate conjugates of paracetamol is achieved by 12 years of age [3]. Our result was in contrast with Anderson et al. [4] who reported hepatotoxicity in term neonates, but it occurred after 3 days of excessive paracetamol intake. Moreover, Alan et al. [2] reported elevated liver transaminases in two out of three preterm neonates treated for PDA.

Our result showed that there was a significant decrease in platelet level after treatment in both ibuprofen and indomethacin groups, while no thrombocytopenia occurred after paracetamol treatment; this was in agreement with other investigators [8, 14, 30]. This can be explained by the fact that paracetamol has a pronounced reduction of prostacyclin synthesis but has no effect on thromboxane unlike indomethacin and ibuprofen [21].

PDA is thought to decrease lung compliance via an increase in pulmonary circulation and resultant increased lung water and pulmonary edema. PDA closure improves dynamic compliance and increases tidal volume in preterm neonates receiving mechanical ventilation. Clinicians usually increase ventilator settings in hs-PDA to address the poor compliance; this finding may explain how a PDA could increase the risk of BPD [29]. This can explain a significant decrease in ventilatory setting in our patients with PDA closure than those with failure of PDA closure.

GIT bleeding was significantly more observed in the indomethacin group followed by the ibuprofen group. This can be due to their vasoconstrictive effects that decreased mesenteric blood flow causing gut ischemia, depletion of COX 1-derived prostaglandins, and their thrombocytopenic effects [23, 24]. Rate of GI bleeding was minimal with the paracetamol group that went with the results of other investigators [5, 33]. In contrast to our results, Dash et al. [7] reported striking high intestinal bleeding rate in the paracetamol group (26.3%) The high intestinal bleeding rate in their study may be related to high osmolality of paracetamol used in their study.

Limitation of the study

The study was not completely blinded due to difference of drug doses, but outcome assessors were completely blinded to the treatment groups. One week lower gestational age in ibuprofen group, but it was found to be statistically not significant.

Conclusion

Paracetamol is as effective as indomethacin and ibuprofen in closure of hs-PDA in preterm neonates with less side effects than both mainly on renal function, platelet count, and GIT bleeding.

Authors' contributions Abd El-Rahman El-Mashad: the idea of the research, supervising the work of research, and revising and approving the manuscript.

Heba El-Mahdy: selecting patients and dividing them into groups, supervising and following up patients, and revising the manuscript.

Doaa El-Amrousy: performing the echocardiography, writing the manuscript, doing the statistical analysis, and following up the patients.

Marwa Elgendy: following up the patients, gathering the data, and helping in writing the manuscript.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants The study was approved by the local Ethics Committee of Faculty of Medicine of our University and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all parents of the participants included in the study.

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