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A COMPREHENSIVE STUDY TO CHECK THE EFFICACY OF INTRAVENOUS PARACETAMOL AND IBUPROFEN IN TREATING PATENT DUCTUS ARTERIOSUS IN PRETERM BABIES

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Abstract
We set out to evaluate the safety and effectiveness of intravenous (i.v.) paracetamol in comparison to other methods. ibuprofen for the management of premature neonates with hemodialysis-significant patent ductus arteriosus (hsPDA). This research held on infants between the ages of 20 and 35 weeks were randomly assigned to undergo intravenous treatment either intravenous (IV) paracetamol 12 mg/kg/6 h for three days or 8-4-4 mg/kg/day of ibuprofen. The main result was the percentage of hsPDA following the initial course of therapy with ibuprofen or paracetamol. The necessity for surgical closure, the re-opening rate, and the constriction rate of hsPDA were among the secondary results. Ibuprofen was given to 96 newborns and paracetamol to 114 infants. Logistic regression analysis indicated that while ibuprofen was more successful in closing hsPDA than paracetamol (P = 0.037), the ductus constriction rate was equal (P = 0.242). Similarities also existed in the rate of reopening, the requirement for surgical closure, and the incidence of side effects. Although ibuprofen was more efficient than intravenous paracetamol in closing hsPDA, the use of paracetamol was linked to the same hsPDA result because of a similar constriction effect. The first-choice medication for the treatment of hsPDA is paracetamol.

Background

A common problem in preterm newborns with respiratory distress syndrome (RDS) is patent ductus arteriosus (PDA), for which 60–70% of preterm children born before 28 weeks of gestation undergo medication and/or surgical therapy[1]. Because randomised controlled trials (RCTs) of PDA closure with non-steroidal anti-inflammatory medicines (NSAIDs) frequently failed to demonstrate substantial advantages in preterm newborns, the optimal therapy of PDA is the topic of intense discussion[2]. On the other hand, a prolonged left-to-right shunt via the ductus arteriosus (DA) that complicates RDS has been linked to bronchopulmonary dysplasia (BPD), a decrease in survival rate, an aggravation of respiratory failure, and an increased risk of intraventricular haemorrhage (IVH). As a result, PDA closure is advised prior to a notable left-to-right shunting[3].

The present therapy for PDA consists of two steps: the first is pharmaceutical treatment with an NSAID; the second, which should be avoided if possible because to the associated serious consequences, is surgical ligation in the event that medical treatment fails[4]. The two primary medications used as standard treatment for PDA closure are ibuprofen and indomethacin. In 70–80% of instances, both are effective in encouraging the ductal closure. Nevertheless, severe side effects such as bleeding problems, acute renal failure, and gastrointestinal perforations might be brought on by these medications[5]. As a result, even though ibuprofen seems to be the preferred medication for PDA pharmacological closure at the moment due to its lower side effect profile when compared to indomethacin, it is not the best option due to its subpar safety profile and roughly 30% failure rate.
RCTs have demonstrated the successful closure of PDA in a number of preterm children with oral paracetamol[6]. Additionally, research has shown that paracetamol has a superior safety profile than both indomethacin and ibuprofen, with a reduced incidence of gastrointestinal and renal side effects and no negative effects on cerebral oxygenation[7]. Nevertheless, the efficiency of IV. The effectiveness of intravenous paracetamol has been called into doubt, given just one RCT has examined this method. When compared to indomethacin and ibuprofen, paracetamol was shown to be more effective in closing PDA, and retrospective investigations revealed a lower rate of PDA closure or constriction (i.e., a lower rate of closed or not hsPDA), particularly in the most immature newborns (gestational age < 26 weeks).

Based on this, we concluded that more research was required to support or refute earlier conclusions about the effectiveness of IV. to find out more about paracetamol's potential adverse effects[8]. Consequently, the current investigation evaluated the effectiveness and safety of IV. paracetamol vs intravenous. ibuprofen for the management of premature babies' hsPDA.

Materials and methods

The present study was planned to find the the effectiveness and safety of IV. paracetamol vs intravenous. ibuprofen for the management of premature babies' hsPDA The institutional review board of SHRI SATHYA SAI MEDICAL COLLEGE AND RESEARCH CENTRE.AMMAPETAI. TAMIL NADU: 603108.INDIA and pertinent authorities authorised the study in accordance with local rules.

