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Original Article

The effects of intravenous paracetamol use on blood parameters in the treatment of patent ductus arteriosus

Patent duktus arteriozus tedavisinde intravenöz parasetamol kullanımının kan parametrelerine etkileri

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ABSTRACT

Background: Patent ductus arteriosus (PDA), a cause of significant hemodynamic imbalance in newborn babies, can be treated using pharmacological or surgical methods. The purpose of this study was to compare intravenous (IV) paracetamol in newborns with hemodynamically significant PDA, with indomethacin and ibuprofen in terms of changes caused in blood parameters.
Methods: Intravenous paracetamol was used for 3-6 days at 4x15 mg/kg/dose in cases diagnosed with PDA and admitted for follow-up between November 2014 and December 2015, and unable to receive oral medication or with contraindications for indomethacin-ibuprofen use. These cases were investigated retrospectively in terms of changes in pre and post-treatment AST (aspartate aminotransferase), ALT (alanine aminotransferase), urea, creatinine, platelet, and neutrophil values.
Results: Intravenous paracetamol was administered to 10 cases of PDA, diagnosed between November 2014 and December 2015. Prior to paracetamol therapy, an increase in urea values was present in one case, increased AST in two, and decreased platelet values in two. Post-treatment values returned to normal ranges in all cases, and hemodynamic improvement was observed after the closure of the ductus arteriosus.
Conclusion: Our analysis of its effect on PDA closure and its potential side-effect profile in patient blood parameters compared to other known therapeutic agents indicates that intravenous paracetamol, which is easily available and accessible in Turkey, may be an important option for the treatment of PDA.

Keywords: Patent ductus arteriosus, paracetamol, blood parameter, preterm, treatment

ÖZ

Amaç: Yenidoğan bebeklerde önemli derecede hemodinamik dengesizliğe yol açan patent duktus arteriyozus (PDA) farmakolojik veya cerrahi yöntemlerle tedavi edilebilmektedir. Bu çalışmadaki amaç hemodinamik olarak önemli PDA saptanan yenidoğan bebeklerde intravenöz parasetamolü, kan tablosunda oluşturduğu değişiklikler açısından indometazin ve ibuprofen ile kıyaslamaktır.
Yöntem: Kasım 2014 ve Aralık 2015 tarihleri arasında Abant İzzet Baysal Üniversitesi Eğitim ve Araştırma Hastanesi, Çocuk Sağlığı ve Hastalıkları, Yenidoğan Yoğun Bakım Ünitemizde PDA tanısı ile yatırılıp takip edilen ve oral alamayan veya indometazin-ibuprofen kullanımı için kontrendikasyonları bulunan vakalarda intravenöz parasetamol 4x15mg/kg/doz 3-6 gün arası kullanılmıştır. Bu vakalar, retrospektif olarak tedavi öncesi ve sonrası AST (Aspartat Aminotransferaz), ALT (Alanin aminotransferaz), üre, kreatinin, trombosit, nötrofil değerlerindeki değişiklikler açısından incelendi.
Bulgular: Kasım 2014 ve Aralık 2015 tarihleri arasında toplam 10 PDA tanılı vakaya iv parasetamol tedavisi uygulanmıştır. Parasetamol tedavisi öncesi bu vakaların 1'inde üre değerinde artış, 2'sinde AST değerinde artış, 2'sinde de trombosit değerinde düşme varken tüm vakalarda tedavi sonrası değerler normal sınırlara ulaşmış, duktus arteriyozusun kapanması sonrası hemodinamik iyileşme görülmüştür.

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Sonuç: PDA kapanmasına olan etkisi ve diğer bilinen tedavi ajanlarına göre hasta kan tablosunda oluşabilecek yan etki profili değerlendirildiğinde, ülkemizde kolay bulunan, ulaşılması mümkün intravenöz parasetamolün PDA tedavisinde önemli bir seçenek olabileceği kanaatine varılmıştır.

