Original Article

A Comparison between the Safety and Efficacy of IV Paracetamol (Acetaminophen) and IV Ibuprofen in Treating Premature Neonates with Patent Ductus Arteriosus (PDA)

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Abstract

Background: Patent Ductus Arteriosus (PDA) is a common Congenital Heart Disease (CHD) that can lead to infant mortality. This study compared the impact of two treatment approaches (*i.e.* intravenous acetaminophen and ibuprofen) on the closure rate of PDA.

Methods: In this randomized controlled trial, 30 infants with PDA were divided into two groups based on the applied treatment approaches (IV acetaminophen and IV ibuprofen). The two groups were compared with each other in terms of primary outcomes including post-intervention PDA grades, length of stay, duration of mechanical ventilation, and patient outcomes (*i.e.* death or discharge).

Results: Based on the results, none of the participants had a moderate or large-sized PDA after the intervention. The post-intervention PDA closure rates in the acetaminophen and ibuprofen groups were 87.5 and 92.1%, respectively (p=0.626). The mortality rate in the acetaminophen and ibuprofen groups were 12.5 and 14.3%, respectively (p=0.886). In addition, no significant difference was found between the two groups in terms of the length of stay and duration of mechanical ventilation (p>0.05).

Conclusion: The results showed that the efficacy of IV acetaminophen was similar to that of IV ibuprofen in the treatment of PDA. However, conducting randomized multicenter clinical trials with larger sample sizes is recommended to confirm the replacement of IV ibuprofen by acetaminophen.

Keywords: Acetaminophen, Congenital heart disease, Ibuprofen, Infants, Patent ductus arteriosus, Zanjan

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Introduction

In normal conditions, the length of pregnancy is 268±37 days following the moment of ovulation. According to the World Health Organization (WHO), infants born before 37th week from the first day of the last menstrual period are called premature infants. Infants who weigh less than 2500 *gr* at birth are known as Low Birth Weight (LBW) infants. This condition may occur due to prematurity, Intrauterine Growth Restriction (IUGR) or both (1). Premature neonates are exposed to many complications such as respiratory, cardiovascular, hematologic, digestive, metabolic, endocrine and renal diseases. Cardiovascular diseases [e.g. low blood pressure, reduced heart rate, and Patent Ductus Arteriosus (PDA)] are among the most important complications of prematurity (1). During fetal development, the ductus arteriosus forms a bridge between the pulmonary artery and the descending aorta (2). In term infants, ductus arteriosus has a muscular contractile structure and functional closure occurs within 10-15 hours after birth (2,3). PDA occurs when a left-to-right shunt develops between the aorta and pulmonary artery through the ductus arteriosus[1] Depending on the gestational age of premature neonates, the incidence of PDA is reported between 30 and 70% (4). Ineffective and untimely treatment of significant hemodynamic disorder caused by PDA can cause many complications and even death (1). PDA complicates the course of respiratory distress syndrome in preterm infants. This condition can lead to pulmonary edema, hyperdynamic heart failure, and systemic ischemia. Some studies have found relationships between PDA and the risk of pulmonary hemorrhage, Bronchopulmonary Dysplasia (BPD), Necrotizing Enterocolitis (NEC), and Intraventricular Hemorrhage (IVH). Complications such as chronic lung disease (CLD) and retinopathy of prematurity (ROP) have also been observed in patients with PDA; however, whether PDA is responsible for their development or not is still unclear (5-7).

The treatment options for PDA closure include fluid restriction, diuretics, medical intervention, and surgical ligation. These options are selected with regard to the condition of each patient, and there is often a six-month interval between medical treatment and surgery (8). Intravenous ibuprofen, oral ibuprofen and indomethacin, and oral or intravenous acetaminophen are available medical treatments for closing PDAs (7,9). Pathophysiologically, prostaglandins are recognized as a key mediator for the patency of the ductus arteriosus (4). Paracetamol inhibits prostaglandin synthase activity at its binding sites for peroxidase whereas indomethacin and ibuprofen inhibit its activity at its binding sites for cyclooxygenase (7). Indomethacin and ibuprofen have successfully closed PDAs in 70-80% of the studied cases. However, some side effects associated with these drugs (Such as peripheral vasoconstriction, gastrointestinal bleeding and perforation, decreased platelet aggregation, hyperbilirubinemia, and renal failure) have restricted their use (10).

