Is high dose intravenous acetaminophen affect liver function in premature neonates with patent ductus arteriosus?

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Abstract

Objectives

The aim of this study was to collect consistent data on the efficacy and safety and evaluation hepatotoxicity of intravenous acetaminophen for the treatment of PDA in preterm infants.

Methods

This is an observational longitudinal prospective study on 46 preterm infants with PDA who treated with high dose of acetaminophen and evaluated with echocardiography and serum liver enzymes at Hafez and Zeinabiyeh hospitals from January 2016 to December 2019.

Result

Forty-six preterm infants with PDA treated with intravenous acetaminophen. Rate of closure of PDA was 82.6. There was no significant difference after treatment regarding AST, ALT, Albumin, total and direct bilirubin (P value > 0.05) and no adverse side effects were observed in association with intravenous acetaminophen.

Conclusion

High dose of acetaminophen is an effective and safe therapeutic option without hepatotoxic side effect for PDA closure.

Introduction

A common complication in preterm neonates is patent ductus arteriosus (PDA). PDA is a congenital heart defect that communicate aorta into the pulmonary artery. patency of PDA is necessary for fetal circulation. In healthy term neonates spontaneous PDA closure happen normally 24–72 hours after birth because of increase pressure of oxygen in artery. (1)

Incidence of PDA in preterm neonates between 30–37 week gestational age is 10%, those delivered in 25–28 week of GA is 80% and 90% is the percentage of infants born before 24 week GA that after a week would reduce to 2%, 65% and 87%. (2, 3)

Hypoxia, acidosis, raised pulmonary pressure and increasing prostaglandin level are risk factors that contributing to ductal patency. Shunt of blood from the aorta into the pulmonary artery can promote pulmonary over circulation that lead to significant clinical consequence such as vital organ perfusion

impairment for example pulmonary hypertension, heart failure, intra ventricular hemorrhage and respiratory disease, periventricular leukomalacia, cerebral palsy or death.(2, 4–7)

PDA intervention is controversial, and there is limitation of evidence to guide treatment. There is 3 strategies for closure of PDA in prelatures: Prophylactic management, treatment of clinically detected asymptomatic PDA, and treatment when the PDA is symptomatic neonates. Management of ductal closure include conservative treatments (i.e. fluid restriction, diuretics, etc and waiting for spontaneous closure), pharmacological management and surgical ligation. (1, 3, 8, 9)

FDA approved intravenous (IV) indomethacin and ibuprofen (cyclooxygenase inhibitors) as first drug use for treatment of PDA. These drug reduce the levels of prostaglandin that promote ductus arteriosus muscular wall constriction lead to fibrosis as anatomical ductal closure. Prenominated NSAIDs were successful in closure of PDA. (10)

Indomethacin decrease incidence of intraventricular hemorrhage, pulmonary hemorrhage and in extremely premature neonate reduce development BPD and death. (2)

Ibuprofen has same mechanism action and efficacy for closure of PDA as indomethacin (success rate 70–85%) but less impairment of renal function because of lower vasoconstrictor effect. However, ibuprofen has significant side effects, such as nephrotoxicity, pulmonary hypertension and hyper-bilirubinemia.(2, 3, 5, 11)

NSAID adverse effect include renal function impairment, GI bleeding, necrotizing enterocolitis, intestinal perforation, thrombocytopenia, pulmonary hypertension and hyperbilirubinemia and etc. (1, 2)

In recent years increasing acetaminophen administration for PDA treatment because this drug is has same efficacy as NSAIDs with fewer side effects because acetaminophen is prostaglandin synthesis inhibitor with affect at peroxidase site of prostaglandin H synthetase (POX) that differs from COX inhibitor. (1, 2)

In neonates who have contraindication for treatment with indomethacin and ibuprofen or the NSAIDs have failed in closure of PDA administration of acetaminophen suggested as a choice before surgical ligation. (2)

Evaluating of advantages and disadvantages of pharmacological treatment by assessment of following outcomes: PDA closure failure (according to clinical evaluation or echocardiography criteria) as primary outcome; require surgical ligation of PDA, death, and selected any untoward medical occurrence, as secondary outcomes., not certainly having a causal association with treatment(8)

Prospective trials may support more perception of acetaminophen effectiveness and safety as a further or even as a first-line option for closure of PDA in neonates (12)

Some hepatic side effects have been happened after usage of iv acetaminophen, which may determine a transient raise in liver enzymes or more serious acute liver toxicity.(13, 14)

acetaminophen itself not directly cause of hepatotoxicity in neonates but can be caused by N-acetyl-p-benzoquinoneimine (NAPQI) produced by hepatic cytochrome P450 (CYP) as metabolite production - dependent mixed function oxidase enzyme. The action of NAPQI formation, sulphate elimination, and glucuronide production rate are not known in preterm neonates exactly. (15, 16)

The hepatic metabolism of acetaminophen happens through sulphation, glucuronidation, and oxidation. Usage therapeutic doses of acetaminophen produces nontoxic metabolites through glucuronidation, or sulphation activation as first mechanism. CYP1A2, 3A4, and 2E1 induce acetaminophen oxidation that generates the highest reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI).