The requirements for inclusion were a gestational age of infants less than 30 weeks, the acquisition of parental permission, and echocardiographic proof of hsPDA during the first 24 to 72 hours of life. By removing patients in which the closure flow pattern suggested a restrictive PDA, and by using echocardiography to demonstrate a ductal left-to-right shunt with a left atrium-to-aortic root ratio > 1.3 or a ductal size > 1.5 mm, the diagnosis of hypertrophic PDA was established. Major congenital malformations, foetal hydrops, life-threatening infection—defined as a positive blood culture sampled at birth, echocardiographic evidence of pulmonary hypertension, and grade > 3 IVH—as well as elevated liver enzymes (ALT, AST) > two times the upper limit of the normal range (ALT 6¬50 U/L; AST 35-140 U/L) and urine output < 1 mL/kg/h during a 24-hour collection period or < 0.5 mL/kg/h during the first 24 hours of life—major bleeding—as evidenced by hematuria, blood in the tracheal aspirate, or stools, or consistent blood oozing from puncture sites—were among the exclusion criteria[8&9].

Methods

Babies were selected randomly for therapy group. Patients in group I had intravenous paracetamol (12 mg/kg/6 h) for three days. Group II patients were given an intravenous dosage of 8 mg/kg at first, and then 4 mg/kg after 24 and 48 hours. For a duration of 15 to 30 minutes, both medications were continuously administered. Infants in both groups who, following the first round of treatment, failed the closure and had a persistent hsPDA were given a second course of intravenous therapy.

The random numbers in the allocation sequences are produced by slip method. Due to the inverse relationship between the gestational age and PDA frequency, patients were enrolled in each therapy group based on one of two gestational ages: 29.2 + 1.8 weeks or 26.4 + 2.5weeks. Attending doctors provided daily clinical care to enrolled patients in compliance with each center's standard procedure. With a goal intake of 150–160 mL/kg by the end of the first week of life, daily fluid intake was initially begun at 70–80 mL/kg and progressively increased by 10–20 mL/kg/day based on changes in body weight, serum sodium concentrations, and osmolality. If the systemic hypotension was not responding to fluid replacement therapy, treatment with dopamine and/or dobutamine was administered. In order to accomplish the following targets for the treatment of RDS, babies received oxygen therapy, respiratory support, and rescue surfactant treatment: pH > 7.20, PaO2 50–60 mmHg, PaCO2 < 65 mmHg, and SpO2 90–95%[10 &11].

During the first course of therapy, 24 hours after the final dosage, at follow-up visits, and in the event of a clinically suspected reopening of PDA, echocardiography was performed every 24 hours. Expert personnel, blind to the research and treatment groups, conducted cardiac ultrasounds. These individuals were paediatric cardiologists or neonatologists with sufficient training in neonatal heart ultrasonography. Heart ultrasounds were done by more people in each of the participating centres. Additional information on the schedule of regular blood tests and respiratory management was previously published[12].

The study's principal finding was that, in contrast to ibuprofen, hsPDA closed following the first round of therapy with paracetamol. The secondary outcomes included the constriction of hsPDA compared to ibuprofen after the first course of treatment with paracetamol (defined as closed DA or not hsPDA), the closure of hsPDA and the constriction rate following the second course of treatment with ibuprofen, and the incidence of needing surgical closure 30 days after enrollment as well as the reopening rate[13]. At patient screening, at the conclusion of the first and second course of therapy, and at follow-up visits 7 & 30 days following enrollment, laboratory tests were conducted. Red blood cell, white blood cell, and platelet counts were among the clinical laboratory tests performed. Serum values for hemoglobin/hematocrit, creatinine, urea nitrogen, total bilirubin, total proteins, liver enzymes, sodium, potassium, and calcium were also measured. Renal failure was defined for research purposes as a 24-hour collecting period with a serum creatinine concentration > 1.5 mg/dL and a urine output < 1 mL/kg/h. Elevated liver enzymes (ALT 6–50 U/L; AST 35–140 U/L) greater than twice the upper bound of the normal range were considered to be indicative of liver failure. Additionally noted were isolated gastrointestinal perforations that happened within 30 days after the enrollment and necrotizing enterocolitis (NEC).

