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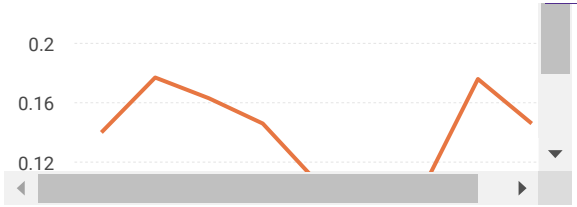

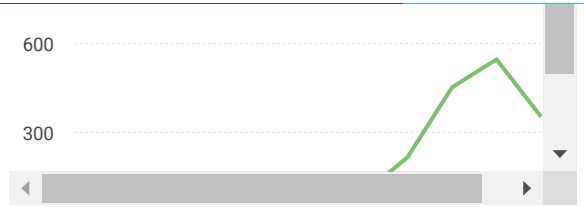

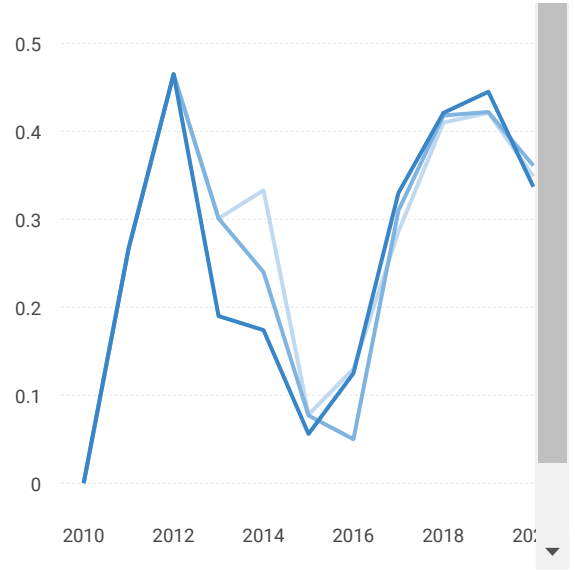

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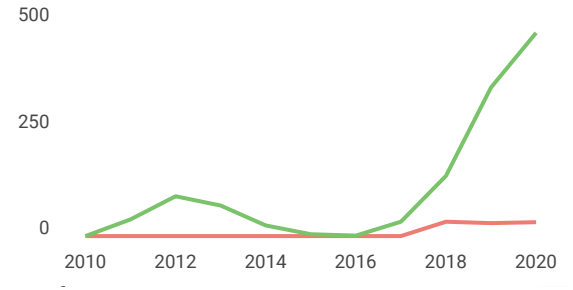

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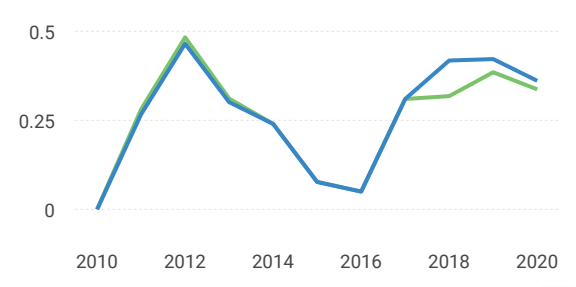

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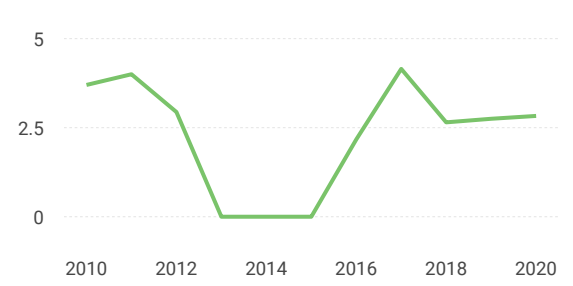

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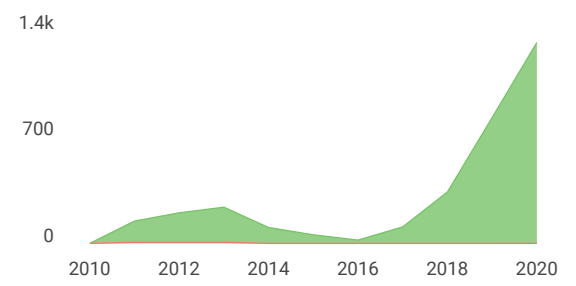

