Original Article

The strategy of paracetamol (acetaminophen) use in closing patent ductus arteriosus in premature neonates.

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Abstract:

Background: Patent ductus arteriosus (PDA) is a common problem in premature neonates which can be closed pharmacologically using nonsteroidal anti-inflammatory drugs (NSAIDs) with many side effects. Recently paracetamol is used in this field when these drugs can not be used like in cases of gastrointestinal (G.I.T) bleeding or perforation, or if the patient doesn't show response to the NSAIDs and it seems to be of good safety. To the best knowledge this is the first paper that describes in details the strategy of using paracetamol in closing PDA in premature neonates and gives recommendations about this therapy.

Objective: To give a guide and recommendations about using paracetamol in closing PDA in premature neonates regarding dosage regimen, route of administration, and about how to select and evaluate the patients before and during this therapy.

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Patients and Methods: A web search was done in MEDLINE, SCOPUS, Cochrane library and ISI Web of Knowledge databases as well as electronic and manual screening of conference abstracts from international meetings of relevant organizations using the words acetaminophen, paracetamol, patent ductus arteriosus, preterm and premature for all English written publications (case reports, case series and studies with no date restrictions) related to the topic.

Results and data synthesis: Twenty article of different types have been evaluated. Best candidates were those premature babies with hemodynamically significant (hds) PDA and had no contraindication for paracetamol therapy. Generally success rate was ranging between 70-100 % using oral or intravenous (IV) paracetamol in a dose of 30-60 mg/kg/24 hours (h) divided every 6-8 h .Therapy commonly started after 48 h of postnatal age, patients were maximally given 2 courses during 7 days period. Pretreatment evaluation included clinical, echocardiography, cranial ultrasonography, liver function tests (LFT), renal function tests (RFT) and platelet count; and the same parameters were used during daily follow up of the patients.

Conclusion: Paracetamol found to be the best choice for pharmacological closure of PDA in premature neonates if they are not responding to the other NSAIDs or when they are contraindicated. Patients should not have contraindications for this therapy and paracetamol was used in a dose that is higher than the analgesic dose with special concentration on intraventricular hemorrhage, liver function, renal function and blood platelets during treatment but generally the drug is safe one with no serious complications being reported.

Key words: Paracetamol, acetaminophen, patent ductus arteriosus, premature, preterm, neonate.

Introduction:

Patent ductus arteriosus in preterm infants is common, with an incidence rate as high as 30% in very low birth weight infants (1). Ductus arteriosus may close spontaneously by day 7 of life in only 70% of infants with birth weight between 1000 to 1500 g and 30-35% of infants with birth weight <1000 g (2,3). After birth, the abrupt increase in oxygen tension inhibits ductal smooth muscle voltage-dependent potassium channels, which results in an influx of calcium and ductal constriction. Prostaglandin E2 and prostaglandin I2 levels fall because of metabolism in the now functioning lungs and elimination of the placental source. The medial smooth muscle fibers in the ductus contract, which results in wall thickening, lumen obliteration, and shortening of the ductus arteriosus. Functional complete closure usually occurs within 24 to 48 hours of birth in term neonates. Within the next 2 to 3 weeks, infolding of the endothelium along with subintimal disruption and proliferation result in fibrosis and a permanent seal (4). The failure of the ductus arteriosus to constrict after birth is due to lower intrinsic tone, less ductal muscle fiber and fewer subendothelial cushions in preterm as compared to term infants. The immature ductus arteriosus has higher sensitivity to the vasodilating effects of prostaglandins and nitric oxide. This is aggravated by hemodynamic derangements due to respiratory distress syndrome and surfactant therapy (5).

Traditional therapies for PDA are pharmacological, catheter- based, or involve surgical ligation. Food and Drug Administration–approved pharmacological treatments of PDA include IV indomethacin and ibuprofen, both work by reversibly inhibiting cyclooxygenase-1 and -2 (COX-1