Although ibuprofen is preferred over indomethacin due to its fewer side effects, it is still not an ideal drug because of its 30 % failure rate (10). Recently, successful closure of PDA with paracetamol has been observed in several preterm infants without signs of toxicity (10). No case of gastrointestinal bleeding has been reported with the use of acetaminophen (7).

Surgical treatment is also associated with many complications such left ventricular dysfunction, chylothorax, pneumothorax, and phrenic nerve injury, recurrent laryngeal nerve injury, scoliosis, vocal cord paralysis, dependence on supplemental oxygen, admission to NICU, and increased duration of hospitalization (2). Therefore, considering the potential complications of surgical procedures, medical intervention remains the first line option (4).

Due to the potential side effects of COX inhibitors, the role of paracetamol as an alternative therapy for closing hemodynamically significant PDA has received interest in recent years (11,12).

Therefore, this study compared the safety and efficacy of IV acetaminophen and IV ibuprofen in treating premature neonates with PDA.

Materials and Methods

This randomized controlled trial was conducted in the NICU of Ayatollah Mousavi Hospital in Zanjan, Iran, from March 21, 2017 to March 21, 2018. It was approved by the University's

Ethics Committee and the Neonatal Department and informed consent forms were signed by infants' parents. This clinical trial was registered with the IRCTC website under the main ID: IRCT2016081729404N1.

All LBW infants at the postnatal age of 48-72 hours with hemodynamically significant moderate to large PDA (demonstrated by echocardiogram) were included in the study. Prior to the study, BUN Cr, CRP, and CBC tests were conducted and no sign of bleeding was observed in the patients. For each patient, daily fluid intake was started at 70–80 *ml/kg* and increased by 10–20 *ml/kg/day* to reach150 *ml/kg/day*. Ampicillin and amikacin were administered to all infants upon admission. The infants received appropriate respiratory care based on their levels of respiratory distress and indication. The neonates with major congenital anomalies, life-threatening infections, renal failure, liver failure, platelet counts below 6000/ mm^3, and grade 3 and 4 IVH were excluded from the study. Using permuted block randomization with a block size of 4, the patients were randomly assigned to the acetaminophen (n=16) or the ibuprofen (n=14) intervention groups. In the first group, patients received 15 *mg/kg* body weight of IV acetaminophen every 6 hours for 3 days. In the second group, patients received 10 *mg/kg* body weight of IV ibuprofen on the first day and 5 *mg/kg* on the second and third days.

The patients were examined for three days by a neonatal sub-specialist and the data were recorded. On the fourth day, the neonatal sub-specialist used echocardiography to decide whether the treatment was successful or a second treatment course was needed. The obtained data were analyzed to compare the therapeutic effects and possible side effects of acetaminophen and ibuprofen.

The data collection tool was the data collection form containing the information related to infants' gender, pre/post-intervention PDA grades, the first-and fifth-minute Apgar scores, and their outcomes [including death, post-intervention PDA grades, length of stay, duration of mechanical ventilation, Retinopathy of Prematurity (ROP), BPD, IVH)]. The type of the intervention was also recorded.

Data analysis

The data were analyzed in SPSS 11.5 (SPSS Inc. Chicago, USA). The descriptive results were expressed using statistics of frequency, percentage, mean, standard deviation, chi-square, Fisher exact test, and independent t tests to analyze and compare the obtained results for the two study groups. $P < 0.05$ was considered statistically significant.

Results

The baseline characteristics of 30 infants who met the aforementioned inclusion criteria are presented in two groups in tables 1 (Acetaminophen receivers) and 2 (Ibuprofen receivers). There was no significant difference between the two groups in terms of the baseline characteristics. The mean and SD of the first-and fifth-minute APGAR scores are recorded in table 3.The mean fifth-minute Apgar score of the acetaminophen group (Sig.=0.043) was significantly lower than that of the ibuprofen group. The primary outcomes of this clinical trial included the frequencies and percentages of PDA grades, length of stay, and duration of mechanical ventilation. The secondary outcomes included IVH, ROP, pneumothorax, and BPD (Table 4). The results also indicated that the two types of outcomes had identical frequency distributions in the two groups. It should be noted that no medical complication (caused by acetaminophen or ibuprofen) was observed in the two groups.