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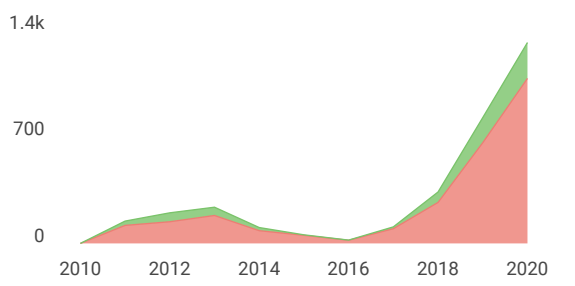

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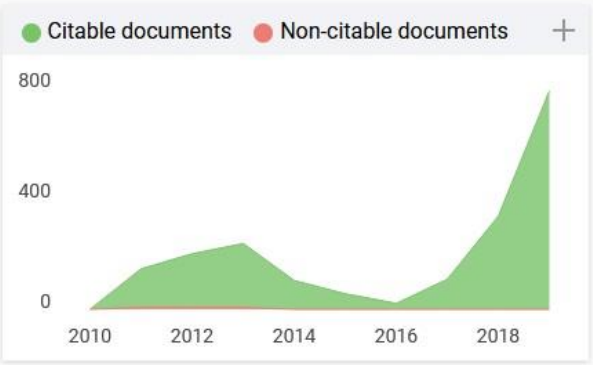

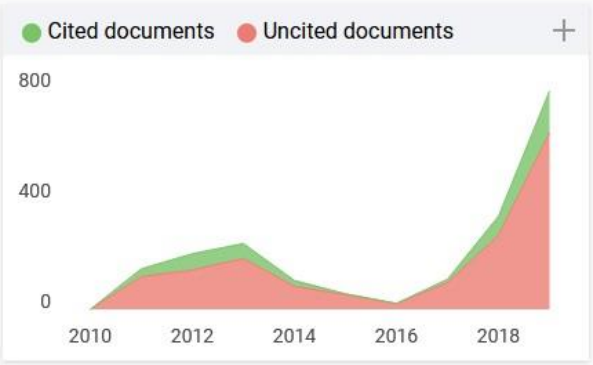

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RESEARCH ARTICLE

The Usage of Paracetamol and Ibuprofen in Children with Persistent Ductus Arteriosus

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Abstract

Backgrounds: Persistent Ductus Arteriosus (PDA) is the structure of the ductus arteriosus that failed to close after the birth of the baby. One of the therapies which are used to overcome the closure of PDA is pharmacological therapy using prostaglandin inhibitors. Aim: to determine usage profiles, including dosage, frequency, route, and duration of paracetamol administration and ibuprofen for DAP. In addition, it also assesses the actual outcomes and side effects of using paracetamol and ibuprofen in children with PDAs. Method: this research was a quantitative research with a retrospective method. The sampling method used random sampling. The total sample was 32 children who were hospitalized with diagnosis of PDA with or without complications. Data was collected by conducting an assessment of the patient's medical record to the documentation sheet. Results: Based on research in 32 patients, 78% of patients received paracetamol therapy, 16% of patients received ibuprofen, and 6% of patients received replacement therapy for paracetamol to ibuprofen. From 25 patients who received paracetamol therapy, 12 patients (48%) gave the outcome of PDA closure and eliminated patient tachypnea and cyanosis. The average dose of paracetamol used for PDA is 7.5-15 mg / kg every 6 hours for 3-7 days by oral route (9%) and intravenously (63%).While the average dose of ibuprofen for PDAs is 10 mg / kg / day for the first day and 5 mg / kg / day for the second and third days by oral route (100%). Conclusion: the use of paracetamol and ibuprofen for PDAs was in accordance with existing literature relating to the dose, route, frequency, and duration of administration for PDAs. However, there were some patients with special conditions that require adjustment of the second dose of the drug. The use of paracetamol and ibuprofen for PDAs did not cause actual side effects. The use of paracetamol for PDAs needs to be further investigated regarding the effectiveness and drug related problems and the need to consider the use of ibuprofen for PDAs related to potential side effects that can be caused.

Keywords: *Patent ductus arteriosus, Paracetamol, Ibuprofen, Pediatrics.*

Introduction

Patent ductus arteriosus (PDA) is the condition of ductus arteriosus that fail to close a few hours after the birth of the baby [1].PDAs in preterm infants (preterm) are caused by impaired prostaglandin metabolic processes because the baby's lung function is not normal, high prostaglandin reactivity, and decreased calcium and oxygen sensitivity in vascular smooth muscle [2].

