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Evaluating the Effectiveness of Ibuprofen from 2 Different Brands in Patent Ductus Arteriosus Closure in Preterm Neonates

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Abstract

Background: Patent ductus arteriosus (PDA) is a common condition in premature babies, with a prevalence rate of 30 - 60%, and often requires medical or surgical intervention.
Objectives: This study aimed to assess the effectiveness of 2 different brands of ibuprofen in PDA closure in preterm infants weighing less than 1500 g.
Methods: This single-blind clinical trial study was performed on 75 premature neonates with PDA in the pediatric ward of Vali-Asr Hospital in Birjand from March 2014 to March 2019. Patients were treated with two brands of ibuprofen at doses of 10 mg/kg for the first day and 5 mg/kg for the second and third days (24 and 48 hours afterward). Before and three days after the last dose, the children were examined by pediatric cardiologist echocardiography. The data were input into SPSS version 23 and analyzed using descriptive statistics, such as mean and SD. Inferential statistics, such as the chi-square test, were also employed with a significance level of P-value < 0.05.
Results: There was a significant difference between the rate of PDA closure, 78.8% in the Pedea group vs. 54.8% in the Ibuprofen group ($P = 0.03$). In the Ibuprofen group, there was no difference in drug efficacy in PDA closure between male and female neonates ($P = 0.663$). Also, in the Pedea group, there was a significant difference in terms of efficacy between male and female neonates ($P = 0.049$). No significant difference was observed in PDA closure between the two medications based on their sizes ($P = 0.616$ in small size, $P = 0.266$ in medium size, and $P = 0.175$ in large size).
Conclusions: Pedea is more effective than Ibuprofen. It reduces complications and the need for surgery. However, there was no significant relationship between the two drugs based on the PDA sizes. Therefore, it seems logical to use the Iranian brand of ibuprofen, considering the benefits equal to the foreign one.

Keywords: Echocardiography, Ibuprofen, Patent Ductus Arteriosus, Pedea, Premature Infants

1. Background

Patent ductus arteriosus (PDA) is a blood vessel that occurs naturally in the embryo and should close completely after birth. However, an open PDA is a congenital defect where the PDA fails to close after birth, causing it to remain open (1, 2). In PDA, excess blood flow, which returns to the lungs from the PDA, causes an increase in pulmonary pressure (3, 4). After respiratory distress syndrome (93.6%), PDA is the second most common disease (41.7%) in premature infants, followed by bronchopulmonary dysplasia (37.8%) (5, 6). According to the conditions, the open PDA can be treated with surgical or non-surgical methods. Most premature infants need medical treatment to close the arterial duct, thus leading to non-surgical methods (7, 8). Pharmacotherapy enables families to avoid the cost of surgery (9, 10). Prostaglandins play an important role in PDA retention. Therefore, cyclooxygenase inhibitors are commonly used to close PDA, and their non-specific cases include indomethacin and ibuprofen (11). Both indomethacin and ibuprofen drugs block arterial duct in

70% of cases; these two drugs compete with arachidonic acid for the reaction site of cyclooxygenase. Therefore, the levels of endogenous arachidonic acid affect the capability of these drugs. If the level of arachidonic acid is high, then there will be more substrate available for cyclooxygenase to convert to prostaglandin production. Conversely, if the level of arachidonic acid is low, then there will be less substrate available for cyclooxygenase to convert to prostaglandin, so ibuprofen and indomethacin may have a more pronounced effect in inhibiting prostaglandin production (12). In 1996, the nonsteroidal anti-inflammatory drug (NSAID) indomethacin has been the treatment of choice for PDA. Numerous studies have been conducted to verify the efficacy of this medication for this particular purpose. As a result, the drug has been approved for neonatal intensive care unit (NICU) use and can be administered intravenously at a dosage of 10, 5, and 5 mg/kg body weight once daily for three consecutive days. Compared to indomethacin, ibuprofen has been shown to have fewer side effects in multiple trials and is often considered in the treatment of PDA (13). It is demonstrated that ibuprofen caused constriction of the ductus arteriosus in newborn lambs, with the degree of constriction increasing with dosage. Furthermore, research has shown that ibuprofen can improve cerebral blood flow (CBF) autoregulation in newborn animals and has the potential for some degree of neuroprotection. In contrast to indomethacin, ibuprofen does not decrease or impair regional blood flow to the brain in newborns and animals. All the mentioned factors have made the use of ibuprofen preferable (14). In addition to the benefits mentioned earlier, treatment with ibuprofen can also reduce the risk of necrotizing enterocolitis (NEC) and transient renal insufficiency. As a result, ibuprofen appears to be the preferred drug of choice compared to other options available (15). Similar to other medications, ibuprofen is manufactured by various pharmaceutical companies. For instance, ibuprofen intravenous injection, 5 mg/mL (Pedea), has received approval for use within NHS Scotland in the treatment of hemodynamically significant infants under 34 weeks of gestational age. However, its safety and efficacy compared to existing alternative treatments have not been formally assessed (16). Caspian Tamin Pharmaceutical Company (Caspian Tamin), located in Guilan Province, Iran, has international licenses to manufacture drugs (17). This company provides ibuprofen in the parenteral form of ampoule, 400 mg/4 mL, and its brand name is Ibuprofen.

