EFFICACY AND SAFETY OF INTRAVENOUS PARACETAMOL VERSUS INDOMETHACIN FOR CLOSURE OF HEMODYNAMICALLY SIGNIFICANT PATENT DUCTUS ARTERIOSUS IN PRETERM NEONATES

By

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ABSTRACT

Background: *Hemodynamically significant patent ductus arteriosus (hs-PDA) is a common cause of morbidity and mortality among preterm infants, affecting more than 40% of preterm infants. A persistent hs-PDA can cause significant problems, especially in premature infants. Thus, the early closure of hs-PDA is important to prevent several comorbidities such as necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), pulmonary edema/hemorrhage, and development of chronic lung disease (CLD).*

Aim of the study: *This study aimed at comparing the efficacy and safety of intravenous (IV) paracetamol compared with IV indomethacin for the pharmacological closure of PDA in preterm infants.*

Study design: *This prospective, randomized study enrolled 100 preterm infants admitted at Bab-elsheria neonatal intensive care unit between August 2020 and August 2022. with gestational age ≤ 35 weeks and postnatal age within first two weeks of life who had hemodynamically significant PDA confirmed by 2 D transthoracic echocardiography. They were randomized into 2 groups, group I (paracetamol group) 50 preterm neonates received 15 mg/kg/6 h IV paracetamol infusion for 3 days, and group II (indomethacin group) 50 preterm neonates received 0.2 mg/kg/12 h indomethacin IV infusion for three doses.*

Results: *The ductus was closed in 38 (76%) infants of the paracetamol group compared with 40 (80%) of the indomethacin group. The reopening rate was higher in the paracetamol group than in the indomethacin group, but the reopening rates were not statistically different (21% [8 of 38] vs 15% [6 of 40]; P =0 .695). The cumulative closure rates after the second course of drugs were high in both groups. Only 2 patient*

(4%) in the paracetamol group and also 2 patients (4%) in the indomethacin group required surgical ligation.

Conclusion: *Our study showed that use of IV paracetamol is effective as IV indomethacin in medical closure of hs-PDA in premature infants, and has no side effects mainly on renal function, platelet count, and gastrointestinal bleeding.*

Key words: *(Preterm, PDA, Paracetamol, indomethacin).*

INTRODUCTION

Hemodynamically significant patent ductus arteriosus is regularly related to morbidity and mortality among premature infants **(Dimitrios et al., 2022)**. Treatment options for the closure of hs-PDA include medical therapy and surgical ligation. The most commonly used drugs for this purpose are cyclooxygenase inhibitors, predominantly indomethacin and ibuprofen, which block the conversion of arachidonic acid to prostaglandins **(Demirel et al., 2012)**.

The reported treatment success with indomethacin for the management of hs-PDA is between 70%-95% **(Yurttutan et al., 2013)**. Several adverse effects have been reported with such medications, including peripheral vasoconstriction, gastrointestinal bleeding and perforation, decreased platelet aggregation, hyperbilirubinemia, and renal failure **(Jacqz-Aigrain and Anderson, 2006)**. Paracetamol acts by directly inhibiting the activity of prostaglandin synthase. Unlike indomethacin, paracetamol is thought to act on prostaglandin synthase at the peroxidase region of the enzyme. Paracetamol inhibition is facilitated by a decreased local concentration of hydroperoxides **(Ohlsson et al., 2020)**. The role of paracetamol as an alternative treatment for the closure of hs-PDA has gained attention in recent years because of the potential side-effects of cyclooxygenase inhibitors **(Schindler et al., 2021)**.

We planned to test the hypothesis of whether IV paracetamol is as effective as IV indomethacin in treatment of hs-PDA. Therefore, we conducted this prospective, randomized, trial in preterm infants with gestational age $\leq$ 35 weeks to compare the efficacy and safety of IV paracetamol and IV indomethacin for the pharmacologic closure of PDA.

