COMPARATIVE STUDY OF THE EFFICACY OF ORAL AND CONTINUOUS VERSUS INTERMITTENT INFUSION OF PARACETAMOL ON CLOSURE OF PATENT DUCTUS ARTERIOSUS

By

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ABSTRACT

Background: *Patent ductus arteriosus (PDA) is a persistent opening between pulmonary artery and aorta leading from the heart.*

Aim of study: *The aim of this study was to know the most effective route of administration of paracetamol (oral & bolus or continuous infusion) in treatment of patent ductus arteriosus.*

Methods: *A considerable number of patients (30) who were admitted in neonatal intensive care unit (NICU) of Pediatric Department at El- Minya health insurance Hospital, Al-Azhar University Assuit, from May 2022 to October 2022. Our studied newborn was classified into 3 groups according to route of administration of paracetamol. Each group included 10 newborns: group 1 (10 NB) received oral paracetamol, group 2 (10 NB) received bolus IV and group 3 (10 NB) received IV continuous infusion. All included neonates received the same dose 60mg/kg/day for 3 days for oral and IV bolus the dose was divided into 15 mg/kg every 6 h. Paracetamol was started at 4th to 7th day of birth.*

Results: *There is statistically significant higher closure rate of PDA in infants received bolus IV and IV infusion paracetamol than those received oral paracetamol.*

Conclusion: *Oral, bolus and continuous infusion administration of paracetamol were safe and effective in the treatment of patent ductus arteriosus. Both standard IV intermittent bolus paracetamol infusion and continuous IV paracetamol infusion were more effective in pharmacologic PDA closure compared with oral paracetamol infusion.*

Key words: *Oral; Infusion; Paracetamol; Patent Ductus Arteriosus.*

INTRODUCTION

Patent ductus arteriosus (PDA) is a persistent opening between the two major blood vessels leading from the heart. The opening (ductus arteriosus) is a normal part of a baby's circulatory system in the womb that usually closes shortly after birth. If it remains open, it's called a patent ductus arteriosus.

A small patent ductus arteriosus often doesn't cause problems and might never need treatment. However, a large patent ductus arteriosus left untreated can allow poorly oxygenated blood to flow in the wrong direction, weakening the heart muscle and causing heart failure and other complications.

Treatment options for a patent ductus arteriosus include monitoring, medications, and closure by cardiac catheterization or surgery **(Kleinman, 2020)**.

Patent ductus arteriosus (PDA) affects approximately 45–55% of infants born at less than 29 weeks of gestational age and under 1500 g. PDA is known to be associated with various comorbidities such as necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), pulmonary edema/hemorrhage, bronchopulmonary dysplasia (BPD), and retinopathy of prematurity (ROP). However, there are some conflicting data about these associations due to the multifactorial natures of those morbidities that RCTs fail to demonstrate these associations **(Evans et al., 2015)**.

Non-steroidal anti-inflammatory drugs (NSAIDs), especially indomethacin and ibuprofen, are widely used for the treatment of hemodynamically significant (hs) PDA. The rate of PDA closure with pharmacological treatment is 70–85%.

NSAIDs are contraindicated in many conditions, including kidney failure, intracerebral hemorrhage (active or ≥ grade3), gastrointestinal problems, and thrombocytopenia (Roofthoot et al., 2015). Until recently, surgical ligation has been performed as a last resort in patients with contraindications for NSAID, despite the risk of poor neurological outcomes. This has led to a need for alternative pharmacological treatment options.

Sample size:

The sample size was done the Epi inf 7 programs for sample size calculation, setting.

The confidence level at 95% and margin of error at 10% based the work done by **cakir et al., (2021)**, a total of 30 patients was estimated to be sufficient sample size.

Ethical Considerations: This study was carried out after being approved by the local Ethics Committee of the Faculty of medicine Al-Azhar University, Assuit, Egypt. Consent will be taken from the patients before including them in the study. Aim of the study and possible risks will be explained to patients. Privacy of collected data will be assured.

Inclusion criteria: Preterm neonates with birth weight (BW) ≤ 1500 g and gestational age (GA) ≤ 30 weeks at birth

Exclusion criteria: Neonates with major congenital and heart anomalies, infants who received paracetamol after having failed ibuprofen and infants treated with paracetamol for other indications besides PDA closure (e.g., pain management).

PATIENTS AND METHODS

This was a prospective comparative study, including. A considerable number of patients (30) who were admitted in neonatal intensive care unit (NICU) of Pediatric department at El- Minya health insurance Hospital, Al-Azhar University Assuit. During the period from May 2022 to October 2022.

Our studied newborn were classified into 3 groups according to route of administration of paracetamol. Each group included 10 newborns:

- Group 1 (10 NB) received oral paracetamol,
- Group 2 (10 NB) received bolus IV and
- Group 3 (10 NB) received IV continuous infusion.