Because Pedea is an abroad brand and more expensive and less available than ibuprofen, we decided to compare the effects of the two drugs so that we can use ibuprofen when needed. We decided to compare two different brands of ibuprofen (the French form of ORPHAN pharmaceutical company [Pedea brand] with the Iranian form of Caspian Tamin pharmaceutical company [Ibuprofen brand]); thus, we can assess the effect of the formulation of the two drugs in this study. The ibuprofen injection produced by Caspian Company is available in a concentration of 400 mg/4 mL, and it needs to be diluted before intravenous infusion. The recommended final concentration is 4 mg/mL or less. Suitable diluents include 0.9% sodium chloride injection USP (normal saline) or lactated ringers' solution. During administration, the infusion time must not be less than 30 minutes as per the guidelines provided by Caspian Tamin Company (17).

Pedea is an injectable form that contains the active substance ibuprofen. Pedea should only be used in the NICU. Pedea is administered as three injections into a vein, with each injection given at 24-hour intervals and lasting for 15 minutes. A second course of 3 doses may be administered if the ductus arteriosus fails to close within 48 hours after the final injection or if it re-opens. If the condition remains unchanged even after the second course of therapy, surgery may be required, as suggested by the European Medicines Agency (18).

2. Objectives

This study aimed to assess the effectiveness of 2 different brands of ibuprofen in PDA closure in preterm infants weighing less than 1500 g.

3. Methods

This single-blind clinical trial study was performed on patients referred to the pediatric ward of Vali-Asr Hospital in Birjand from March 2014 to March 2019. The Ethics Committee of Birjand University of Medical Sciences approved this study (code: IR.BUMS.REC.1397.325). Inclusion criteria had no underlying heart disease, having gestational age greater than 27 weeks but less than 32 weeks, and a PDA size that responds positively to drug therapy. In addition, premature infants with PDA having a gestational age of at least 32 weeks or a birth weight less than or equal to 1500 g were also included in the study. Exclusion criteria were having other heart disease and other underlying diseases, major congenital anomalies, life-threatening sepsis, ductal dependent congenital heart disease, major congenital malformations, renal failure (creatinine > 1.5 mg/dL), pulmonary hemorrhage, thrombocytopenia < 60,000/m^3, high level of alanine aminotransferase, urinary output less than 1 mL/kg/h, bleeding from any part of the body,

coagulation disorders, clinical/radiological evidence of NEC, moderate to severe intraventricular hemorrhage (grade 3 or 4 with or without intraparenchymal spread) or the progression of intraventricular hemorrhage that was recognized in an ultrasound earlier, hyperbilirubinemia, and dissatisfaction. Finally, 75 premature infants with PDA were enrolled in this study, and their demographic information was extracted from their files. Then, a checklist was designed based on similar studies that included the patient's first and last name, file number, code assigned for the confidentiality of patient information, gender, type of drug, and echocardiographic results. In this single-blind study, due to the importance of parents' awareness and satisfaction with the treatment, it was the parents' choice to carry out drug treatment with any of the two brands. For this reason, the distribution of neonates with PDA in the study groups was not the same.

The information recorded from the patients' files was related to the effective rate of the drug on boys and girls, and the rate of PDA closure was related to the size of the lesion. In the treatment of these patients, ibuprofen drug from 2 different brands was used. Patients were treated with two brands of ibuprofen by injection at doses of 10 mg/kg on the first day and 5 mg/kg on the second and third day (24 and 48 hours later), which were examined by echocardiography before starting treatment and three days after receiving the last dose of treatment by a pediatric cardiologist.