Pharmacological therapy used is a type of COX inhibitor Indomethacin and ibuprofen, besides that it can also be given paracetamol. However, the administration of paracetamol is still in the category of off label drugs, ie drugs used outside the usual indications [3].Therefore, sufficient knowledge of dosage, frequency of use, potential side effects, and the outcome of using ibuprofen and paracetamol for PDAs are related to the role of pharmacists in counseling drug information to patients so that therapeutic goals can be achieved.PDAs are congenital heart disorders that often occur with a frequency of occurrence by 31% in low-weight infants [4].The prevalence of PDAs in normal infants is 2-8 cases per 10,000 births [5].

This can increase in the condition of premature babies. PDA occurs 5-10% of congenital heart disease [1].About 60-70% of premature babies born less than 28 weeks get therapy for PDA [6].PDA occurs in 55% of premature babies born less than 28 weeks

and weighing less than 1000 grams [7].The ductus arteriosus can close by itself on the 7th day in 70% of babies born weighing between 1000-1500 grams [8].The therapy that can be given to PDAs can be pharmacological and non-pharmacological therapy (surgery) [9]. Surgical therapy is carried out if the patient does not respond with the use of at least two drug therapies. In addition, surgery is also performed when large ducts are found, patients using ventilators and patients with high oxygen requirements [9].

Meanwhile, pharmacological therapy that can be given to PDA patients is by giving indomethacin which is a COX inhibitor. The use of this drug has been approved by the Food and Drug Administration [10]. Indomethacin for PDAs works by inhibiting cyclooxygenase which will convert arachidonic acid into systemic prostaglandins so as to reduce prostaglandin levels and cause PDA closure [11].

The efficacy of indomethacin for PDA therapy is around 60% to 80% [8]. Indomethacin is often used as prophylactic therapy and provides good results for infants weighing less than 1000 grams at a dose of 0.1 mg / kg / day for 3 to 6 days [12]. This drug is contraindicated for patients who experience intraventricular hemorrhage (IVH), acute renal failure, and thrombocytopenia [13].

Some things that need to be observed in the use of indomethacin are kidney disorders, disorders of platelet aggregation, hyperbilirubinemia, gastrointestinal perforation and necrotizing enterocolitis (NEC) [8].Because there are many side effects, this drug is rarely used for PDA therapy [11].In addition to indomethacin, PDA therapy treatment can be done by administering another NSAID drug, ibuprofen.

The use of ibuprofen for PDAs is preferred over indomethacin because it has lower side effects [6]. In addition, ibuprofen also received approval from the FDA as a PDA therapy drug in 2009 [14]. Ibuprofen can be used as a PDA therapy because it can inhibit COX which is an enzyme that plays a role in the formation of prostaglandins so as to reduce prostaglandin levels and trigger PDA closure [15]. The efficacy of ibuprofen for PDA therapy is around 60% to 80% [8].

The dosage of ibuprofen given is different from the dosage of ibuprofen which is indicated for anti-inflammatory and mild analgesics. For analgesics and anti-inflammation, ibuprofen is given at a dose of 4-10 mg / kg body weight, a maximum of 40 mg / kg body weight / day [15].While for PDAs, ibuprofen is given for 3 days at a dose of 10 mg / kg body weight on the first day and 5 mg / kg body weight on the second and third days [16].

Ibuprofen has side effects of kidney disorders that are lower than indomethacin, but can increase the risk of pulmonary complications, namely chronic lung disease (CLD) and pulmonary hypertension [4]. Another literature mentions that ibuprofen side effects are kidney disorders, disorders of platelet aggregation, hyperbilirubinemia, gastrointestinal perforation and necrotizing enterocolitis (NEC) [8].Ibuprofen is contraindicated for patients who experience

Intraventricular Hemorrhage (IVH), acute renal failure, and thrombocytopenia [13].In addition to COX inhibitors (NSAIDs), there are other drugs that can be used to treat PDA, namely paracetamol. Paracetamol is commonly used for patients who are intolerant of ibuprofen or who do not respond with ibuprofen [7].Prostaglandin which plays a role in the pathogenesis of PDA comes from the enzyme prostaglandin H2 synthetase (PGHS) which has two active sides, namely COX and peroxidase.