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and -2), leading to decreased prostaglandin production. The approved indomethacin PDA treatment dose is 0.2 mg/kg IV initially followed by 2 subsequent IV doses based on postnatal age (6). The approved ibuprofen lysine dose is 10 mg/kg IV followed by 5 mg/kg IV at 24 and 48 hours. (7). Oral ibuprofen, at the same dose, is also effective for significant PDA. (8). The reported success rate of traditional nonsteroidal anti-inflammatory drugs (NSAIDs) for treatment of PDA is approximately 70% to 85% (8-10). COX-inhibitors are frequently contraindicated in early life and their use has been associated with serious adverse events, such as gastrointestinal perforation, renal failure and bleeding (11, 12). Paracetamol is efficacious in closure of PDA in preterm infants. It acts mainly by inhibiting the peroxidase enzyme activity. Peroxidase is activated at lower peroxide concentration than that of cyclooxygenase, suggesting that paracetamol may work well at decreased peroxide concentrations like in hypoxia. It also has a wide margin of safety .Paracetamol in a dose of 15 mg/kg/dose every 6 hourly for 3 days had comparable efficacy (73-81%) to ibuprofen , in obtaining PDA closure(13,14) and Fig1.

Method of search:

Search was conducted in MEDLINE, Scopus, the Cochrane Library and ISI Web of Knowledge databases as well as electronic and manual screening of conference abstracts from international meetings of relevant organizations. Electronic search was conducted using the search terms acetaminophen, paracetamol, patent ductus arteriosus, preterm and premature for all English written publications (case reports, case series and studies with no date restrictions) related to the topic. All searching processes were conducted during November 2015.

Selection criteria and data extraction: Evaluated resources involved case report, case series, controlled or uncontrolled trials, randomized trials, open trials and retrospective studies included premature neonate who born before 37th gestational week and diagnosed to have hemodynamically significant (hds) PDA and received paracetamol (acetaminophen) therapy aiming for its closure weather given versus COX inhibiters, placebo or no intervention.

A total of 97 papers of different types were e identified as result of the initial searching effort; however only 20 articles left for evaluation after excluding papers not describing our topic, duplications and non-English published articles; of those 4 case reports, 13 case series and 3 controlled trials. All publications were evaluated considering the following points (when to consider the PDA as hds, gestational age of patients, when and how to start the treatment, drug dosage and rout of administration, duration of treatment, number of paracetamol therapy courses, patient's followup, primary and secondary outcomes).

Results:

Case reports (Table 1)

Table (1) case reports

Reference	Patient	GA (weeks)	Hemodynamically significant PDA	Age of starting treatment	Previous use of other NSAID	Route, dose and duration of paracetamol	Outcome and comments
Hammerman c et al [15] (2011)	N=5	26-32	PDA internal diameter 2-3 mm , LA/PDA 1.48-2.07, PDA /Aortic 0.5-1.0	3-35 d	2/5	Oral 15 mg/kg/6 h For 48 h-7 d	Complete closure within 48 h or ductal constriction leading to closure within 1 week (5/5)
Alan S et al [16] (2013)	N=3	26.2-33.5	LA/AO > 1.57	9-19 d	3/3	I.V , 15 mg/kg/6 h, 3-5 d	All failed to have closure and 2 patients developed side effects as elevated transaminases
Pérez Domínguez ME et al [17] (2015)	N=2	23-27	?	2,6 days	1/2	I.V 15 mg/kg/6 h 2-5 d, second course 7.5/mg/kg/6h,48 h	Ductal closure in 1/2 Within 48 h. Initial improvement, reopening, surgical ligation and death in 1/2.
Cynthia H et al [18] (2015)	N=1	28	PDA internal diameter 1,9 mm	5 month	none	Oral 12 mg/kg/dose every 12 h for 4d.	Complete closure

N (number), GA (gestational age), PDA (patent ductus arteriosus), LA (left atrium), Ao (aortic), h (hour), NSAID (non-steroidal anti-inflammatory drugs), d (days), I.V (intravenous). Four case report articles were evaluated (15-18), with the first one has been published in 2011 as shown in table (1).Only Hammerman c et al (15) gave clear definition of hds PDA which was a ductus with internal diameter more than 2 mm, left atrium to aortic ratio more than 1.48 and ductal internal diameter to aortic ratio more than 0.5 (15), while Alan S et al (16) considered left atrium to aortic ratio (LA/AO) of >1,57 as hds PDA and Cynthia H et al considered a PDA with an internal diameter of 1,9 mm as hds PDA. In all cases paracetamol was given in a dose of 15mg/kg/dose /6 hours for 48 hours regardless to the rout of administration except for Pérez Dominguez ME et al (17) who gave IV paracetamol in a dose of 7.5 mg/kg/6 hours to a premature neonate when it was necessary to give a second course of paracetamol and 12mg/kg/12 hours for 4 days given for a different purpose to the child as reported by Cynthia H et al (18) and all patients followed by echocardiographic evaluation for up to 1 week to give the final decision about ductal closure. Paracetamol was started at a wide range of postnatal ages from 2-35 days (15-17) with successful closure as primary outcome, even surprisingly Cynthia H et al (18) reported this successful approach accidentally in a 5 months old infant, however Alan S et al reported therapy failure for 3 neonates without reasonable explanation (16). Four premature neonate among all the reported babies had unsuccessful approach and as a secondary outcome one of them died due to sepsis after surgical ligation of his PDA. The rationale for giving paracetamol instead of other NSAIDs were either the presence of thrombocytopenia, hyperbilirubinemia, intraventricular hemorrhage (i.e. contraindications to NSAIDs treatment) or failure of response to NSAIDs therapy. None of the investigators reported serious side effects of their paracetamol trials. The main drug related complications were elevated hepatic transaminases.