AIM OF THE WORK

This study aimed at comparing the efficacy and safety of IV paracetamol compared with IV indomethacin for the

pharmacological closure of PDA in preterm infants.

PATIENTS AND METHODS

A. Ethical consideration:

1. The study was approved by the pediatric department Ethics Committee.
2. The Faculty of medicine –Al-Azhar university Ethics Research Committee approved the study.
3. Written informed consent was obtained from the caregiver of enrolled neonates in this study.
4. The authors declared no potential conflicts of interest with respect to the research, authorship, and / or publication of this article.
5. The data of the study are conferential and the caregiver has the right to keep it.
6. The author declared that there is no fund regarding the study or publication.

B. Study design & research steps:

This study was a prospective randomized controlled trial which carried out at neonatal intensive care unit of Bab-elheria University Hospital between August 2020 and August 2022. 100 preterm neonates were enrolled in the study with certain inclusion and exclusion criteria:

Inclusion criteria were: The study enrolled 100 preterm infants with:

- Gestational age ≤ 35 weeks,
- Postnatal age within first two weeks of life,
- One of the following echocardiographic criteria: a duct size >1.5 mm, a left atrium-to-aorta ratio >1.5, end diastolic reversal of blood flow in the aorta, or poor cardiac function in addition to clinical signs of PDA.

Exclusion criteria were:

- The presence of major congenital abnormalities,
- Right to left ductal shunting,
- Life-threatening infection,
- Grade III or grade IV IVH,
- Urine output of less than 1 mL/kg/h during the preceding 8 hours,
- Serum creatinine level >1.6 mg/ dL, platelet count <60 000/mm3, liver failure, hyperbilirubinemia requiring exchange transfusion, and persistent pulmonary hypertension.

All study infants were subjected to:

- Full perinatal history: maternal illness, mode of delivery, sex, age, birth weight.
- Thorough clinical evaluation (general examination & complete cardiac assessment) with emphasis on: presence or absence of murmur, pulse pressure, mode of ventilation & ventilator setting and presence of respiratory distress syndrome.

Monitoring for potential complications:

- Signs of renal adverse effects (oliguria with urine output less than 1cc/kg/hour) (were monitored during receiving of treatment and 7 days later). Urine output was calculated by weighting the diapers pre and post urination by a special measuring scale.
- Monitoring for any signs of CNS insults as convulsions, disturbed conscious level, hypo or hypertonia, full fontanel or unexplained apnea. Cranial ultrasound would be done with rise of suspicion.
- Monitoring for signs of NEC (feeding intolerance – abdominal distention and tenderness- bleeding per rectum, melena or thrombocytopenia). Accordingly, X-ray abdomen (erect) would be ordered.
- Monitoring for symptoms and signs of bleeding diatheses (Hematemesis, epistaxis, melena or excessive bleeding from puncture sites).

Investigations: (Before and after treatment):

- Complete blood count (CBC) with differential (Sysmex).
- Arterial blood gases & serum electrolytes (Bayer Rapid point400).
- Liver function tests (AST and ALT) (Biomed Diagnostic)
- Bilirubin Total and direct (Biomed Diagnostic).
- Urea and creatinine (Biomed Diagnostic).
- Chest X ray for evaluation RDS and cardiomegaly.

Echocardiography:

- Two-dimensional color Doppler echocardiography (PHILIPS HD7XE) using 8mz prope was performed by an experienced pediatric echocardiographer unaware of the infants' treatment assignments. Before and 24 hours after treatment, all patients were evaluated with a complete blood count; renal function tests (serum

creatinine, blood urea nitrogen, and urine output), aspartate amino transferase (AST), alanine amino transferase (ALT) and bilirubin levels, cranial ultrasonography, and echocardiography.