Peroxidase can be inhibited by paracetamol so that it can reduce systemic prostaglandins and help close the PDA [17]. The use of paracetamol is also preferred because it has the same effectiveness as ibuprofen and indomethacin with lower side effects [7].The risk of side effects of gastrointestinal bleeding and hyperbilirubinemia from paracetamol is lower than ibuprofen. Ibuprofen will bind 99% with albumin and at high levels can shift the bond between bilirubin and albumin which causes an increased risk of hyperbilirubinemia [18].

Method

This study was an observational study using retrospective data. The study was carried out Pediatrics Department at Dr. Soetomo Hospital Surabaya, Indonesia. Samples were neonates' patients with inclusion criteria with a diagnosis of persistent or

uncomplicated ductus arteriosus who received ibuprofen or paracetamol therapy, had complete medical record and underwent treatment in the period January 2013 to December 2016. The sample size was 32 children. Data collection with the stages of selecting patients in accordance with the inclusion criteria, then from the medical record, the data would be collected and transferred to the data collection sheet.

Data collected were name, age, body weight, gender, diagnosis, clinical data, and therapy given includes the name of the drug, dose, frequency, duration of administration, potential side effects of the drug, clinical data and treatment outcomes.

The data obtained was processed by descriptive analysis method, namely data regarding the relationship of clinical data of patients who received ibuprofen or paracetamol therapy with successful therapy.

Results

Demographic data of respondents can be seen in Table 1.As many as 53% of patients were female. The patient's gestational age was at most at the term of 37-42 weeks, as much as 47%. The results of the assessment of the birth weight of patients, most of them had moderate birth weight about 50% of total sample.While the most common PDA category of the patient was moderate category with 44%.

Table 1: Demographic data of the respondent

	N	%
Gender		
Male	15	47
Female	17	53
Gestational Age		
<37 weeks	14	44
37-42 weeks	15	47
>42 weeks	1	3
No data	2	6
Birth Weight		
Low	15	47
Moderate	16	50
High	1	3
PDA Category		
Very Small (<1,5 mm)	1	3
Small (1,5-3 mm)	9	28
Moderate (3-5 mm)	14	44
Large (>5 mm)	8	25

Clinical manifestations based on collected data can be seen in Table 2. Most patients (50%) with congested clinical manifestations and 34% had no congestion and cyanosis.

Table 2: Clinical manifestations of patients with PDAs

Clinical Manifestation	∑ Patient (%)	Description
Tachypnea	16 (50%)	Cyanosis is caused by dirty blood from the pulmonary artery mixed with clean blood in the arteries (19).
Cyanosis	0 (0%)	
Tachypnea + Cyanosis	5 (16%)	
There is no Tachypnea dan Cyanosis	11 (34%)	
Total	32 (100%)	Tachypnea due to pulmonary edema thereby decreasing pulmonary compliance leading to increased oxygen demand (20)

The profile of ibuprofen used in PDA patients can be observed in Table 3. Based on table 3, patients with PDAs who closed after ibuprofen administration were 40%, PDA reduced by 1 patient (20%), PDA reopening as much as 1 patient (20%) and none data of 1 patient (20%) * out of 5 patients.

Table 3: Profile of Ibuprofen usage in patients with PDAs

Respondent	Body Weight (gram)	Route	Doses	Duration of usage	Initial Condition → Outcome	Description
R1	1900	PO	1 x21,5 mg	1 day	Moderate (0,39cm) → closed	The dosage increases because the new patient gets therapy in H15. With Increasing age after post natal, the clearance of ibuprofen is getting faster [3]
			1 x 10,75 mg	2 days		
R2	1900	PO	1x10 mg	1 day	Moderate PDA (0,3 cm) → Small PDA (0,1 cm) → reopening (0,2 cm) → KRS starts to recover	In hypoalbumin patients, the dose is lowered because ibuprofen is bound 99% with albumin and will shift albumin-bilirubin bonds and increase the risk of hyperbilirubinemia. Ibuprofen can be repeated up to 3 cycles.
			1x5 mg	2 days		
		Repeated to 2 cycles				
		PO	1x10 mg	1 days		
			1x5 mg	2 days		
		PO	1x10 mg	1 days		
			1x5 mg	2 days		
R3	2450	PO	1x25 mg	1 days	Moderate PDA → the patient recovered	Dosage according to literature
			1x37,5 mg	2 days		
R4	3350	PO	1x15 mg	8 days	Large PDA > Moderate PDA	The age of 17 days> patients was less sensitive to prostaglandin inhibitors 2. Patients with hypalbumin, the dose was lowered because ibuprofen could bound 99% with albumin and would shift albumin-bilirubin bonds and increase the risk of hyperbilirubinemia.
R5	3500	PO	1x35 mg	1 days	Small PDA > Closed	Dosage according to literature, aterm, Body weight is sufficient
			1x17,5 mg	2 days		