Case series Table (2).

A total number of 13 case series have been evaluated (19-31). The lowest success rate of PDA closure with paracetamol of 18.18 % was reported by. Roofthooft DW et al (25) with the studied infants had the lowest gestational age (23-26 weeks) as compared to the other series and very close success rates of 20% and 27.77 % were reported by Roofthooft DW et al (26) and EL-Khuffash A et al (24) with very similar range of gestational age for the studied sample ranging between 23-27.9 weeks . Nearly all of those infants were given I.V paracetamol in a dose of 15 mg/kg/6 h for 3-8 days depending on the results of their echocardiographic evaluation during the treatment course. The highest successful closure rate of 100 % were reported by Sinha R et al (20), Oncel MY et al (28) and Kessel I et al (29) with obviously more mature neonates with gestational age of 24-33 weeks who were given the drug either orally (20,29) or intravenously (28) and even . Sinha R et al (20) gave the drug at low dose of 10 mg/kg/8 h for a comparable treatment duration (of 48 h-7 days) to those with low success rate of closure. There was wide range of birth weights which were as low as 365 grams as reported by Roofthooft DW et al (25, 26) up to 2790 grams as reported by Oncel MY et al (19) with no clear difference in the success rate in relation to the body weight during treatment. The success rate reported by other series is comparable to that of NSAIDs ranging between 70-90,90 % (19,21,22,23,30,31).Whether the patients has already given COX inhibiters or not , it didn't show clear impact on the success rate of closure although COX inhibiters were given to all of those with low gestational age and lowest success rate before starting paracetamol therapy(24,25,26).With the exception of the series of Oncel MY et al (19), D.W.E Roofthoft et al (26) and Kessel I et al (29) there was clear definition of hds PDA generally considering patient's cardiopulmonary symptoms and signs like features of heart failure and need for ventilatory support, internal ductal diameter with clear left to right shunt, PDA to body weight ratio (mm/Kg) , left atrium to aortic ratio (LA/AO), PDA to left pulmonary artery ratio(PDA/LPA), pulmonary to systemic blood flow (Qp/Qs), , reversed aortic diastolic flow any of these criteria considered as an indicator of hds PDA. Regarding drug safety and its related complications, it was extremely safe with these used doses and such complications were reported in only one patient by Kadir Tekgündüz et al (23).

Table (2) case series.