Once the data were collected, they were entered into SPSS version 23 (SPSS Inc, Chicago, IL, USA). The data was then analyzed using descriptive statistics such as mean and SD, as well as inferential statistics such as the chi-square test. P-values less than 0.05 were considered statistically significant.

4. Results

Seventy-five premature neonates with PDA were enrolled in this study. They were hospitalized in the pediatric ward of Vali-Asr Hospital, affiliated with Birjand University of Medical Sciences, from March 2014 to March 2019. The Ibuprofen group included 25 boys (59.5%) and 17 girls (40.5%), and the Pedea group included 23 boys (69.7%) and 10 girls (30.3%). The mean gestational age in this study was 29.00 ± 1.00 weeks (range, 27 to 31 weeks).

According to Table 1, of the 42 patients in the Ibuprofen group, 23 (54.8%) recovered, and 19 (45.2%) did not respond to treatment according to echocardiographic results. Also, of the 33 patients in the Pedea group, 26 (78.8%) recovered, and 7 (21.2%) did not respond to treatment. Therefore, according to the chi-square test, there was a significant difference in the rate of PDA closure between the Ibuprofen and Pedea groups (P = 0.03).

Table 1. The Results of Treatment in the 2 Groups According to the Echocardiographic Results

Medication Brand	Echocardiography Results		P-Value
	Closed, No. (%)	Open, No. (%)	
Ibuprofen	23 (54.8)	19 (45.2)	0.03
Pedea	26 (78.8)	7 (21.2)	

As shown in Table 2, in the Ibuprofen group, there was no difference in terms of efficacy in PDA closure between male and female neonates (P = 0.663). Also, according to the chi-square test in the Pedea group, there was a significant difference in terms of efficacy in PDA closure between male and female neonates (P = 0.049).

Table 2. Relationship Between Gender and Echocardiographic Results in the 2 Groups of Preterm Neonates Using Ibuprofen and Pedea

Medication Brands	Echocardiography Results		P-Value
	Closed, No. (%)	Open, No. (%)	
Ibuprofen			0.663
Male	13 (52.0)	12 (48.0)	
Female	10 (58.8)	7 (41.2)	
Pedea			0.049
Male	16 (69.6)	7 (30.4)	
Female	10 (100.0)	0 (0.0)	

Considering that the variable distribution of PDA size in the two drug groups was not normal, so according to the chi-square test, it can be said that the PDA size in the two groups did not differ significantly (Table 3).

Table 3. Frequency Distribution of Patent Ductus Arteriosus Size in the 2 Drug Groups

PDA Size	Ibuprofen, No. (%)	Pedea, No. (%)	Total, No. (%)
Small*	15 (35.7)	7 (21.2)	22 (29.3)
Medium**	18 (42.9)	15 (45.5)	33 (44.0)
Large***	9 (21.4)	11 (33.3)	20 (26.7)

Abbreviation: PDA, patent ductus arteriosus.
[a] * Small PDA: 0.8>, LA/AO < 1.4; ** Medium PDA: 0.8 - 1.5, LA/AO < 1.4; *** Large PDA: 1.5 <, LA/AO > 1.4.

According to Table 4, no significant difference was observed in PDA closure between the two medications based on their size (P = 0.616 in small size, P = 0.266 in medium size, and P = 0.175 in large size).

Table 4. Comparison of the Effect of the 2 Drugs on Patent Ductus Arteriosus Closure in Different Sizes [a]

PDA Size and Medication Brands	Closed PDA, No. (%)	Open PDA, No. (%)	P-Value
Small*			0.616
Ibuprofen	5 (83.3)	10 (62.5)	
Pedea	1 (16.7)	6 (37.5)	
Medium**			0.266
Ibuprofen	8 (72.7)	10 (45.5)	
Pedea	3 (27.3)	12 (54.5)	
Large***			0.175
Ibuprofen	6 (66.7)	3 (27.3)	
Pedea	3 (33.3)	8 (72.7)	

Abbreviation: PDA, patent ductus arteriosus.
[a] * Small PDA: 0.8 >, LA.AO < 1.4; ** Medium PDA: 0.8 - 1.5, LA.AO < 1.4; *** Large PDA: 1.5 <, LA.AO > 1.4.