Anahtar kelimeler: Patent duktus arteriozus, parasetamol, kan paramatreleri, preterm, tedavi

INTRODUCTION

The failure of the closure of the ductus arteriosus after the first 72 hours of life is defined as patent ductus arteriosus (PDA). Functional closure is completed in 48 hours in 90% of newborns and 72 hours in almost all. Anatomical closure results in the ductus arteriosus becoming the ligamentum as a result of cell death in the ductus arteriosus and accompanying fibrosis.

Effective pharmacological agents are used for the closure of the ductus. Cyclooxygenase (COX) inhibitors (indomethacin and ibuprofen) stimulate contraction and closure of the ductus by reducing prostaglandin (PG) synthesis through inhibition of COX 1 and 2. Indomethacin or ibuprofen are the first-choice treatments for PDA. Similar closure rates are observed in PDA following the administration of intravenous (IV) indomethacin and ibuprofen. However, both agents have potential side effects. Indomethacin reduces the risk of intracranial hemorrhage (ICH), while ibuprofen entails a lower risk of necrotizing enterocolitis (NEC) and transient renal failure (1). Both agents have similar effects in terms of retinopathy of prematurity, sepsis, surgical ligation rates, length of hospital stay, and mortality (2). Potential side effects of indomethacin include transient renal disorder, gastrointestinal (GI) bleeding, and focal GI perforation. Indomethacin impairs PG-dependent renal, mesenteric, and cerebral blood flow reduces cerebral oxygenation, and compromises platelet adhesion. Decreased creatinine clearance and oliguria are problems frequently seen after the first dose of indomethacin.

Contraindications, including proved or suspected sepsis, active bleeding (particularly intracranial or gastrointestinal), thrombocytopenia (<50,000/mm^3) and/or coagulation disorder, suspected or confirmed NEC, renal failure, urine output <0.6 ml/kg/h, creatinine >1.6 mg/dl, gastrointestinal/renal anomaly, and ductus-dependent congenital heart disease restrict the use of COX inhibitors.

A third treatment option is the non-selective COX inhibitor paracetamol. This treatment option was first used in babies with PDA who had no treatment and contraindications for COX inhibitors, and at the end, ductal closure rates exceeded 90% (3,4).

The purpose of this study was to examine the effect of IV paracetamol use on blood parameters in babies diagnosed with PDA.

MATERIALS AND METHODS

Ten patients, diagnosed with PDA and admitted for follow-up between November 2014 and December 2015, were enrolled in the study.

Twelve babies were initially included, but two were excluded due to mortality associated with prematurity and congenital malformations. Ten babies diagnosed with PDA, unable to use indomethacin and ibuprofen due to contraindications, and in whom oral intake was not possible for reasons such as prematurity, low birth weight, sepsis, and NEC, and therefore treated with paracetamol via the IV route, were enrolled in the study. All patients received paracetamol at 4x15 mg/kg/dose. Duration of the treatment ranged between three and six days, depending on the responses received. Babies contraindicated for paracetamol therapy or with major congenital anomalies were excluded. The study was performed retrospectively by reviewing the patient files. Gestational age, birth week, birth weight, sex, APGAR score, mechanical ventilator support requirement, number of days and

paracetamol therapy and the dosage involved, pre and post-treatment electrocardiogram (ECG) imaging, pre and post-treatment liver and kidney function tests, and platelet and neutrophil counts were recorded for analysis. (Ethics committee approval date and number: 24.04.2017/ 87)

Statistical analysis

Statistical analysis was carried out on SPSS version 21.0 (IBM SPSS) software. Pre- and post-treatment dependent variables were compared using the Paired Samples T-test and the non-parametric Wilcoxon test.

RESULTS

Only one patient was a term (10%), and the remaining nine (90%) were preterm. One case (10%) had normal birth weight, five (50%) were low birth weight, one (10%) was very low birth weight, and four (40%) were extremely low birth weight. Two (20%) of the 10 babies had APGAR scores lower than 7 at one and five minutes, and these were regarded as asphyctic. All patients were receiving respiratory support when paracetamol therapy was administered due to PDA.