Reference	No	GA (week)	Weight (grams)	Hemodynamically significant PDA	Age of starting treatment	Previous use of other NSAID (Patient Number)	Route, dose (mg/ kg/24 h),time interval between doses(h) and duration of paracetamol therapy	Successful closure/ drug related complications /significant duct constriction
Oncel MY et al [19]	N=8	23-36	2970–630	??	5-27 d	6/8	Oral ,60,6 ,48 h-7 d	87.75/0/0
Sinha R et al [20]	N=10	27-33	800 -1400	Features of heart failure ,left to right shunt ,LA/Ao > 1.8	4-7 d	None	Oral ,45,8,48-72h	100/0/0
Peña-Juárez RA . et al [21]	N=10	30-36	840-1350	Qp/Qs > 1.1, PDA diameter >1 mm, LA/Ao >1 and need of ventilator support.	Less than 10 d	None	Oral ,60,6, 48 h-6 d	70/0/0
Terrin G et al [22]	N=8	24-28	551-897	Internal ductal diameter ≥ 1.5 mm, LA/Ao >1.5, reversed or absent aortic diastolic flow. Unrestrictive pulsatile transductal flow	38-94 h	None	I.V, 30-45 maximum 60, 4-6, 48.	75 /0/0
Tekgündüz KŞ et al[23]	N=13	24 - 31	470 -1390	internal ductal diameter ≥ 1.5 mm, LA/Ao >1.5,symptoms of shunt or left heart enlargement	2 to 9 d.	None	Oral=1 ,60,6 I.V =12 ,30,8 Both for 1-5 d ay.	76.92/7.69/0
EL-Khuffash A et al [24]	N=36	–24.6 27.9	954–645	PDA diameter > 2.8 mm, LA/Ao >1.7	39 d–16	10/36	I.V, 60,6, 3-6 d	27.77/0/22
Roofthooft DW et al[25]	N=33	23-26	1130–365	Ductal diameter of >2.0 mm, PDA: LPA diameter >0.8 and/ or LA/Ao ratio >1.6.	2-26 d	12/33	I.V, 60, 6, 3–7 d	18.18//0/0
Roofthooft DW et al [26]	N=10	23-27	950–365	?	13-30 d	6/10	(I.V/oral =9/1), 60, 6, 3–8 d.	20/0/0
Ozdemir OM . et al [27]	N=7	32–23	1,615–620	Symptoms, signs, LA/Ao ratio >1.4 ,LVD, reversed aortic diastolic flow	47 d–20	7/7	Oral ,60,6,3-6 d	71.42/0/0
Oncel MY et al [28]	N=10	24-29	590-990	PDA diameter > 1.5 mm, LA/Ao >1.6	2-15 d	None	I.V, 60,6, 3-6 d	100/0/0
Kessel I et al [29]	N=7	26 -30	789 -1322	?	?	7/7	NGT,60,6, ,3-7 d	100/0/0
Sancak S et al [30]	N=18	<30	<1250 g	Internal ductal diameter ≥ 1.5 mm, LA/Ao >1.5, reversed aortic diastolic flow.	2-24 d	?	(I.V/Oral=10/8), 60,6,3 d	77.77/0/0
Memisoglu A et al [31]	N=11	23-30	415-1580	PDA 1.4 mm/kg body weight or more, LA/Ao > 1.4, unrestrictive pulsatile transductal flow, reverse or absent diastolic flow in the descending aorta along with clinical findings.	?	11/11	I.V, 60,6, 3 d	90.90/0/0

* N (number), GA (gestational age), PDA (patent ductus arteriosus), LA (left atrium), Ao (aortic), h (hour), NSAID (non-steroidal anti-inflammatory drugs), d (days), Qs (systemic flow), Qp (pulmonary flow), LPA (left pulmonary artery), LVD (left ventricle dilatation), I.V (intravenous), NGT (naso-gastric tube).

Controlled studies. Table (3).

Three controlled studies have been evaluated with statically comparable success rate to that of the NSAIDs which were used as control agents ranging between 77.5-100 %. Oncel MY et al (32) and Dang D et al (33) used oral ibuprofen as control agent while Dash SK et al (34) used I.V indomethacin as control agent, however all of them used oral paracetamol in a dose of 15 mg/kg/6 h for 3-6 days during their studies. Author's definition of hds PDA is more or less based on the same criteria considered above although Dang D et al (33) didn't give clear description of the hds PDA. Dang D et al (33) and Dash SK et al (34) gave the drug to more mature neonates had a gestational age ranging between (29.4-33 weeks) and (25.8-31.5 weeks) respectively while Oncel MY et al (32)

described his patients as having gestational age of < 30 weeks without clear limits for evaluation. Generally the investigators started the therapy at postnatal age of 48 hours-14 days. None of the investigators demonstrated a statistically significant difference between paracetamol and control group in term of development of drug related side effects.

Table (3) controlled trials

Reference	Patients number Pa/Con	GA (weeks) Pa/Con	Birth Weight (grams) Pa/ Con	Hemodynamically significant PDA	Age of starting treatment	Control agent	Route, dose (mg/kg/24 h) ,time interval between doses (h), duration of paracetamol therapy	Success rate (%) (Pa/ Con), drug related complications (%) (Pa/Con), significant duct constriction (%) (Pa/Con)
Oncel MY et al [32]	40/40	<30	<1250	≥ 1.5mm, Duct size LA/Ao >1.5, end diastolic reversal of blood flow in the aorta, or poor cardiac function in addition to clinical signs of a PDA.	48-96 h	oral 1	Oral,60,6,3 d	(77.5/ 72.5),(0/0), (0/0)
Dang D et al [33]	80/80	29.4-33	1242.6-1940.5	?	<14 d	oral 1	Oral,60,6,3-6 d	(81.25/78.75), (0/0), (0/0)
Dash SK et al [34]	36/36	25.8-31.5	≤1500	PDA size ≥1.5 mm LA:AO >1 ,Lt to Rt ductal shunt	48 h	I.V 2	Oral,60,6,3-6 d	(100/94.6), (0/0), (0/0)