Discussion

This study compared the effects of IV acetaminophen and IV ibuprofen on the closure rate of PDA. A total of 30 premature infants (with gestational age between 28 and 34 weeks) were studied. The gestational age of 66.6% of them was less than 30 weeks. According to primary echocardiography performed by a cardiologist, the infants had moderate to severe PDA. Using a random number table, the patients were assigned to two groups of acetaminophen and ibuprofen treatment groups. Three days after starting the treatments, the neonatal sub-specialist used echocardiography to measure PDA dimensions. The results showed that the efficacy of IV

Table 1. The baseline characteristics of the participants in terms of gender, multiple birth, delivery status, gestational age, and birth weight

Baseline CharacterIstics of the ParticiPants	Status	Acetaminophen Group	Ibuprofen Group	Sig.
		Frequency (Percentage)		
Gender	Male	50 (8)	50 (7)	1
	Female	50 (8)	50 (7)	
Multiple birth	Yes	25 (4)	57.1 (8)	0.301
	No	75 (12)	42.9 (6)	
Delivery status	Normal Delivery	12.5 (2)	21.4 (3)	0.642
	Cesarean Section	17.5 (14)	78.6 (11)	
Gestational age (week)	<30	75 (12)	57.1 (8)	0.301*
	30-34	25 (4)	42.9 (6)	
	>34	0	0	
Birth weight (*g*)	<1000	56.2 (9)	28.6 (4)	0.306*
	1000-1499	25 (4)	21.4 (3)	
	1500-1999	12.5 (2)	28.6 (4)	
	2000-2499	6.2 (1)	21.4 (3)	
	≥2500	0	0	

* Fisher exact test p value

Table 2. The baseline characteristics of the participants in terms of cardiovascular life support, airway status, congenital heart disease, maternal hypertension, surfactant treatment, underlying maternal disease, maternal history of drug use, and pre-intervention PDA grades

Baseline characteristics of the participants	Status	Acetaminophen group	Ibuprofen group	Sig.
		Percentage (frequency)		
Cardiovascular life support	Basic cardiac life support	62.5 (10)	85.7 (12)	0.151
	Advanced cardiac life support	37.5 (6)	14.3 (2)	
Airway status	Intubated	75 (12)	64.3 (9)	0.780
	NCPAP	12.5 (2)	21.4 (3)	
	NIV	12.5 (2)	14.3 (2)	
Maternal hypertension	Yes	31.2 (5)	28.6 (4)	0.873
	No	68.8 (11)	71.4 (10)	
Surfactant treatment	Received	43.8 (7)	50 (7)	0.732
	Did not receive	56.2 (9)	50 (7)	
Underlying maternal disease	Yes	12.5 (2)	0	0.485*
	No	87.5 (14)	100 (14)	
Maternal history of drug use	No drug use	50 (8)	50 (7)	0.710*
	Magnesium sulfate	25 (4)	28.6 (4)	
	Corticosteroids	12.5 (2)	21.4 (3)	
	Antihypertensive drugs	6.2 (1)	0	
	Antibiotics	0	0	
	Levothyroxine	6.2 (1)	0	
	Others	0	0	
Pre-intervention PDA grade	Moderate	87.5 (14)	57.1 (8)	0.061
	Large	12.5 (2)	42.9 (6)	

* Fisher exact test p value

Table 3. The mean and SD of the first- and fifth- minute Apgar scores

Variable	Mean ± SD		Sig.
	Acetaminophen Group	Ibuprofen Group	
The 1st Minute Apgar Score	6.44 ± 1.20	7.29 ± 1.49	0.142
The 5th Minute Apgar Score	7.87 ±1.41	8.64 ±1.28	0.043

Table 4. The percentage and frequency of primary and secondary patient outcomes in both groups after the treatment