5. Discussion

This study investigated the effect of ibuprofen from 2 different brands on PDA closure in premature infants referred to the pediatric ward of Vali-Asr Hospital in Birjand from March 2014 to March 2019. The results showed that the efficacy of PDA closure in the Pedea brand was 78.8% and in the Ibuprofen brand was 54.6%, indicating the greater effect of the Pedea brand on PDA closure; however, no significant difference in PDA closure was found between the two drugs based on their sizes.

Tofe et al. (19) demonstrated that paracetamol was effective in PDA closure in premature neonates under 32 weeks of gestation. They showed that paracetamol was comparable to ibuprofen and indomethacin in treating PDA, with a closure rate of 77.7% observed in the paracetamol group vs. 81.1% in the ibuprofen group. They indicated that paracetamol could be an effective option in PDA closure as a first-line treatment when ibuprofen was not effective. In this study, the rate of PDA closure by ibuprofen was slightly higher than in our study, but there was no relationship between the size of the lesion and the effect of the drug.

Al-Lawama et al. (20) conducted a study to assess the safety and effectiveness of oral paracetamol vs oral ibuprofen in treating PDA in 120 preterm neonates. They revealed that the mortality rate was nearly the same in both groups, with 23% in the paracetamol group vs. 22% in the ibuprofen group. Additionally, the initial closure rate was 69% for the paracetamol group and 78% for the ibuprofen group. They indicated that there was no significant difference in the mortality rate or initial closure rate between the two groups (20). The short-term neonatal outcomes were also found to be comparable for both oral paracetamol and oral ibuprofen. These findings suggest that both medications can be safely and effectively used to treat PDA in premature infants. This study was similar to the French type of ibuprofen in our study in terms of the effect of ibuprofen, but it did not study the effect of the two brands of the same drug.

In the study by Demir et al. (21), the efficacy and safety of rectal ibuprofen for PDA closure in 72 premature infants with very low birth weight (VLBW) were studied with the aim of comparing rectal ibuprofen with oral ibuprofen. They showed that rectal ibuprofen was as effective as oral ibuprofen in closing PDA in VLBW neonates. The efficacy rate in this study in both rectal and oral ibuprofen was above 80%, while in our study, only the French form of the drug had a result of about 78.8%, but its Iranian form had a result of 54.6%. Since this study used a drug brand with two different forms, it may be more similar to our study.

In a retrospective study by Olgun et al. (22), the efficacy and safety of repeated courses of oral ibuprofen in premature infants with PDA were evaluated to explain the rate of PDA closure and side effects after repeated courses of oral ibuprofen. A total of 100 patients received oral ibuprofen, of whom 6 were unable to complete the treatment due to death and side effects. Additionally, three experienced side effects of oral ibuprofen, including thrombocytopenia and renal dysfunction, during the treatment period. After the treatment period, the PDA closure rate was 88%. Also, in our study, only the French form of the drug had a result of about 78.8%, but its Iranian form had a result of 54.6%, which unlike it, we did not have any side effects in our study.

In a randomized prospective study by El-Mashad et al. (23), a comparative study of the effectiveness and safety of paracetamol, ibuprofen, and indomethacin in PDA closure was performed on 300 preterm infants. The patients were randomly divided into three groups of 100 patients,

and each group was treated separately with paracetamol, ibuprofen, or indomethacin. The closure rate in the ibuprofen group was 83%, which is similar to the effect of the French form in our study.

In a randomized prospective study by Saad et al. (24), the effect of intravenous paracetamol vs. oral ibuprofen on PDA closure was studied on 40 neonates in the NICU of Cairo University Children's Hospital, which the rate of closure by ibuprofen was 75% that is close to the effective rate of the French form in our study, but neither of the two final studies examined the effect of ibuprofen on lesion size.

In Italy, Dani et al. (25) conducted a randomized prospective study on 110 premature infants with PDA in 2 groups of 55 to compare paracetamol with ibuprofen. They concluded that paracetamol had more significant benefits than ibuprofen and could be considered the treatment of choice due to fewer side effects, which is upstream, unlike previous similar studies.

5.1. Conclusions

The rate of PDA closure was 78% in the Pedea group and 54.6% in the Ibuprofen group. Pedea was significantly more effective than ibuprofen, but the two drugs did not have a significant difference in PDA closure based on size. Therefore, it seems logical to use the Iranian brand of ibuprofen, considering the benefits equal to the foreign one.