GA (gestational age), PDA (patent ductus arteriosus), LA (left atrium), Ao (aortic), h (hour), d (days), I.V (intravenous), Pa (paracetamol), Con (control), Lt to Rt (left to right), 1 (ibuprofen), 2 (indomethacin)

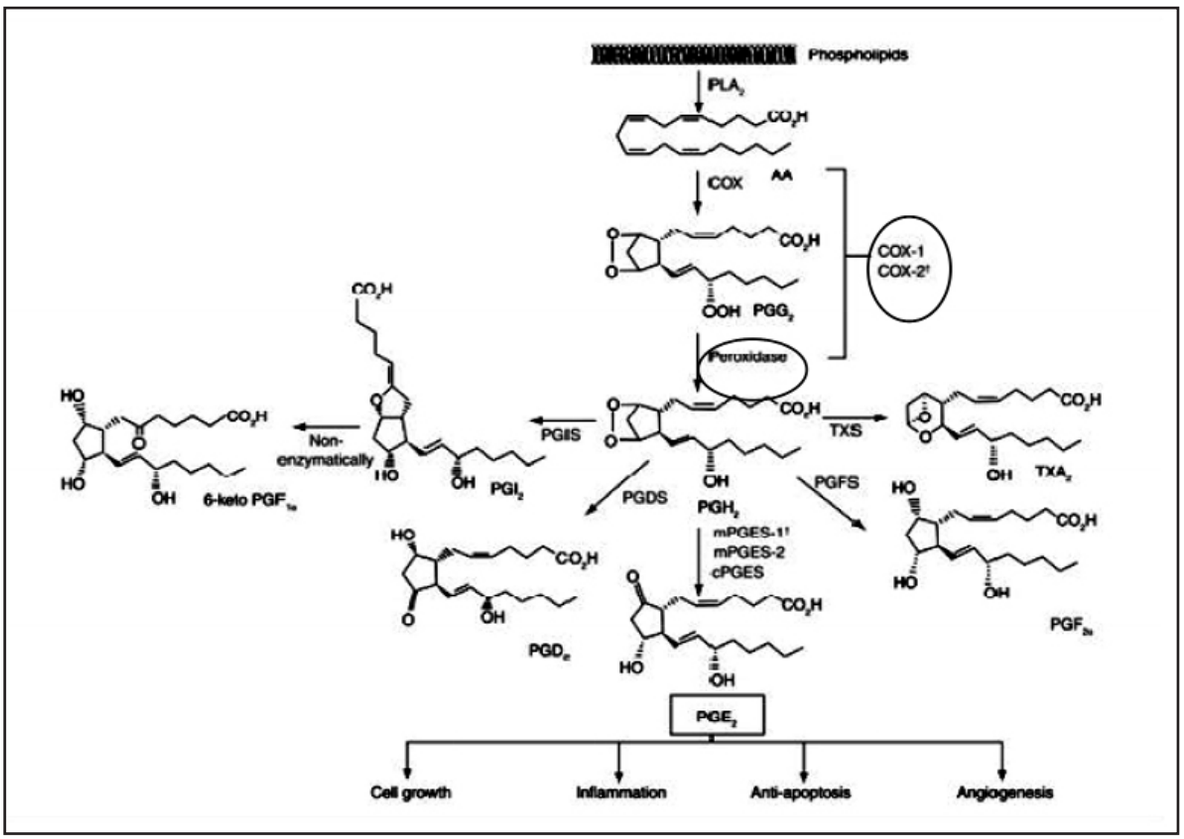

Fig (1): Cyclooxygenase and peroxidase catalytic activity for prostaglandin synthesis.