Descriptions

- The use of ibuprofen for PDA patients does not cause actual side effects.
- The dosage of ibuprofen for PDAs according to literature is 10 mg / kg / days for the first days and 5 mg / kg / days for the second and third days [16]. Another literature mentions high doses of ibuprofen for PDA, 20 mg / kg / days for the first day and 10 mg / kg / days for the second day and third for aterm and preterm infants [21].
- *There is no data regarding the size of the patient's PDA.
- **Premature babies
- The percentage of total outcomes was obtained from a total of 5 patients.

The profile of paracetamol use in PDA patients can be seen in Table 4. It can be concluded that PDA was closed in as many as 12 patients (48%), PDA condition was reduced in 7 patients (28%), there are no data for 6 patients (24%).

Table 4: Profile of paracetamol usage in patients with PDAs

Respondent	Body Weight (gram)	Route	Doses	Duration of Use	Initial Condition → Outcome	Description
R6	1000	IV	4x15 mg	8 days	Moderate PDA > Small PDA	Dosage according to literature. After 4 days treatment, the PDA was reduced, so the therapy was continued for 4 days but the patient died. Body weight is low & premature so the Ductus Arterious hasn't closed.
R7	1200	IV	4x15 mg	5 days	Small PDA > closed	Dose according to body weight and in accordance with literature to close the PDA
R8	1400	IV	4x20 mg	13 days	PDA besar > closed	Dosage according to literature, Patients received Paracetamol therapy for 7 days but the PDA had not yet closed so that the paracetamol was given again for 6 days and PDA was fully closed. Ibuprofen is not given because of contraindications for patients with sepsis condition.
R9	1500	IV	4x22 mg	10 days	Small PDA (0,27 cm) > Small PDA (0,13 cm)	The dose was in accordance with the literature, preterm, low body weight, the drug therapy given in the 18th day so that it was less sensitive to prostaglandin inhibitors. Ibuprofen is not given because of contraindications for patients with sepsis contiditon.
R10	1500	IV	4x25 mg	8 days	Small PDA L to R shunt > Discharged from hospital, improved condition	Dosage according to literature (aterm baby)
R11	1900	PO	3x20 mg	4 days	Small PDA > Discharged from hospital improved condition	Dosage according to literature. Frequency of drug therapy was 1 times a day because at H1 the SGOT value is> normal
R12	1950	IV	4x30 mg	10 days	Large PDA > closed	Dosage according to literature. Medicines given 4 days continue to 6 days. Sufficient weight for increasing

						PDAs. Ibuprofen is not given because of contraindications for patients with sepsis condition
R13	2000	IV	4x40 mg	1 days	Large PDA > Small PDA (0,15 cm)	Referred Patient, previously received 4x40 mg paracetamol, then lowered to 4x30 mg because it exceeded the usual dose.
			4x30 mg	2 days		
R14	2050	PO	4x35 mg	4 days	Small PDA > Closed	Dosage according to literature
R15	2100	IV	4x30 mg	10 days	Moderate PDA L to R shunt > Small PDA L to R shunt (0,12 cm) > Small PDA (0,09 cm)	Dosage according to literature. Preterm, low body weight> PDA has not closed. Ibuprofen was not given because hyperbilirubinemia and paracetamol administration have responded.
R16	2200	IV	4x32	9 days	Moderate PDA > closed	Paracetamol given for 6 days, PDA has not closed, so the therapy is continued. Not given ibuprofen because of sepsis condition
R17	2440	IV	4x45 mg	3 days	Small PDA > closed	Dosage is not according to literature
R18	2600	PO	4x45 mg	3 days	Moderate PDA L to R shunt (0,4 cm) > closed	The initial dose given is higher because the PDA is with L to R shunt, then the dose is lowered because the direct bilirubin levels was increasing.
R19	2650	IV	4x40 mg	5 days	Small PDA L to R shunt (0,2 cm) > Improved Condition	Dosage according to literature, aterm, normal weight
R20	2750	IV	4x40 mg	7 days	Moderate PDA > closed	Dosage according to literature, aterm, normal weight
R21	2800	IV	4x40 mg	3 days	Moderate PDA > Discharged from hospital, improved condition	The patients just got therapy in H12
R22	2900	IV	4x44 mg	9 days	Moderate PDA > Small PDA	Dosage according to literature, aterm, normal weight
R23	3100	IV	4x50 mg	4 days	PDA 0,3 cm > closed	Dosage according to literature, aterm, normal weight
R24	3200	IV	4x50 mg	1 days	Large PDA > Small PDA	Dosage according to literature, aterm, normal weight. Patients die due to other congenital abnormalities (hyperplasiatoraks, cardiomegaly, polydactyl).
			4x48 mg	5 days		
R25	3300	IV	4x50	5 days	Small PDA > closed	Dosage according to