All included neonates received the same dose 60mg/kg/day for 3 days for oral and IV bolus, the dose was divided into 15 mg/kg every 6 h. Paracetamol was started at 4^{th} to 7^{th} day of birth

The studied group was subjected to:

- full history intake,
- Complete general and local examination, also
- Laboratory Investigation was done as: Complete blood count, kidney and liver function and electrolytes.
- CXR and Echo. also were done.

Statistical analysis design: Data collected were reviewed and coding of the collected data was done manually. The numerical

codes were fed to the computer where statistical analysis was done using the Statistic Package for Social Science Version 22 (SPSS 22) for windows.

Comparing groups was done using: Chi square-test (X^2): for comparison of qualitative data. Student's "t"- test for comparison of quantitative data of 2 independent sample. ANOVA test for comparison of quantitative data of more than 2 independent sample. Study of the relationship between variables was done using correlation coefficient **"Pearson correlation"**.

RESULTS

Our data will be demonstrated in the following tables:

Table (1): Comparison of the gestational age, birth weight and the time of paracetamol administration and clinical data of the studied groups

			Mean SD	Rang		X^2	f	P-value	Sig.
				Min.	Max.				
GA (weeks)	-	Group 1	28.6000±0.843	27	30	-	0.955	0.397	NS
		Group 2	28.4000±0.966	27	30				
		Group 3	28.1000±0.876	27	30				
Sex	Male	Group 1	7(70%)	-		0.278	-	0.866	NS
		Group 2	6(60%)						
		Group 3	6(60%)						
	female	Group 1	3 (30%)	-					
		Group 2	4(40%)						
		Group 3	4(40%)						
Birth weight (gm)	-	Group 1	1200.0±115.47	1000	1400	-	0.788	0.465	NS
		Group 2	1177.0±108.63	1000	1300				
		Group 3	1237.0±60.38	1100	1320				
Mode of labor	NVD	Group 1	6(60%)	-		0.271	-	0.873	NS
		Group 2	5(50%)						
		Group 3	6(60%)						
	CS	Group 1	4(40%)	-					
		Group 2	5(50%)						
		Group 3	4(40%)						
Respiratory support	MV	Group 1	8(80%)	-		0.373	-	0.83	NS
		Group 2	8(80%)						
		Group 3	7(70%)						
	CPAP	Group 1	2(20%)	-					
		Group 2	2(20%)						
		Group 3	3 (30%)						
Time of Intake (days)	-	Group 1	5.5000±1.080	4	7	-	0.265	0.769	NS
		Group 2	5.2000±1.033	4	7				
		Group 3	5.5000±1.080	4	7				

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
*: One way ANOVA *: chi square test

There is no statistically significant difference between infants received paracetamol oral, bolus IV and IV infusion as regard the gestational age , sex , birth weight , mode of delivery , type of respiratory support and the time of administration of paracetamol.

Table (2): Comparison of PDA diameter before and after Treatment

	Before ttt		After ttt		z	P-value	Sig.
	Mean	SD	Mean	SD			
Oral paracetamol	2.78	0.12	1.98	1.04	2.408	0.027	S
Bolus IV paracetamol	2.79	0.15	0.91	0.71	8.169	<0.0001	HS
IV infusion paracetamol	2.77	0.15	0.90	0.66	8.727	<0.0001	HS

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
*: Mann Whitney U test

There is statistically significant lower PDA diameter in infants after receiving oral paracetamol, bolus IV and IV infusion paracetamol than before receive paracetamol.

Table (3): Comparison of left atrium: aortic ratio before and after tttt

	Before ttt		After ttt		z	P-value	Sig.
	Mean	SD	Mean	SD			
Oral paracetamol	2.41	0.12	1.85	0.64	2.701	0.023	S
Bolus IV paracetamol	2.43	0.15	1.19	0.94	7.569	<0.0001	HS
IV infusion paracetamol	2.40	0.15	1.18	0.48	7.709	<0.0001	HS

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
*: Mann Whitney U test

There is statistically significant lower left atrium: aortic ratio in infants after receiving oral paracetamol, bolus IV and IV infusion paracetamol than before receive paracetamol.

Table (4): Comparison of PDA size and the severity of pulmonary hypertension

	Mild pulmonary hypertension N=19		Moderate pulmonary hypertension N=11		z	P-value	Sig.
	Mean	SD	Mean	SD			
PDA diameter before (mm)	2.800	0.149	2.768	0.126	0.572	0.576	NS
PDA diameter after (mm)	2.051	1.043	1.540	1.078	1.250	0.227	NS

There is no statistically significant association between PDA size and the severity of pulmonary hypertension

Table (5): Comparison of the clinical outcome of the studied groups

		Group 1 N=10	Group 2 N=10	Group 3 N=10	X^2	P-value	Sig.
Outcome	**PDA closure**	3 (30%)	8 (80%)	8 (80%)	7.177	0.028	HS
	Need surgical intervention	7 (70%)	2 (20%)	2 (20%)			

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
*: chi square test

There is statistically significant higher closure rate of PDA in infants received bolus IV and IV infusion paracetamol than those received oral paracetamol.