Discussion

PDA is frequent in premature babies. With an incidence of 1:2500-5000, it accounts for 9% to 12% of congenital heart disease. Several different drugs have been tried for closure of hds PDA. The first to be used was indomethacin, with a success rate of 70% and a reopening rate of 35%; however, the high cost of this drug has driven the search for other options such as ibuprofen. But such drugs are not harmless and are associated with decreased renal, mesenterial, and cerebral perfusion, and ibuprofen is associated with hyperbilirubinemia. Recently, paracetamol has been demonstrated to be effective in this indication, with no reports of toxicity to date. Paracetamol is readily available and innocuous in neonates (21).

Paracetamol therapy for closing PDA in premature neonates starts with determining whether the PDA is hds and whether the patient is a suitable candidate for this therapy. One systemic review done by Zonnenberg I and de Waal K stated that most trials used clinical and ultrasound criteria to define the hds of PDA, but there was a wide variety in criteria and cut-offs used. Of the clinical criteria, a murmur or hyperdynamic circulation was most used, and of the ultrasound criteria, the left-atrium-to-aorta ratio (LA ⁄ Ao ratio) was most used (36). In this review some authors didn't show the hds definition of their patients PDA like Pérez Domínguez ME et al (17), Oncel MY et al (19), Roofthoft DW et al (26) , Kessel I et al (29) and Dang D et al (33), however the others gave varied definitions of the hds PDAs they treated . According to the evaluated articles, PDA is considered as hds one if the patient has PDA murmur , symptoms and signs of left ventricular overload or of respiratory distress specially if it needs ventilatory support and this should be supported by one or more of the following ultrasound features demonstrated by echocardiography, a PDA narrowest internal diameter 1.5 mm or more with left to right shunt and reversed aortic diastolic flow in severe cases and/ or LA to AO ratio of 1.5 or more as common selective criteria because the diameter will contribute most to the amount of flow over a vessel and should be incorporated into the definition of hds PDA (36). Importance of reverse flow in the descending aorta at the level of the diaphragm and a pulsatile shunt is supported by other author's opinion (37). The LA⁄Ao ratio of 1.5 or more used by the investigators is a valid measurement of left ventricular volume loading, and this cut-off value represents what has been adopted by Groves AM et al (37). Other ultrasound features considered by the reviewed articles are less commonly accepted by all authors such as Qp/Qs ratio of >1.1, PDA/LPA ratio of >0.8 or PDA > 1.4 mm/kg body weight. Patient selection came second in such a way excluding patients who were not suitable for the therapy either because they were in need of ductal patency or had some contraindication to the therapy, on the other hand paracetamol was the best choice for suitable patients if they were not responding to 2 courses of other NSAIDs or had contraindications for their use. The main exclusion criteria for paracetamol therapy were a ductus-dependent cardiac anomaly that was proved by means of Doppler echocardiography, right-to-left ductal shunting, life-threatening infection, grade III or grade IV IVH, urine output of less than 1 mL/kg/h during the preceding 8 hours, serum creatinine level >1.6 mg/dl, platelet count <60000/mm, liver failure, hyperbilirubinemia requiring exchange transfusion, and persistent pulmonary hypertension (22, 32). When to start paracetamol therapy? Is the next coming question. None of the reviewed papers showed that paracetamol therapy has been initiated before the age of 48 hours, this is going with the idea of high percentage of spontaneous closure of PDA in premature neonates by 48 hours of life as stated by Koch J et al (38), but it seems that there is no clear cut-off about the maximal postnatal age suitable for this therapy because a wide range of postnatal ages up to 47 days by Ozmert M. et al (27) have been included in the reviewed articles, however restricting this therapy to the neonatal period appears more logical although success outside this period has been reported by Cynthia H et al (18). Gestational age appears to be important among the treated patients because in 3 series with patients GA 23-27.9 weeks the success rates were the lowest ranging between 18.18-27.77% compared to the general success rate of 70-100 % for other more mature groups (24, 25, and 26). Probably this is because even in normal neonates the rate of spontaneous closure is higher in the premature infants with GA> 27 weeks, an issue that needs more future studies to evaluate. At the same time birth weight differences didn't show significant impact on the treatment results. Before starting paracetamol therapy a baseline patient evaluation seems to be logic and important for giving decision about continuation of therapy during followup of patients and that included a complete blood count; renal function tests (serum creatinine, blood urea nitrogen, and urine output), aspartate amino transferase (AST), alanine amino transferase (ALT) and bilirubin levels, cranial ultrasonography, and echocardiography (32). Route of drug administration varied between I.V, oral or through NG tube and none tried the rectal route but there was no demonstrable clear association between the success rate and the rate of development of complication with the route of administration. Sometimes I.V route was preferred when there was feeding intolerance which is defined as the inability to digest enteral feedings presented as gastric residuals volume of more than 50%, abdominal distension, or emesis, or both