5.2. Limitations

Conducting a study with a higher statistical population, using a higher quality drug, with regard to performing different studies with paracetamol and similar and close to ibuprofen effects, it is also suggested considering that the French type of ibuprofen has a ready concentration, but the Iranian type of ibuprofen needs preparation; the presence of a pharmacist is recommended to monitor the preparation of the exact concentration.

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Footnotes

Authors' Contribution: Study concept and design: Dr. Salehi Forod and Taghizadegan; Analysis and interpretation of data: Dr. Salehi Forod and Dr. Abedini; Drafting of the manuscript: Dr. Riasi and Dr. Salehi Shiva; Critical revision of the manuscript for important intellectual content: Dr. Davoudi and Kafian; Statistical analysis: Dr. Salehi Forod and Dr. Davoudi.

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References

1. Gersony WM, Peckham GJ, Ellison RC, Miettinen OS, Nadas AS. Effects of indomethacin in premature infants with patent ductus arteriosus: results of a national collaborative study. *J Pediatr.* 1983;**102**(6):895–906. [PubMed ID: 6343572]. https://doi.org/10.1016/s0022-3476(83)80022-5.
2. Kabra NS, Schmidt B, Roberts RS, Doyle LW, Papile L, Fanaroff A, et al. Neurosensory impairment after surgical closure of patent ductus arteriosus in extremely low birth weight infants: results from the Trial of Indomethacin Prophylaxis in Preterms. *J Pediatr.* 2007;**150**(3):229–34. 234 e1. [PubMed ID: 17307535]. https://doi.org/10.1016/j.jpeds.2006.11.039.
3. Allen HD, Goldberg SJ, Valdes-Cruz LM, Sahn DJ. Use of echocardiography in newborns with patent ductus arteriosus: a review. *Pediatr Cardiol.* 1982;**3**(1):65–70. [PubMed ID: 7155942]. https://doi.org/10.1007/BF02082335.
4. Neumann R, Schulzke SM, Buhrer C. Oral ibuprofen versus intravenous ibuprofen or intravenous indomethacin for the treatment of patent ductus arteriosus in preterm infants: a