Ductus diameters were measured using echocardiography (echo) due to suspicion of PDA in some cases (during the active study by a pediatric cardiology specialist) giving clinical findings such as increased respiratory support requirement, diastolic hypotension, emergence of new murmur, hepatomegaly, and widened pulse pressure. Echocardiography imaging was performed in five cases after IV paracetamol treatment, and a decrease in PDA dimensions and clinical improvement was observed in all cases.

Eight patients (80%) were treated for three days. One patient (10%) received IV paracetamol therapy for five days due to the persistence of clinical findings. The other patient (10%) received IV paracetamol treatment for six days.

No increase in AST (aspartate aminotransferase) values occurred following the IV paracetamol treatment in the seven patients (70%) with pre-treatment AST (aspartate aminotransferase) elevation and decreases in AST were observed in all seven. One patient (10%) who was neutropenic before treatment exhibited normal neutrophil values after the treatment. No pre-treatment ALT (alanine aminotransferase) elevation was present in any patient, and no increase in ALT values occurred in any patient after treatment. This improvement was also statistically significant.

Table 1. Pre- and Post-Paracetamol Treatment AST, ALT, Urea, and Creatinine Values.

Patients	Pre-Treatment AST U/L	Post-Treatment AST U/L	Pre-Treatment ALT U/L	Post-Treatment ALT U/L	Pre-Treatment Urea mg/dL	Post-Treatment Urea mg/dL	Pre-Treatment Creatinine mg/dL	Post-Treatment Creatinine mg/dL
BABY 1	69	52	9	18	73	13	0.7	0.37
BABY 2	52	55	8	7	56	36	0.8	0.4
BABY 3	67	32	16	15	75	49	0.79	0.45
BABY 4	67	45	12	7	73	39	0.67	0.37
BABY 5	212	27	33	19	60	36	0.82	0.5
BABY 6	39	72	6	10	88	79	0.9	1.00
BABY 7	27	30	6	6	71	60	0.54	0.53
BABY 8	73	12	12	9	25	39	0.9	0.4
BABY 9	166	23	14	7	64	62	0.56	0.37
BABY 10	93	59	12	11	36	49	0.51	0.36

AST: Aspartat Aminotransferaz
ALT: Alanin Aminotransferaz

Table 2. Pre- and Post-Paracetamol Treatment Platelet and Neutrophil Values.

BABY	PRE-TREATMENT PLATELET/mL	POST-TREATMENT PLATELET/mL	PRE-TREATMENT NEUTROPHIL/mm^3	POST-TREATMENT NEUTROPHIL/mm^3
BABY 1	224,000	272,000	8100	5900
BABY 2	107,000	138,000	1000	4400
BABY 3	102,000	420,000	18.400	8090
BABY 4	184000	276000	5500	4600
BABY 5	153,000	492,000	9400	10,400
BABY 6	217,000	132,000	3800	10,400
BABY 7	210,000	138,000	23,400	14,200
BABY 8	173,000	270,000	6300	17,500
BABY 9	195,000	268,000	5500	5400
BABY 10	139,000	145,000	2200	2300

Pre-treatment urea elevation was present in nine (90%) patients. A decrease in urea values was observed in eight (80%) of them following the paracetamol treatment, while post-treatment increases in urea values were determined in two (20%) patients (Table 1). Three patients (30%) were thrombocytopenic before treatment. No decrease compared to baseline was observed after the treatment in any patient. On the contrary, increases were observed in all. Low pre-treatment neutrophil value in one patient (10%) increased to normal level after treatment (Table 2).

DISCUSSION

The impairment in AST, ALT, urea, creatinine, platelet, and neutrophil values observed with indomethacin and ibuprofen use in the treatment of PDA did not occur with the paracetamol therapy in this study. On the contrary, improvement in these impaired values was determined after the treatment.