Sepsis was diagnosed by positive blood cultures and supported by clinical and laboratory findings (white cell count, C-reactive protein concentration) . A Papile classification was used to assess IVH. After 40 weeks of pregnancy, cerebral ultrasonography was used to identify cystic regions, which led to the diagnosis of PVL. The oxygen demand at 36 weeks postmenstrual age was used to define BPD. The international classification of retinopathy of prematurity was used to grade ROP. According to traditional Bell's criteria, NEC was diagnosed[14].

Table 1 - Clinical characteristics of infants in the paracetamol and ibuprofen

	Variable	Paracetamol (n = 114)	Ibuprofen (n =96)	P
1	Gestational age (weeks)	29.2 + 1.8	26.4 + 2.5	0.434
2	25-27 weeks	35 (68)	34 (72)	0.985
3	28-31 weeks	54 (85)	62 (95)	0.932
4	Birth weight (g)	1121 + 254	1231 + 315	0.516
5	< 10° percentile	15(32)	21 (44)	0.431
6	Male	43 (83)	44 (86)	0.782
7	Apgar score at 5 min	8 (8-8)	8 (8-8)	0.801
8	Cesarean section	85 (112)	54 (95)	0.321
9	Abruptio placentae	7(17)	2 (5)	0.397

10	Hypertension disorders of pregnancy	18 (40)	17 (35)	0.422
11	pPROM	6(12)	6 (12)	1
12	Gestational diabetes	5(16)	14(29)	0.321
13	Surfactant	56 (98)	53 (92)	0514.
14	Non-invasive respiratory support	87 (110)	56 (90)	0.645
15	Mechanical ventilation	16(31)	10 (25)	0.847
16	IVH	5(12)	8(15)	0.687
17	Gastrointestinal perforation	1 (4)	1	0.547
18	Hospital stay duration (d)	47.1 + 11.2	45.1 + 17.5	0.569
19	Age at enrolment (h)	49.5±14.9	45.9±17.9	0.985
20	Heart rate (bpm)	164±25	169±29	0.749
21	Systolic arterial blood pressure (mmHg)	69±16	78±19	0.684
22	Diastolic arterial blood pressure (mmHg)	29±14	35 ±9	0.4
23	Mean arterial blood pressure (mmHg)	46±11	49±14	0.254
24	Hemoglobin (g/dL)	13.9 ± 1.7	16.8 ± 3.6	0.048
25	Platelets (10^9/L)	180.2 ± 115.3	256.1 ± 101.2	0.67
26	**First course of treatment**			
	Closed DA	45 (56)	48 (83)	0.001
	Not hsPDA	24(53)	9(15)	0.021
	Constricted DA (closed or not hsPDA)	36(88)	56 (90)	0.216
	hsPDA	16(29) n=20	8(20) n=10	0.218
27	**Second course of treatment with ibuprofen**			
	Closed DA	6(60)	3(70)	0.493
	Not hsPDA	4 (45)	2 (65)	0.765
	Constricted DA (closed or not hsPDA)	8(90)	2(70)	0.306
	hsPDA	4 (40)	0 (0)	0.080
	Re-opening within 30 days of life	14 (36)	8 (19)	0.078
	Surgical closure within 30 days of life	0	1(2)	0.338

Data presented as mean ± SD, rate (%), or median

Results

The research was done between December 2013 and January 2015. The patient disposition is displayed in Figure 1 along with the number of m-ITT, PP, and SP populations. The m-ITT and PP populations matched because no significant procedure infractions were found. 114 and 96 babies (m-ITT population) who started their first treatment course with ibuprofen or paracetamol, respectively, had their primary and secondary end goals assessed. The clinical characteristics of the infants and mothers in both groups were similar (Table 1). Heart rate, haemoglobin, platelet count, systolic, diastolic, and mean arterial blood pressure were comparable in the paracetamol and ibuprofen group at the beginning of treatment.