Outcome	Status	Acetaminophen Group Frequency (Percentage)	Ibuprofen Group Frequency (Percentage)	p value	Statistical Power
Primary Outcome					
Post-Intervention Patent Ductus Arteriosus (PDA) grade	Closed	87.5(14)	92.1 (13)	0.626*	65.4%
	Small	12.5 (2)	7.1 (1)		
	Moderate	0	0		
	Large	0	0		
Length of stay	< 10 days	62.5 (10)	64.3 (9)	0.942*	94.2%
	10-30 days	18.8 (3)	21.4 (3)		
	> 30 days	18.8 (3)	14.3 (2)		
Duration of mechanical Ventilation	None	25 (4)	35.7 (5)	0.926*	94%
	< 10 days	50 (8)	42.9 (6)		
	10-20 days	18.8 (3)	14.3 (2)		
	> 20 days	6.2 (1)	7.1 (1)		
Death rate	Cured and discharged	87.5 (14)	85.7 (12)	0.886*	88.7%
	Dead	12.5 (2)	14.3 (2)		
Secondary Outcome					
Intraventricular Hemorrhage (IVH)	No	75(12)	78.6 (11)	0.548*	55.8%
	Grade 1	12.5 (2)	21.4 (3)		
	Grade 2	6.2 (1)	0		
	Grade 3	6.2 (1)	0		
	Grade 4	0	0		
Retinopathy of Prematurity (ROP)	Yes	12.5 (2)	0	0.485*	78%
	No	87.5 (14)	100 (14)		
Pneumothorax	Yes	0	7.1 (1)	0.467*	65.8%
	No	100 (16)	92.9 (13)		
Bronchopulmonary Dysplasia (BPD)	Yes	6.2 (1)	7.1 (1)	0.999*	99%
	No	93.8 (15)	92.9 (13)		

* Fisher exact test p value

acetaminophen was similar to that of IV ibuprofen in treating PDA.

Dang *et al* conducted a clinical trial on 160 premature infants to investigate the effects of oral paracetamol and ibuprofen on PDA closure rates. They found that the closure rate of paracetamol was comparable to (and even equal to) that of oral ibuprofen (13). The present study compared the efficacy of the IV form of these two drugs and no significant difference was found in terms of PDA closure rates and other outcomes. However, use of acetaminophen was accompanied by lower risk of hyperbilirubinemia and gastrointestinal bleeding in the study by Dang *et al* (13).

Sinha *et al* conducted an observational study on 10 neonates with large-sized PDA and ibuprofen was contraindicated for use in them. They found that oral paracetamol (Acetaminophen) was able to effectively close these types of PDAs. The preterm neonates were born at gestational age of 27-33 weeks with birth weight of 800-1400 *gr* and different stages of congestive heart failure. Acetaminophen and ibuprofen were not compared with each other; however, their study confirmed the efficacy of oral acetaminophen in the treatment of Hemodynamically Significant PDA (HSPDA) (14).

In a meta-analysis, Huang *et al* collected the results of five Randomized Controlled Trials (RCTs) on a total number of 677 neonates to compare the effects of acetaminophen and ibuprofen (Regardless of their oral or intravenous administration) in treating preterm neonates with PDA. They concluded that the efficacy of ibuprofen was comparable to that of paracetamol (Acetaminophen) in the treatment of PDA. However, due to the increased risk of developing renal dysfunction and GIB in ibuprofen receivers, this study suggested that acetaminophen was safer than ibuprofen. The findings also showed that there was no significant difference between the two groups in terms of incidence of PDA-related complications such as NEC, IVH, BPD, and, ROP (15). In the present study, these two treatment methods had similar efficacies and follow-up examinations showed no difference between the two groups in terms of PDA-related complications.

Ratcliffe *et al* conducted an RCT on 80 neonates with gestational age ≤ 30 weeks. They found that oral forms of paracetamol and ibuprofen were equally effective in treating PDA. However, they did not provide any specific recommendation regarding the treatment indications (16). Moreover, a noteworthy point in this research was the similarity of the post-intervention PDA closure rate with the reported spontaneous closure rate among infants born before 28 weeks, which further complicated interpretations of this study. Therefore, they recommended that more precise diagnostic and predictive tools were required to prevent the exposure of infants who would not benefit from PDA-therapy to the unnecessary risks and adverse effects of treatment (16,17). Yang *et al* reported similar efficacies for oral ibuprofen and acetaminophen in the treatment of sympathetic PDA in preterm infants. However, the Prostaglandin E2 (PGE2) levels of acetaminophen group were lower than the ibuprofen group. In addition, oliguria was less frequent in the acetaminophen group than in the ibuprofen group (18). Dani *et al* conducted a clinical trial on 110 infants (born between 25 and 31 weeks' gestation) to compare the effects of intravenous acetaminophen and ibuprofen on the closure rate of PDA. In line with the results of the present study, they found that the two drugs were equally effective in the treatment of PDA. They even suggested that due to its fewer side effects, IV acetaminophen could be considered a suitable substitute for ibuprofen (10).