C. Therapeutic intervention:

- The patients were randomly assigned to a treatment group by cards in sequentially numbered sealed opaque envelopes, and 100 patients completed the study protocol. They were randomized into 2 groups. Group I (paracetamol group) 50 preterm neonates received 15 mg/kg/6 h IV paracetamol infusion for 3 days. Group II (indomethacin group) 50 preterm neonates received 0.2 mg/kg/12 h indomethacin IV infusion for three doses One day after the treatment,
- An echocardiographic evaluation was performed by a pediatric cardiologist who was blinded to the treatment group to determine the success of the treatment and the need for a second course via the same route.
- The success rate, defined as a closed duct on echocardiography after the completed course and the safety of the drugs in preterm infants were the major outcomes of the study.

D. Statistical Methods:

- Sample size was calculated by Open Epi program in order to detect a difference of 4% in the closure rate of PDA between paracetamol and indomethacin groups with a type I error of 0.05 and statistical power of 90%, 49 patients were required in each group.
- Data were analyzed using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA) and MedCalc© version 14 (MedCalc© Software bvba, Ostend, Belgium). The Shapiro-Wilk test was used to examine the normality of numerical data distribution. Normally distributed numerical variables were presented as mean ± SD and inter-group differences were compared using unpaired Student t test. Within-group differences were compared using the paired Student t test. Categorical variables were presented as number (%) and differences were compared using Fisher's exact test. Multivariable binary logistic regression analysis was used to examine the relation between the treatment drug and success of PDA closure as adjusted for gestational age

and PDA size. P-value <0.05 was considered statistically significant.

RESULTS

Our results will be illustrated on the following tables:

Table (1): Demographic characteristics of the two studied groups

Variable	Group I (n=50)	Group II (n=50)	p-value
Gender			
Female	26 (52.0%)	22 (44.0%)	0.778¶
Male	24 (48.0%)	28 (56.0%)	
Gestational age (weeks)	32.0 ± 1.8	32.6 ± 1.7	0.228§
Birth weight (kg)	1.7 ± 0.5	1.7 ± 0.4	0.736§

Data are presented as number (%) or mean ± SD.
¶Fisher's exact test. §Unpaired Student t test.

This table shows no statistically significant difference regarding the demographic and clinical parameters of the two studied groups before treatment initiation.

Table (2): Maternal risk factors of the tow studied groups

Variable	Group I (n=50)	Group II (n=50)	p-value
Preeclampsia	10 (20.0%)	8 (16.0%)	1.000¶
PROM >18 h	12 (24.0%)	6 (12.0%)	0.463¶
DM	6 (12.0%)	4 (8.0%)	1.000¶

Data are presented as number (%) or mean ± SD.
¶Fisher's exact test. §Unpaired Student t test.

This table shows no statistically significant difference between the 2 groups before treatment initiation regarding the maternal risk factors.

Table (3): Echocardiographic findings of the two studied groups before treatment initiation

Variable	Group I (n=50)	Group II (n=50)	p-value
PDA diameter (mmHg)	2.4 ± 0.5	2.3 ± 0.4	0.572¶
LA/AO ratio	1.2 ± 0.1	1.3 ± 0.2	0.120¶

Data are presented as number (%) or mean ± SD.
¶Fisher's exact test. §Unpaired Student t test.

This table shows no statistically significant difference between the 2 groups regarding echocardiographic measures.

Table (4): Comparison between the two studied groups regarding to the treatment efficacy

Variable	Group I (n=50)	Group II (n=50)	p-value
PDA closure			
Failed to close	12 (24.0%)	10 (20.0%)	1.000¶
Closed	38 (76.0%)	40 (80.0%)	
Number of courses to achieve closure			
Single course	30 (78.9%)	34 (85.0%)	0.695¶
Two courses	8 (21.1%)	6 (15.0%)	
Size of non-closed PDA (mm)	3.3 ± 0.7	3.3 ± 0.6	0.895§

Data are presented as number (valid %) or mean ± SD. ¶Fisher's exact test. §Unpaired Student t test.