systematic review and meta-analysis. *Neonatology*. 2012;**102**(1):9–15. [PubMed ID: 22414850]. https://doi.org/10.1159/000335332.
5. Bancalari E, Claure N, Gonzalez A. Patent ductus arteriosus and respiratory outcome in premature infants. *Biol Neonate*. 2005;**88**(3):192–201. [PubMed ID: 16210841]. https://doi.org/10.1159/000087582.
6. Lu J, Li J, Li Q, Li Z. Meta-Analysis to Assess Efficacy and Safety of High-Dose Ibuprofen Compared with Standard Treatment of Patent Ductus Arteriosus in Premature Infants. *Iran J Pediatr*. 2016;**27**(4). https://doi.org/10.5812/ijp.6328.
7. Smyth JM, Collier PS, Darwish M, Millership JS, Halliday HL, Petersen S, et al. Intravenous indometacin in preterm infants with symptomatic patent ductus arteriosus. A population pharmacokinetic study. *Br J Clin Pharmacol*. 2004;**58**(3):249–58. [PubMed ID: 15327584]. [PubMed Central ID: PMC1884560]. https://doi.org/10.1111/j.1365-2125.2004.02139.x.
8. Tefft RG. The impact of an early Ibuprofen treatment protocol on the incidence of surgical ligation of the ductus arteriosus. *Am J Perinatol*. 2010;**27**(1):83–90. [PubMed ID: 19784912]. https://doi.org/10.1055/s-0029-1239492.
9. Novick WM, Watson DC, Alpert BS, Becker JA, DiSessa TG, Ring JC, et al. Patent ductus arteriosus ligation: are we doing better? *Ann Thorac Surg*. 1995;**59**(4):822–4. [PubMed ID: 7695403]. https://doi.org/10.1016/0003-4975(95)00047-o.
10. Shenassa H, Sankaran K, Duncan W, Tyrrell M, Bharadwaj B. Surgical ligation of patent ductus arteriosus in a neonatal intensive care setting is safe and cost effective. *Can J Cardiol*. 1986;**2**(6):353–5. [PubMed ID: 3100008].
11. Pacifici GM. Ibuprofen and indomethacin for the closure of the patent ductus arteriosus. *Med Express*. 2016;**3**(3). https://doi.org/10.5935/MedicalExpress.2016.03.01.
12. Rheinlaender C, Helfenstein D, Walch E, Berns M, Obladen M, Koehne P. Total serum bilirubin levels during cyclooxygenase inhibitor treatment for patent ductus arteriosus in preterm infants. *Acta Paediatr*. 2009;**98**(1):36–42. [PubMed ID: 18764861]. https://doi.org/10.1111/j.1651-2227.2008.01007.x.
13. de Klerk JCA, van Paassen N, van Beynum IM, Flint RB, Reiss IKM, Simons SHP. Ibuprofen treatment after the first days of life in preterm neonates with patent ductus arteriosus. *J Matern Fetal Neonatal Med*. 2021;**34**(15):2411–7. [PubMed ID: 31510826]. https://doi.org/10.1080/14767058.2019.1667323.
14. Aranda JV, Thomas R. Pharmacology Review. *NeoReviews*. 2005;**6**(11):e516–23. https://doi.org/10.1542/neo.6-11-e516.
15. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. *Cochrane Database Syst Rev*. 2018;**9**(9). CD003481. [PubMed ID: 30264852]. [PubMed Central ID: PMC6513618]. https://doi.org/10.1002/14651858.CD003481.pub7.
16. *Ibuprofen intravenous injection 5 mg/ml (PedeaÒ)*. Scottish Medicines Consortium; 2006. Available from: https://www.scottishmedicines.org.uk/medicines-advice/ibuprofen-intravenous-injection-5mgml-pedea-abbreviatedsubmission-23306/.
17. *Ibuprofen*. Tehran, Iran: Caspian Tamin Pharmaceutical Co; 2023, [updated 2022 May 16; cited 2023 Feb 14]. Available from: https://caspiantamin.com/en/product/ibuprofen.
18. *Pedea*. United Kingdom: European Medicines Agency, Inc; 2023, [updated 2022 Jul 11; cited 2023 Feb 14]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/pedea.
19. Tofe I, Ruiz-Gonzalez MD, Canete MD, Pino A, Rueda RL, Parraga MJ, et al. Efficacy of Paracetamol in Closure of Ductus Arteriosus in Infants under 32 Weeks of Gestation. *Front Pediatr*. 2018;**6**:25. [PubMed ID: 29492399]. [PubMed Central ID: PMC5817073]. https://doi.org/10.3389/fped.2018.00025.
20. Al-Lawama M, Alammori I, Abdelghani T, Badran E. Oral paracetamol versus oral ibuprofen for treatment of patent ductus arteriosus. *J Int Med Res*. 2018;**46**(2):811–8. [PubMed ID: 29239259]. [PubMed Central ID: PMC5971505]. https://doi.org/10.1177/0300060517722698.
21. Demir N, Peker E, Ece I, Balahoroglu R, Tuncer O. Efficacy and safety of rectal ibuprofen for patent ductus arteriosus closure in very low birth weight preterm infants. *J Matern Fetal Neonatal Med*. 2017;**30**(17):2119–25. [PubMed ID: 28052714]. https://doi.org/10.1080/14767058.2016.1238897.
22. Olgun H, Ceviz N, Kartal I, Caner I, Karacan M, Tastekin A, et al. Repeated Courses of Oral Ibuprofen in Premature Infants with Patent Ductus Arteriosus: Efficacy and Safety. *Pediatr Neonatol*. 2017;**58**(1):29–35. [PubMed ID: 27238078]. https://doi.org/10.1016/j.pedneo.2015.04.017.
23. El-Mashad AE, El-Mahdy H, El Amrousy D, Elgendy M. Comparative study of the efficacy and safety of paracetamol, ibuprofen, and indomethacin in closure of patent ductus arteriosus in preterm neonates. *Eur J Pediatr*. 2017;**176**(2):233–40. [PubMed ID: 28004188]. https://doi.org/10.1007/s00431-016-2830-7.
24. Saad IA, Malash AH, Hussein NF, Abdelmasih AF, Kassem RE. OP-150 [AJC » Cardiac imaging - Echocardiography] PDA Closure with Paracetamol Versus Ibuprofen. *Am J Card*. 2017;**119**(8). e11. https://doi.org/10.1016/j.amjcard.2017.03.066.
25. 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;**17**:182. [PubMed ID: 27038924]. [PubMed Central ID: PMC4818852]. https://doi.org/10.1186/s13063-016-1294-4.