Generally, low arterial oxygen pressure in the uterus, prostaglandins, and nitric oxide are the most important factors leading to PDA. Among them, PGE2 plays a key role in this regard (3,19). Cyclooxygenase (COX) can catalyze arachidonic acid to convert prostaglandin into active prostaglandin. This enzyme (COX) has two isoforms, COX-1 and COX-2. However, with the discovery of COX-3, this recent isozyme was widely evaluated in several studies and it was shown to be highly sensitive to the inhibitory effects of acetaminophen. Ibuprofen is a non-selective COX-1 and COX-2 inhibitor that exerts its therapeutic effects and complications through influencing active COX sites. On the other hand, although the inhibitory effect of acetaminophen on COX-1, COX-2, and COX-3 has been largely investigated and confirmed, there are still controversies over the mechanism by which it affects PDA. There are two theories in this regard: (1) acetaminophen selectively exerts its inhibitory effects on COX-3; or (2) it does not selectively exert its inhibitory effects on COX, but it degrades the active oxidic COX to its inactive COX form thereby blocking its biological activity (20,21).

In general, the two drugs can significantly reduce PGE2 levels, which can emphasize the mechanism of action of their effect on PDA closure. Moreover, studies have shown that acetaminophen shows better inhibitory effects

than ibuprofen in hypoxic environments such as ductus arteriosus endothelial cells (21).

Considering the prevalence of HSPDA in preterm infants, the hemodynamic instability of these patients, and the uncertainty about sufficient absorption of the oral forms of these drugs, this study investigated the effects of IV forms of acetaminophen and ibuprofen on the closure rate of PDA. Several studies have investigated the effects of oral forms of these two drugs on PDA, but few studies have addressed the effects of their IV forms. This study also evaluated different outcomes (Closure rates in the two groups in addition to length of stay, duration of mechanical ventilation, mortality rates, ROP rates, IVH rates, *etc.*) and showed that there were no significant differences between the two groups in terms of both the primary and the secondary outcomes. Although this study strongly confirmed the equal effects of acetaminophen and ibuprofen injections in treating PDA, it still suffered from some limitations. One of them is associated with its small sample size. Nevertheless, no significant clinical difference was found between the frequencies of the evaluated outcomes. There was no case of moderate or large PDA in either of the two groups, only small PDAs were 5% higher in the acetaminophen group. Nevertheless, the frequency of death was slightly (non-significantly) lower in the acetaminophen group than in the ibuprofen group. Although all the baseline variables were equal in the two groups, the fifth-minute Apgar score was significantly lower in the acetaminophen group. Considering the equality of all outcomes in the two groups, this difference is considered to be in favor of treatment with acetaminophen. Another limitation of this study was that the safety aspect of these drugs was not studied. However, most previous studies found that acetaminophen caused fewer complications than ibuprofen. As Ratcliff *et al* pointed to the association between post-intervention closure rate of PDA, its spontaneous closure, and overtreatment of neonates, appropriate RCTs with large sample sizes are required in which a third group is treated with a placebo in order to compare the effects of paracetamol and ibuprofen on PDA (16).

In general, many studies should be carried out to compare various therapeutic options and identify different indications for PDA treatment.

Conclusion

The results showed that the efficacy of IV acetaminophen was similar to that of IV ibuprofen in the treatment of PDA. However, authors recommend that randomized multicenter clinical trials with larger sample sizes should be conducted to confirm replacement of IV ibuprofen by acetaminophen.

References

1. Bernstein D. The cardiovascular system. In: Kliegman RM, Stanton BF, St. Geme JW, Schor NF. Nelson Textbook of Pediatrics. 20th ed. Volume 2. Philadelphia: Elsevier, Saunders; 2016. p. 2197-202.

2. Katzung BG, Anthony J, *editors.* Basic & Clinical Pharmacology, A Lange Medical Book. 13th ed. New York, USA: McGraw-Hill Education; 2015. p. 618-34.