DISCUSSION

Indomethacin and ibuprofen, prostaglandin inhibitors that are commonly used to achieve PDA closure **(Gulack et al., 2015)**, act on active cyclooxygenase (COX) receptors to promote ductal constriction by inhibiting prostaglandin synthesis **(Hammerman et al., 2012)**.

However, these drugs may induce severe adverse effects including isolated perforation, renal impairment, hyperbilirubinemia, and necrotizing enterocolitis (NEC) **(Ohlsson & Shah, 2018)**.

The current study included three well matched groups as

regard all baseline characteristics, there was no statistically significant difference between infants received paracetamol oral, bolus IV and IV infusion as regard the gestational age, birth weight, the time of administration of paracetamol, sex, mode of delivery and the type of respiratory support as well as the echocardiographic parameters.

Regarding outcome the current study showed that there was statistically significant higher closure rate of PDA in infants received bolus IV and IV infusion paracetamol than those received oral paracetamol. Both bolus IV and IV infusion groups resulted in similar closure rate of PDA.

Sancak et al., 2016 aimed to compare the efficacy of oral and intravenous paracetamol for closure of hemodynamically significant patent ductus arteriosus in very low birth weight preterm infants. 18 infants treated with either intravenous (n=10) or oral (n=8) paracetamol at 60 mg/kg/day for 3 consecutive days were analyzed retrospectively. All baseline characteristics were comparable in both groups. In disagreement with our results the study reported that PDA closure rate was higher in oral paracetamol group than that in the intravenous paracetamol group (88% vs. 70%), but it was not statistically significant (p=0.588).

However, **Mehralizadeh et al., 2021** revealed that there was no statistically significant difference between oral and IV Acetaminophen as regard first and second left atrium: aortic ratio.

Furthermore, **Cakir et al., 2021** revealed that PDA ligation was significantly higher in Continuous infusion than standard bolus infusion.

Comparison of PDA diameter before and after tttt, showed that there is statistically significant lower PDA diameter in infants after receiving oral paracetamol, bolus IV and IV infusion paracetamol than before receive paracetamol.

In agreement with our results **El-Khuffash et al., 2014** revealed that the short and long course of oral paracetamol, and intravenous administration of paracetamol resulted in significant improvement in PDA diameter.

Comparison of left atrium: aortic ratio before and after tttt, showed that there is statistically significant lower left atrium: aortic ratio in infants after receiving oral paracetamol, bolus IV and IV infusion paracetamol than before receive paracetamol.

In agreement with our results **Mehralizadeh et al., 2021** revealed that there was statistically significant improvement in left atrium:aortic ratio in both oral and IV Acetaminophen treatment.

In agreement with our results **Vaidya et al., 2021** revealed that larger PDA was significantly associated with non-closure of PDA with acetaminophen in preterm infants. But in contrast to our results, they reported that left atrium:aortic ratio was no significantly associated with closure of PDA.

In the present study we found that PDA closure was higher in male and in normal vaginal delivery neonates. There is no statistically significant difference between infants closed and not closed PDA as regard the type of respiratory support, GA and birth weight.

Also, **Vaidya et al., 2021** reported that PDA closure of Intravenous Paracetamol was significantly associated with GA and birth weight but non-significantly associated with gender, vaginal delivery, and mechanical ventilation.

As well, **Valerio et al., 2016** revealed that there was no statistically significant difference between closed and non-closed PDA as regard with gender, mode of delivery, GA and birth weight.

Comparison of ductus arterosus parameters of the studied groups, showed that there was statistically significant lower PDA diameter and left atrium: aortic ratio in infants received bolus IV and IV infusion paracetamol than those received oral paracetamol.

However, **Mehralizadeh et al., 2021** revealed that there was no statistically significant difference between oral and IV Acetaminophen as regard first and second left atrium: aortic ratio.

Also, **Sancak et al., 2016 2021** revealed that there was no statistically significant difference between oral and IV Acetaminophen as regard PDA diameter and atrium: aortic ratio. Furthermore, **Cakir et al., 2021** revealed that PDA ligation was significantly higher in Continuous infusion than standard bolus infusion.

LIMITATIONS

1. Sample size is relatively not large.
2. To date, only a handful of non-randomized studies exist to support the effectiveness of i.v. paracetamol in PDA closure.

RECOMMENDATION

Early closure or ligation PDA is recommended to avert the development of pulmonary hypertension in children especially those with large PDA.

CONCLUSIONS

1. Oral, bolus and continuous infusion administration of paracetamol were safe and effective in the treatment of patent ductus arteriosus.
2. Both standard IV intermittent bolus paracetamol infusion and continuous IV paracetamol infusion were more effective in pharmacologic PDA closure compared with oral paracetamol infusion.
3. All regimens were associated with significant improvement in PDA diameter and left atrium: aortic ratio.
4. The current study also suggested that higher RVD, PDA diameter and left atrium: aortic ratio, male gender and vaginal delivery were significant predictors of PDA non-closure.

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