			mg			literature, aterm, normal weight
R26	3300	IV	4x50 mg	12 days	Moderate PDA > Small PDA (0,17 cm)	Patients did not get ibuprofen therapy because of hyperbilirubinemia and low albumin levels.
R27	3500	IV	3x50 mg	5 days	Large PDA > Discharged from hospital, improved condition	Dosage according to literature, aterm, normal weight
R28	3700	IV	4x55 mg	3 days	Large PDA > cloed	Dosage according to literature, aterm, normal weight
		PO	4x55 mg	3 days		
R29	3900	IV	4x40 mg	4 days	Large PDA (0,7 cm) > closed	Dosage is not according to literature. The PDA does not close and the dose is increased. Did not get ibuprofen because of low albumin levels.
			3x40 mg	6 days		
			4x60 mg	4 days		
R30	4200	IV	4x65 mg	6 days	Moderate PDA > Discharged from hospital, improved condition	High birth weight so the dose is increased, aterm.

Description:

- The use of paracetamol for PDA patients does not cause actual side effects.
- The dose of paracetamol for PDA according to literature is 15 mg / kg every 6 hours for 3 days. Another literature states that the dose of paracetamol for PDA is 7.5 -15 mg / kg every 4-6 hours, a maximum of 60 mg / kg / day
- *There is no data: there is no data regarding the size of the patient's PDA.
- ** Premature babies (<37 weeks)
- The percentage of total outcomes was obtained from a total of 25 patients.
- Intravenous paracetamol is given by infusion for 15 minutes

The profile of paracetamol replacement into ibuprofen in Table 5, it can be concluded that PDA closes in 1 patient (50%), PDA decreases by 1 patient (50%).

Table 5: Profile of paracetamol replacement into ibuprofen in children with PDAs

Respondent	Body Weight (gram)	Drug	Route	Doses	Duration of usage	Initial condition → Outcome	Kajian
R31	3050	Parasetamol	PO	3x45 mg	3 days	Small PDA → closed	The PDA has not closed so that the frequency of paracetamol is increased to 4ddl, but the PDA has
				4x45 mg	4 days		
		Ibuprofen	PO	1x35 mg	1 days		

				1x16,5 mg	2 days		not closed so it replaces ibuprofen (the patient is not contraindicated).
R32	3120	Parasetamol	IV	4x45 mg	4 days	Large PDA → Small PDA	
		Ibuprofen	PO	1x30 mg	1 days		
				1x15 mg	2 days		

Information:

- Replacement of paracetamol therapy to ibuprofen for PDA patients does not cause actual side effects.
- The dose of paracetamol for PDA according to literature is 15 mg / kg every 6 hours for 3 days. Another literature states that the dose of paracetamol for PDA is 7.5-15 mg / kg every 4-6 hours, a maximum of 60 mg / kg / day. The dosage of ibuprofen for PDAs according to literature is 10 mg / kg / days for the first days and 5 mg / kg / days for the second and third days.
- ** Premature babies (<37 weeks).
- The percentage of total outcomes was obtained from a total of 2 patients.
- The doses of paracetamol and ibuprofen used are in accordance with the literature.

The profile of PDA therapy outcome in Table 5 can be seen that PDA closes or decreases, reduced tachypnea or disappear, and cyanosis was disappeared or reduced.