3. Clyman RI. Patent ductus arteriosus in the preterm infant. In: Avery's Diseases of the Newborn. Gleason CA and Devaskar S (eds.). 9th edition. Philadelphia, PA: Saunders; 2012. p.751-61.

4. Huang X, Wang F, Wang K. Paracetamol versus ibuprofen for the treatment of patent ductus arteriosus in preterm neonates:a meta analysis of randomized controlled trials. J Matern Fetal Neonatal Med 2018 Aug;31(16):2216-22.

5. Clyman RI. Mechanisms regulating the ductus arteriosus. Biol Neonate 2006;89(4):330-5.

6. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev 2010;(4):CD003481.

7. Aikio O, Härkin P, Saarela T, Hallman M. Early paracetamol treatment associated with lowered risk persistent ductus arteriosus in very preterm infants. J Matern Fetal Neonatal Med 2014;27(12):1252-6.

8. Benitz WE. The Cardiovascular System. Martin RJ, Fanaroff AA, Walsh MC, eds. Fanaroff & Martin's Neonatal Medicine-Diseases of the Fetus and Infant. 10th edition. Volume 2. Philadelphia: Elsevier Saunders; 2015. p. 1223-9.

9. Allegaert K, Anderson B, Simons S, van Overmeire B. Paracetamol to induce ductus arteriosus closure: is it valid? Arch Dis Child 2013;98(6):462-6.

10. Dani C, Poggi C, Mosca F, Schena F, Lista G, Ramenghi L,et al. Efficacy and safety of intravenous paracetamol in comparison to ibuprofen for the treatment of patent ductus arteriosus in preterm infants: study protocol for a randomized control trial. Trials 2016 Apr 2;17:182.

11. Hammerman C, Bin-Nun A, Markovitch E, Schimmel MS, Kaplan Fink D. Ductal closure with paracetamol: a surprising new approach to patent ductus arteriosus treatment. Pediatrics 2011;128(6):1618-21.

12. Oncel MY, Yurttutan S, Uras N, Altug N, Ozdemir R, Ekmen S, et al. An alternative drug (paracetamol) in the management of patent ductus arteriosus in ibuprofen-resistant or contraindicated preterm infants, Arch Dis Child Fetal Neonatal Ed 2013;98(1):F94.

13. Dang D, Wang D, Zhang C, Zhou W, Zhou Q, Wu H. Comparison of oral paracetamol versus ibuprofen in premature infants with patent ductus arteriosus: A randomized controlled trial. PLoS One 2013 Nov 4;8(11):e77888.

14. Sinha R, Negi V, Dalal SS. An interesting observation of PDA closure with oral paracetamol in preterm neonates. J ClinNeonatol 2013 Jan;2(1):30-2.

15. Huang X, Wang F, Wang K. Paracetamol versus ibuprofen for the treatment of patent ductus arteriosus in preterm neonates: a meta-analysis of randomized controlled trials. J Matern Fetal Neonatal Med 2018 Aug;31(16):2216-22.

16. Ratcliffe SJ, Sherlock LG, Wright CJ. Oral paracetamol or oral ibuprofen to close the ductus arteriosus: both 'work', but do we know when to use them? Acta Paediatrica, 2017 Sep;106(9):1539.

17. Rolland A, Shankar-Aguilera S, Diomande D, Zupan-Simunek V, Boileau P. Natural evolution of patent ductus arteriosus in the extremely preterm infant. Arch Dis Child Fetal Neonatal Ed 2015;100(1):F55-8.

18. Yang B, Gao X, Ren Y, Wang Y, Zhang Q. Oral paracetamol vs. oral ibuprofen in the treatment of symptomatic patent ductus arteriosus in premature infants: A randomized controlled trial. Exp Ther Med 2016 Oct;12(4):2531-6.

19. Hamrick SE, Hansmann G. Patent ductus arteriosus of the preterm infant. Pediatrics 2010 May;125(5):1020-30.

20. Chandrasekharan NV, Dai H, Roos KL, Evanson NK, Tomsik J, Elton TS, et al. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. Proc Natl Acad Sci USA 2002 Oct 15;99(21):13926-31.

21. Graham GG, Davies MJ, Day RO, Mohamudally A, Scott KF. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. Inflammopharmacology 2013 Jun;21(3):201-32.