One previous study compared the clinical results of patients with symptomatic PDA undergoing surgical ligation and medical treatment and reported no difference between two groups in terms of mortality, bronchopulmonary dysplasia, bleeding, NEC, sepsis, renal failure, or ICH (5). None of our patients required surgical treatment.

Both indomethacin and ibuprofen are known to cause adverse effects on platelet functions (6). No significant difference has been determined between the two drugs in terms of their effects on NEC, bronchopulmonary dysplasia (BPD), and neuromotor development (7). Indomethacin and ibuprofen were not therefore employed in our cases with low platelet values. Rather than a decrease in platelet values following the paracetamol therapy in our cases with low platelet values, we observed that these approached normal limits.

Indomethacin reduces PG-dependent renal, mesenteric, and cerebral blood flow and cerebral oxygenation, while the renal perfusion-reducing side effect of ibuprofen is less than that of indomethacin (8). Indomethacin and ibuprofen were not employed in eight of our patients due to urea elevation.

The most recent Cochrane systematic review stated that ibuprofen exhibits fewer side effects than indomethacin in the treatment of PDA, while the two agents possess similar efficacy (9). Two randomized, controlled studies compared acetaminophen with oral ibuprofen and reported no difference in effectiveness between the two in the Cochrane review (10). This also represents medical evidence for our use of this preparation in the treatment of PDA.

One study comparing oral ibuprofen and IV indomethacin showed that the two were comparable in terms of PDA closure and side effects (11). We employed IV paracetamol in the present study in patients who were unable to use ibuprofen and indomethacin since oral intake was

not possible and/or contraindicated. However, indomethacin is routinely employed in cases capable of receiving oral treatment in our clinic.

In recent years, the Cochrane and other meta-analyses have discussed the use of IV paracetamol in cases where oral nutrition or oral indomethacin use is not possible. Intravenous paracetamol has been shown to exhibit good efficacy, but the case numbers involved were low. In the present study, we also decided to use IV at similar doses in indications discussed in these meta-analyses. Our number of cases was quite low since we only employed this in cases in which oral intake was not possible. The number of cases in the Cochrane meta-analysis, published in 2016 involving 14 studies, ranged between three and 21. Our case number was thus similar to that in the meta-analysis (12).

Paracetamol was administered IV in six studies in the 2016 Cochrane meta-analysis, and orally in eight. Similar to the present study, paracetamol was selected as the first-line treatment for PDA in five of those studies.

The paracetamol dose used in the treatment of PDA in the previous literature and the 2016 Cochrane review was 4x15 mg/kg/dose. We, therefore, applied that dosage to our own cases. Lengths of treatment in the literature range between three and six days (12). Our patients were also treated for between three and six days.

Urea elevation prior to paracetamol treatment was present in nine (90%) of our cases. A decrease in urea levels was observed after the paracetamol treatment in eight (80%) of these. In the remaining cases, urea values were within normal limits, and no increase occurred. We also attributed this to better tissue perfusion, and particularly renal perfusion, following closure or contraction of the ductus. The most common side effects of indomethacin and ibuprofen include increased urea and creatinine values and impaired kidney functions.

Three patients (30%) had lower than normal platelet counts before treatment, and no decrease in platelet levels compared to baseline was observed in any patient after the treatment. On the contrary, platelet counts approached normal limits in one case with low values and reached near normal ranges in the other two. Increases in platelet numbers compared to baseline were observed in all patients. Thrombocytopenia, a side effect of ibuprofen and indomethacin use, was not seen in our cases (12). Hammerman et al.[18] described severe thrombocytopenia as the main limitation of ibuprofen use, and paracetamol did not exacerbate thrombocytopenia in the present study. Weisz et al.[13] and Mohanty et al.[14] retrospectively examined 26 and 40 patients, respectively, and reported that a large proportion of babies receiving paracetamol healed without complications.