Discussion

In this work, we evaluated the effectiveness of IV. paracetamol as opposed to intravenous. ibuprofen for the management of hypertension in preterm newborns, and we discovered that ibuprofen was more successful than paracetamol in stopping hypertension. Our results are at odds with other researchers who discovered that oral paracetamol was just as effective as oral ibuprofen in halting hypertension-related pain[3&13]. Even if paracetamol serum levels after 48 hours of an IV are different, these differing results might be the consequence of a different method of delivery. period have been seen to be greater than those attained following a 48-hour oral course (this may indicate that there is no relationship between the serum level of paracetamol and its closure action). Conversely, it has also been discovered that oral ibuprofen works better than IV in stopping PDA. ibuprofen because of unclear processes. Explaining the discrepancy between our results and other researcher , who discovered that i.v. IV

paracetamol worked well[15]. ibuprofen and indomethacin in closing hsPDA in a large RCT (n = 300): the only noteworthy distinction between the two trials is that our investigation included fewer immature newborns than the other, but both employed the same course of paracetamol and ibuprofen at the same post-natal age. Furthermore, these findings align with a previous research conducted on isolated mouse DA, which showed that indomethacin had a greater effect on prostaglandin production inhibition and DA constriction than paracetamol[16].

It is significant that babies treated with paracetamol or ibuprofen had comparable success rates (81 vs. 90%) in narrowing hsPDA (classified as closed DA or not hsPDA). This finding contradicts the findings of a research conducted by researchers, which indicated that indomethacin and ibuprofen had a greater hsPDA constriction impact than paracetamol[17]. However, the multicenter PDA-TOLERATE experiment, in which babies were treated with both oral and intravenous medication later than in our trial (during the second week of life), was the subject of this study's retrospective secondary data analysis. aspirin. Whatever the case, we think our results are critical because they demonstrate that, despite paracetamol's inferior efficacy versus ibuprofen in closing hsPDA, the same proportion of babies in both groups received the second course of therapy[18]. Additionally, we proved that beginning paracetamol treatment for hsPDA did not adversely influence the success of the second course of treatment with ibuprofen in closing and constricting the disease, preventing PDA reopening, or necessitating surgical closure[19 &20]. Our findings thus support the use of paracetamol as a first choice in the treatment of hsPDA and, in the future, the re-evaluation of a prophylactic approach of the hsPDA, which is not largely diffused due to the adverse effects of ibuprofen and indomethacin. This is in light of the well-known better safety profile of paracetamol in comparison with ibuprofen and indomethacin.

We saw that the preterm infant's hsPDA resistant to the first treatment course was effectively closed with a second pharmaceutical regimen using ibuprofen. This outcome is consistent with other research that showed repeated ibuprofen courses are a safe and effective alternative to surgical closure and should be taken into consideration if the first course of ibuprofen fails.

We also gathered information on medication side effects for our investigation, which were comparable for ibuprofen and paracetamol. Despite the fact that both were essentially safe, our population size prevented us from drawing clear conclusions on this matter.

A constraint of the research was the absence of a double-blind methodology because of the varying daily dosages of ibuprofen and paracetamol[6,8,13]. Nonetheless, we are certain that the objective echocardiographic cardiovalvular measures used to assess the major end point (closure of hsPDA) may help to reduce the possibility of bias. Another drawback is that, despite being universally accepted, our echocardiogram diagnostic criteria for hsPDA diagnosis—left atrium-to-aortic root ratio > 1.3 or a ductal size > 1.5 mm—may differ significantly across observers. Furthermore, because there was no comparison group employing a non-interventional conservative care of PDA, we were unable to assess the impact of hsPDA closure or constriction on patients' primary outcomes, such as mortality and BPD. These results, however, were not the study's goals[16]. While we acknowledge that our study is not as original as some others, we still think it might be very helpful for further meta-analyses. Because we did not get serial data on FiO2 and pO2 over the course of treatment, we were unable to assess how oxygen therapy affected PDA closure.

Conclusion

It was discovered that the initial round of hsPDA therapy with IV. IV therapy was more successful than paracetamol. ibuprofen in sealing hypertensive posterior drainage area (hsPDA) in preterm babies with gestational ages more than 25 weeks; nevertheless, it has a comparable constricting effect and its usage was linked to the same hsPDA result, i.e., the demand for surgical closure, re-opening rate, and need for a second course of treatment. Each drug's safety profile was comparable. These findings provide credence to the usage of IV. The first-choice medication for the treatment of hsPDA is paracetamol.

Conflict of interest : NO

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