as defined by Moore TA, Wilson ME (40), but we should not forget that impaired hemodynamics may be a relative contra-indication for I.V paracetamol in neonates (22, 39). Generally the used dose varied between 30-60 mg/kg/24 h divided in equal doses every 6-8 hours regardless to the route of administration even in those with the least maturity and the lowest birth weight, with the most commonly used dose was 60 mg/kg/24 h divided every 6 hours and the lowest effective dose was reported by Tekgündüz KŞ (23) and the same dose of 30 mg /kg/24 h was found to effective in decreasing PDA incidence in the premature neonates when given in the first 72 hours of life as prophylaxis (35) . These doses were higher than the analgesic dose published by two European centers which were 20 mg/kg/day in premature neonates <31 weeks postmenstrual age (PMA) through to 40 mg/kg/day for term neonates >37 weeks PMA (41). Treatment duration varied from minimum of 24 hours by Tekgündüz KŞ et al (23) to a maximum of 8 days by Roofthoft DW et al (26) but generally it varied between 48 h- 7 days (19-24, 27-34) depending on the response shown by the patient. Not more than 2 courses of paracetamol given to the patients without changing the treatment dose and 24, 48 and 72 hours after initiation of therapy the effectiveness of the first course evaluated with majority of patients (72.5%) as reported by Oncel MY et al (32) showed complete closure by the end of the first course. Patients underwent daily evaluation using the same pretreatment parameters with daily echocardiographic evaluation. If the patient didn't show complete closure or significant ductal constriction a second course were given with the same evaluation method for the next 4-5 days regardless weather the patient already received one of the NSAIDs or not.The intended primary outcome of all reviewed papers were complete ductal closure or the development of significant ductal constriction (15-34) which is defined by the absence of shunt or diameter < 0.5 mm without any other hemodynamic implications at echocardiographic examination performed daily during the study period as described by Terrin G et al (22) .Secondary outcome of treated patients can be summarized as the need for surgical ligation of the PDA , mode and duration of ventilation; increase in blood urea nitrogen, serum creatinine, bilirubin, AST, or ALT levels after treatment, rates of ductal reopening, surfactant treatment, pneumothorax, pulmonary hemorrhage, Chronic lung disease, IVH, necrotizing enterocollitis (NEC), gastrointestinal bleeding, retinopathy of prematurity, definite sepsis, and death. It seems that the drug is a safe and none of the papers showed increase in the incidence of the complications when compared to the other NSAIDs. Only Alan S et al (16) and Tekgündüz KŞ et al (23) reported drug related complications in a total number of 4 patients in the form of elevated transaminase enzymes.

Conclusion

Paracetamol is the best choice for the pharmacological closure of PDA in the premature neonates if they have contraindications to the other NSAIDs (G.I.T bleeding or perforation mainly or thrombocytopenia) or if they don't respond to 2 courses of such therapy and it should be tried before surgical ligation. Suitable candidates for such therapy are premature neonates who have cardiopulmonary problems related to PDA if such PDA is hds (defined by PDA narrowest internal diameter of 1.5 mm or more with left to right shunt and /or LA/Ao 1.5 or more, especially if there is reversed aortic diastolic flow). Contraindications for PDA closure using paracetamol include ductus-dependent cardiac anomaly that is proved by means of Doppler echocardiography, right-to-left ductal shunting, life-threatening infection, grade III or IV IVH, urine output of less than 1 mL/kg/h during the preceding 8 hours, serum creatinine level >1.6 mg/ dl, platelet count <60000/mm, liver failure, hyperbilirubinemia requiring exchange transfusion, and persistent pulmonary hypertension Pretreatment patient evaluation includes echocardiography, cranial ultrasonography, LFT, RFT, and platelet count. The same parameters are used daily starting 24 hours after initiation of therapy for the purpose of followup. Paracetamol is given orally or through NG tube or through IV route if there is gastrointestinal intolerance for oral intake. Irrespective to the route of administration or pervious use of NSAIDs the dose is 30-60 mg/kg/24 h divided every 6-8 hours for up to 72 hours as the first course then after with the same dose for another 4 days as a second course .If the PDA doesn't close after 2 courses of paracetamol therapy then surgical ligation is advised.

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