No increase in AST or ALT values occurred after treatment in one study in which paracetamol was used as the first-choice treatment of PDA (11). In the present study, too, no increase occurred in AST values after the IV paracetamol administration in any of the seven (70%) patients with pre-treatment AST elevation and these values normalized. This improvement was also statistically significant. No abnormal increase in ALT values occurred in any of our patients following paracetamol use. One patient (10%) was neutropenic before treatment, but neutrophil values were within normal ranges after treatment. Enrico Valerio et al.[19] also determined that paracetamol in PDA treatment did not exacerbate hepatotoxicity.

Gokmen et al.[15] reported a closure rate of 80% in eight patients after oral paracetamol therapy, and a closure rate of 70% in 10 patients following IV paracetamol use. These rates were compatible with Sancak et al.[16] No paracetamol-related hepatotoxicity was also reported in either group. Rostas et al.[20] also determined that paracetamol can be used when ibuprofen or indomethacin use is contraindicated (17). Meta-analysis findings concerning paracetamol use in the treatment of babies with PDA published in 2016 were similar to those of the present study (Table 3).

Table 3. Studies of Paracetamol Use in the Treatment of PDA.

Author and date	No. of patients	Birth weight (gram)	Birth week	Postnatal age	Administration route	Dose mg/kg/day	Timing
Alan 2013	3	840 (810–1240)	26 (26–33)	9 (8–19)	iv	60	After COX inh failure
El-Khuffash 2014	21	790 (530–1200)	25 (24–28)	25 (3–56)	9 iv 12 po	60	16 after COX-i failure 5 first-line therapy
Hammerman 2011	5	935 (720–1210)	26 (26–29)	10 (3–17)	po	60	2 after COX-i failure 3 first-line therapy
Jasani 2013	6	1107 (1040–1234)	29 (28–31)	5.5 (3–10)	po	60	4 after COX-i failure 2 first-line therapy
Kessel 2014	7	991 (789–1322)	28 (26–30)	6 (2–27)	po	60	2 after COX-i failure 5 first-line therapy
Nadir 2014	7	853 (656–951)	26 (24–27)	5 (2–22)	po	60	3 after COX-i failure 4 first-line therapy
Oncel 2013	8	995 (630–2970)	28 (23–36)	9.5 (5–27)	po	60	6 after COX-i failure 2 first-line therapy
Oncel 2013	10	775 (590–990)	27 (24–29)	6 (2–15)	iv	60	First-line therapy
Ozdemir 2013	7	820 (620–1615)	820 (620–1615)	35 (20–47)	po	60	After COX-i failure
Roofthooft 2013	10	700 (365–950)	25 (23–26)	22 (13–30)	9 iv 1 po	60	6 after COX-i failure 4 first-line therapy
Sinha 2013	10	995 (800–1380)	29 (27–33)	5 (4–7)	po	45	First-line therapy
Tekgunduz 2014	13	950 (470–1390)	29 (24–31)	3 (2–9)	iv	30-60	First-line therapy
Terrin 2014	8	700 (530–930)	26 (23–29)	2 (2–5)	iv	30-60	First-line therapy
Yurttutan 2013	6	1260 (920–1600)	28 (26–32)	4 (3–7)	po	60	First-line therapy
AIBU Neonatal Intensive Care Unit	10	1512 (615-2950)	30 (24-38)	5 (3-12)	iv	60	First-line therapy

PDA: Patent Duktus Arteriyozus
COX-i: Cyclooxygenase Inhibitors
AIBU: Abant İzzet Baysal University

Normalization of liver and kidney function tests and blood count values was evaluated as an effect of the closure of the ductus arteriosus. The limitations of the present study include its retrospective nature, the relatively small sample, and the fact that it was performed in a single center.

In conclusion, IV paracetamol therapy occupies an important place among other therapeutic options due to its low side effect profile in cases where oral therapy is not possible, its easy availability, and the fact it causes no marked adverse effects on the body.

Ethics Committee Approval: The study protocol was approved by the Abant İzzet Baysal University Clinical Research Ethics Committee (24.04.2017/87).

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