Table 6: Profile of PDA therapy outcomes

Outcome Criteria	Outcome	Amount of Patients (%)		
		Paracetamol (N=25)	Ibuprofen (N=5)	Drug Replacement* (N=2)
Size of PDA	Closed	12 (48%)	2 (40%)	1 (50%)
	Reduced	7 (28%)	2 (40%)	1 (50%)
	No Data	6 (24%)	1 (20%)	0
Tachypnea	Disappeared	15 (60%)	1 (20%)	1 (50%)
	Reduced	2 (8%)	1 (20%)	0
	Still Occured	2 (8%)	0	0
Cyanosis	Disappeared	4 (16%)	0	1 (50%)
	Reduced	0	0	0

Description:

- TAD: there is no data about PDA size.
- *Substitution of drugs from paracetamol to ibuprofen.

Potential side effects of paracetamol and ibuprofen in Table 6, but there were no actual side effects from the use of paracetamol and ibuprofen for PDAs in this study.

Table 7: Potential side effects of the drug

Drug Type (Usage Percentage)	Potential Side Effects
Paracetamol (78%)	Lower incidence of gastrointestinal bleeding and hyperbilirubinemia than ibuprofen and hepatotoxic (18,22)
Ibuprofen (16%)	Gartrointestinal bleeding, renal impairment, impaired platelet aggregation, peripheral hyperbilirubinemia and vasoconstriction (13).

Discussion

Ibuprofen and paracetamol are drugs that can reduce prostaglandin production. Because one of the causes of PDAs is high circulating prostaglandin levels, namely PGE2 and PGI2 which cause vasodilation of DA [2].

Ibuprofen has received FDA approval in 2009 as a PDA therapy [14].While paracetamol is still classified as an off-label category for PDAs or drugs with unusual indications [3]. The results of administration of ibuprofen and paracetamol can be seen in Table 5, with the results that most patients experience PDA closure and others experience a reduction in PDA size. There is no actual side effects were found by giving ibuprofen and paracetamol,.

The route for administration of ibuprofen and paracetamol in this study was oral and intravenous. The profile of ibuprofen use in 5 PDA patients has shown in Table 3. Ibuprofen can inhibit COX enzymes which play a role in the formation of prostaglandins so as to reduce prostaglandin levels and trigger DA closure [15]. Ibuprofen is given for 3 days at a dose of 10 mg / kg body weight in the first day and 5 mg / kg body weight in the second and third day [16].

Another literature states that high-dose ibuprofen, which is 20 mg / kg body weight in the first day and 10 mg / kg body weight in the second and third day. That dose is more effective in triggering PDA closure and not causing side effect [21]. From the results of the study, there was one patient who used ibuprofen with a dose greater than 10 mg / kg / day but not exceeding 20 mg / kg / day. Because patients experience moderate DAP and moderate weight and close to normal gestational age of 35/36 weeks.The use of ibuprofen for DAP can be repeated up to 3 cycles [23]. Based on the data obtained, the use of ibuprofen is in accordance with the library, but some are not in accordance with the library.

Another side effect of ibuprofen is hyperbilirubinemia. Ibuprofen binds 99% with albumin and at high doses will shift albumin bonds with bilirubin and cause increased bilirubin levels [18]. However, in this study there were no side effects from the use of ibuprofen because there were no lab data that supports it so that it means that there were no side effects. In addition, hyperbilirubinemia is already common in newborns [16].

In this study, there were patients with hypalbumin conditions (<3.4 g / dL), therefore it was necessary to decrease the dosage of ibuprofen to half that which was due to competition between ibuprofen-albumin-bilirubin. In addition, ibuprofen can cause an increase in total bilirubin levels due to the inhibition of glucoronidation of bilirubin in the liver [22]. The use of ibuprofen therapy can cause reopening of the ductus arteriosus in premature infants, if we continue the theraphy, the duct will close again [18]. Premature babies may experience DA reopening because DA muscle walls in premature babies are thinner than in normal infants so that blood vessels must constrict more to cause hypoxic conditions [24].

In Table 3, there was 1 patient who was just starting ibuprofen therapy at the age of 17 days, the increasing age the ability to respond to prostaglandin inhibitors would decrease so the outcome in these patients was reduced PDA size from large PDAs to medium PDAs [25]. In Table 3, there was 1 preterm patient who received high-dose ibuprofen because the PDA in the patient was only discovered in H15 which would accelerate clearance of ibuprofen. Ibuprofen clearance will be faster with age due to the maturity process of CYP2C8 and CYP2C9 cytochrome which is responsible for metabolizing ibuprofen [26]. Besides ibuprofen, another drug that can be used to treat PDAs is paracetamol.