This table shows no statistically significant difference between the 2 groups regarding the treatment efficacy.

Table (5): Multivariable binary logistic regression model for the relation between the successful closure of PDA and gestational age, PDA diameter, and type of treatment (paracetamol (group I) versus indomethacin (group II)

Variable	Regression coefficient	Standard error	Wald	p-value	Odds ratio	95% CI
(Group I = 0) (Group II = 1)	0.53	0.95	0.232	0.639	1.51	0.24 to 9.19
Gestational age (weeks)	0.47	0.27	3.231	0.075	1.59	0.93 to 2.46
PDA diameter (mm)	-2.51	0.82	8.528	**0.003**	0.07	0.01 to 0.39
Constant	-3.78					

After adjustment for the effect of gestational age and PDA diameter, there was no statistically significant relation between the type of treatment and the success of PDA closure (odds ratio, 1.54; 95% CI, 0.26 to 9.21; p-value, 0.636). Of the three variables, the only independent predictor for successful closure of PDA was the PDA diameter (odds ratio, 0.08; 95% CI, 0.01 to 0.43; p-value, 0.004).

Table (6): Comparison of the laboratory parameters of organ function, hemoglobin level and platelet count before and after treatment of both studied groups

Group	Variable	Before treatment		After treatment		p-value¶
		Mean	**SD**	**Mean**	**SD**	
Group I (n=50)	UOP (ml/kg/h)	2.3	0.6	2.5	0.6	0.71
	Creatinine (mg/dl)	0.7	0.3	0.6	0.3	0.214
	BUN (mg/dl)	41.2	29.5	43.9	37	0.798
	Bilirubin (mg/dl)	6.4	2.1	5.6	1.9	0.086
	ALT (IU/l)	19.3	12.6	18.9	12.4	0.587
	AST (IU/l)	25.2	13.1	25	17.2	0.942
	Hemoglobin level	12.5	0.9	12.3	0.7	0.522
	Platelet count	236	40.7	244	36.5	0.537
Group II (n=50)	UOP (ml/kg/h)	2.7	0.5	1.4	0.6	<0.001
	Creatinine (mg/dl)	0.7	0.3	1.1	0.4	<0.001
	BUN (mg/dl)	44.8	39.6	56.1	38.7	<0.001
	Bilirubin (mg/dl)	6.5	1.8	5.8	2	0.108
	ALT (IU/l)	22.9	12.2	20.2	7.2	0.256
	AST (IU/l)	21	17	21.4	8.2	0.831
	Hemoglobin level	11.3	0.7	11	0.8	0.107
	Platelet count	233	39.4	139	27.5	<0.001*

¶Paired Student t test.

This table shows a highly statistically significant difference in group II before and after treatment regarding daily urine output, blood urea, serum creatinine, hemoglobin level and platelet count with p value<0.001. While in the group I there was no statistically significant difference regarding daily urine output, blood urea, serum creatinine, hemoglobin level and platelet count.

Table (7): Incidence of adverse outcomes in the two studied groups

Variable	Group I (n=50)	Group II (n=50)	p-value
IVH	4 (8.0%)	8 (16.0%)	0.667¶
BPD	6 (12.0%)	4 (8.0%)	1.000¶
Sepsis	30 (60.0%)	26 (52.0%)	0.776¶
Pneumothorax	2 (4.0%)	2 (4.0%)	1.000¶
NEC	0 (0.0%)	2 (4.0%)	1.000¶
Mortality	12 (24.0%)	16 (32.0%)	0.754¶

Data are presented as number (%).
¶Fisher's exact test.

This table shows that there was no statistically significant difference between the 2 studied groups regarding the incidence of the adverse outcome.

DISCUSSION

Among various treatment modalities, pharmacotherapy seems to be the therapy of choice before any surgical or catheter closure because it's proven safety and effectiveness in the treatment of the hs-PDA in preterm neonates **(Wang et al., 2020)**.