The profile of the use of paracetamol therapy in PDA patients is shown in Table 4. The mechanism of action of paracetamol to help trigger DA closure is still unclear, thought to be associated with inhibition of prostaglandin production. Paracetamol inhibits the peroxidase enzyme so that it can reduce prostaglandin production and help with DA closure [17]. The dose of paracetamol for PDA according to literature is 15 mg / kg every 6 hours for 3 days [7].

Another literature states that the dose of paracetamol for PDA is 7.5-15 mg / kg every 4-6 hours, a maximum of 60 mg / kg / day [17]. Administration of paracetamol for PDA for a maximum of 6 days depends on the patient's PDA status [27]. Meanwhile, the use of paracetamol in patients with low birth weight is 2 to 7 days [28]. In table 4 there are some patients who get paracetamol therapy for more than 7 days because the patient's DAP has not closed so that paracetamol therapy is continued. Ibuprofen is not given because the patient is contraindicated with ibuprofen. If the patient fails to respond with 2 drug therapies, surgery will be performed [29].

In this study, there was 1 patient who received a dose of paracetamol more than the recommended dose in the literature. It is still considered safe because the therapeutic index is quite wide from paracetamol. From the literature studies conducted, the efficacy of paracetamol for PDAs still varies. The efficacy of paracetamol to trigger the closure of PDA is similar to ibuprofen with lower gastrointestinal side effects and hyperbilirubinemia compared to ibuprofen [18]. Paracetamol can trigger PDA closure of 81.2%, while ibuprofen is 78.8%. Therefore, paracetamol can be used as first-line PDA therapy [18].

The opposite result, in the RCT study, stated that the efficacy of paracetamol for PDA closure was 72.5% and ibuprofen 77.5% [18]. The RCT study from another literature states that paracetamol is safe to use, but does not produce a better outcome than indomethacin i.v for preterm infants [8]. Another source states that paracetamol provides the same efficacy as ibuprofen to trigger PDA closure [30].Because there are still many controversies regarding the efficacy of paracetamol for PDA therapy, further research needs to be done. Based on this study, of a total of 25 patients who received paracetamol, 20 patients (63%) received paracetamol by the intravenous route.

Intravenous paracetamol is given in the form of infusion for 15 minutes. The timing of starting therapy will also affect the outcome. In Table 4 there is 1 patient who just started pharmacological therapy when he was 18 days old. The use of pharmacological therapy must be performed first in PDA patients with age of > 7 days even though the possibility of PDA closure is very small, but this step must be tried before deciding to perform surgery on patients [29].

In addition to ibuprofen and paracetamol, some PDA patients get replacement therapy from paracetamol to ibuprofen as seen in Table 5. Replacement of this therapy is aimed at patients who are not contraindicated with the drug given. New PDA patients will be operated if they have failed with two pharmacological therapies [29]. The first drug would be used when there is a substitution of therapy is paracetamol, if it fails, it is replaced with ibuprofen. This is related to the higher safety factor of paracetamol compared to ibuprofen in terms of drug side effects [30].

In addition, other studies suggest that paracetamol used for PDA patients with low birth weight who have previously received ibuprofen does not produce a good outcome. Paracetamol is also not recommended for PDA patients with postnatal age more than 2 weeks [16].The outcome criteria seen from this study were reduction in size or closure of the PDA, Disappearance of tachypnea, and Disappearance of cyanosis.

The use of paracetamol, ibuprofen, or a change of therapy from paracetamol to ibuprofen can relieve symptoms of tachypnea and cyanosis in patients (Table 6). Paracetamol used in PDA patients provides better closure results compared to the use of ibuprofen. Patients who died were not caused by PDAs, but were caused by comorbidities suffered by patients, such as ASD, mild TR, pneumonia, NEC Grade II, sepsis, and congetinal abnormalities (hyperplasiaatorax, cardiomegaly).

Conclusion

The most widely used therapy in patients with PDAs is paracetamol, but in certain cases paracetamol therapy is replaced with ibuprofen. The dosage of paracetamol and ibuprofen is adjusted to the clinical condition of the patient. In addition, the use of paracetamol and ibuprofen can reduce tachypnea and cyanosis in patients with PDAs. No actual side effects were found in patients with paracetamol and ibuprofen therapy.

Ethical Clearance

This study was approved by the Health Research Ethics Commission of the Dr. Soetomo Hospital with a Certificate of Ethical Eligibility Number 91 / Panke.KKE / II / 2017.

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