Commonly used medical therapies are indomethacin and ibuprofen with variable success and notable side effects **(Noori et al., 2010)**. Intravenous paracetamol infusion has been evaluated in many trials, as an alternative therapy for PDA closure in patients with contraindications for indomethacin or ibuprofen or those who have not been successfully treated with these drugs effective as traditional non-steroidal anti-inflammatory drugs in PDA closure with fewer side effects **(Van Overmeire, and Chemtob, 2005)**.

Our study was designed with sufficient power to determine if IV paracetamol and IV indomethacin are equally efficacious for PDA closure. Our results demonstrated that IV paracetamol and IV indomethacin were similarly effective for the closure of PDA with 1 course of treatment. However, patients treated with IV paracetamol (group 1) had no change of renal and liver variables, as well as a lack of statistically significant difference in major complications (daily urine output, hyperbilirubinemia, gastrointestinal bleeding, NEC, IVH, CLD, and ROP).

In our study the rate of closure in iv paracetamol therapy (76%) was more or less similar to that after iv indomethacin (81%), after

the first course of the treatment. This was in agreement with other studies **(Ohelsson et al., 2020)**. Also, our results in agreement with comparative study by **Elmashed et al., 2017** they found that iv paracetamol is as effective as iv indomethacin and iv ibuprofen in closure of PDA in preterm neonates. **Dash et al, 2015**, found that the PDA closure rate was 95% in indomethacin group and 100% in paracetamol group.

On the other side **Davidson et al., 2019** reported that in their small randomized trial they were unable to show successful treatment of hsPDA with IV acetaminophen when compared to IV indomethacin in preterm infants born prior to 32 weeks. The side effects with both drugs were similar, but many babies in IV acetaminophen group needed interventional closure later.

Safety measurements for both drugs should be interpreted cautiously because the study was not large enough to evaluate safety. For example, although there was no difference in ALT, this should be carefully interpreted because the dose of paracetamol that was used in this trial is designed for full-term infants rather than preterm infants, and there have already been 2 reports of altered liver function tests in preterm infants when higher doses of paracetamol were administered **(Tekgunduz et al., 2013)**.

Regarding the caution of hepatotoxicity of paracetamol in neonates, we found that there was no significant change in ALT or AST serum levels in both paracetamol and indomethacin group. This result was in agreement with **Jacqz-Aigrain et al., 2006**, who reported that neonates tend to suffer less from the hepatotoxic effects of paracetamol than do older children.

As regard side effects of the tow drugs the risk of elevation of serum creatinine, BUN level accompanied by oliguria was reported in the indomethacin group while the renal function was unaffected in the paracetamol group. Similar results were reported by **El-Mashad et al., 2017** and **Meena et al., 2020** This could be explained by the fact that paracetamol has no vasoconstrictive effects and consequently less decreased organ blood flow adverse effects than indomethacin-treated patients.

Our results showed that there was significant change in the platelet level after treatment in indomethacin group but paracetamol group showed no

changes in platelet count. Also, **El-Mashad et al., 2017** showed a significant difference in the platelet level after treatment in indomethacin groups, while no thrombocytopenia occurred after paracetamol treatment.

CONCLUSION

The results of our study showed that IV paracetamol is as effective as IV indomethacin and ibuprofen in promoting closure of the hs-PDA in premature infants with better safety profiles.

RECOMMENDATIONS

We suggest that further studies need to address a comparison of treatments in a group of infants who are more likely to have a PDA (<1000 g) that is unlikely to close spontaneously for several weeks and who are most likely to benefit from these treatments.

LIMITATIONS OF STUDY

Our study was limited by a relatively small number of the studied patients and a lack of blinding of the caregivers to the study intervention. We did not follow all patients to assess long-term outcomes, especially for neurodevelopmental adverse effects. These limitations could be addressed in future studies.

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