Glutathione conjugate it into a renal metabolite that is safe. Sulphation and glucuronidation pathways saturate after an high dose of acetaminophen and lead to excessive dose of NAPQI use glutathione resource and Becomes toxic as a results. the toxic acetaminophen dose is higher than therapeutic concentration about ten times in adults and the growth changes acetaminophen metabolism. (17) The rate of glucuronidation in neonates is variable and the ability of glutathione conjugation is limited with the sulphation pre dominancy, and the expression of CYP is early in postnatal life in full-term neonates while this is unknown exactly in preterms. (18–20)However, the existence of a large therapeutic serum concentration range for acetaminophen suggested by clinical evidence that demonstrate a low or absent hepatic toxicity in neonates. (2, 10, 18, 21)

In this study we use high dose acetaminophen in infants with a clinically significant PDA to determine efficacy and hepatic side effects of iv acetaminophen.

Methods

This is an observational longitudinal prospective study.

The study involved 46 preterm infants (gestational age < 37 weeks, mean birth weight 1099.3 g) with hemodynamically significant patent ductus arteriosus (HsPDA) born at our hospitals (Hafez and Zeinabiyeh) hospitals with the approval of the local ethics committee from January 2016 to December 2019

Exclusion Criteria

Preterm neonates with complex congenital heart disease, those were PDA as life saving for them, the cases who ibuprofen or indomethacin administrated before treatment with acetaminophen, and if the parents did not accept to enroll in this study.

Treatment Eligibility Criteria And Drug Administration Protocol

Infants with a gestational age < 37 weeks and who Had clinical signs of significant PDA within the first week of life, diagnosed by pediatric cardiologist were enrolled in the study after obtaining written consent from their parents.

Echocardiography for diagnosis of PDA was done by pediatric cardiologist.

Treatment with high dose of i.v route acetaminophen was started at a dose 20 mg/kg every 6 h for 4 d, with echocardiographic evaluation performed at the end of the treatment.

Treatment success was defined as complete ductal closure on echocardiography. Pre- and post-treatment levels of liver enzymes (alanine transaminase (ALT), aspartate aminotransferase (AST), albumin, total and direct bilirubin) were measured for evaluation liver toxicity.

Data and analysis done with SPSS version 19 and p value < 0.05 consider as significant.

Result

46 preterm infants were included in this study (January 2016 to December 2019). The median gestational age was 30.1 weeks (minimum–maximum: 25.5–36) and the median birth weight was 1099.3 g (800–3300) were PDA positive born at our institution began “first-line” i.v acetaminophen treatment (dose 20 mg/kg every 6 h for 4 d). PDA echocardiographic parameters before starting any i.v acetaminophen treatment are given in Table 1.

Table 1
Baseline characteristics and echocardiographic data of preterm infants

		Frequency	Percent	Bitrh weigh(gram)	Gestational age(weeks)
Valid	Small:<2 mm	14	30.4	1395	30.54
	Medium between 2 to 4 mm	19	41.3	1528.4	30.08
	Large:>4 mm	9	19.5	1409	29.7
	Total	42	91.3		
Missing	System	4	8.7		

Medical treatment of the PDA failed in 8 patients out of 46 infants and 1 patient because of sepsis, expired during course of treatment. The echocardiography of 46 patients with PDA on treatment cardiac

ultrasound resulted in successful closure of PDA among 38 patients (82.6%).

Pre- and post-treatment levels of liver enzymes and bilirubin levels of all infants for the purpose of assessing the treatment's safety are summarized in Table 2.

There was no significant difference after treatment regarding AST, ALT, Albumin, total and direct bilirubin (P value > 0.05). Pre- and post-treatment levels of liver enzymes and bilirubin levels were normal in all patients, and no adverse side effects were observed in association with iv acetaminophen. The liver size and clinical examination of the 46 infants during and after treatment were normal. No sign and symptom of hepatotoxicity such as Jaundice, yellowish sclera and hepatomegaly were seen during and after treatment with high dose acetaminophen. Bleeding tendency, GI complication and oliguria did not detect. 39 cases cured in first course of acetaminophen administration and improved signs and symptoms due to PDA. PDA closure improves dynamic compliance and increases tidal volume in preterm neonates receiving mechanical ventilation and a significant decrease in ventilator setting in our patients with PDA closure than those with failure of PDA closure.7 infants failed in closure of PDA treated with second course combination acetaminophen and ibuprofen.

Table 2
Comparison between value before and after treatment (paired t test)

		Mean Serum level	Number	Std. Deviation	P-value
albumin	before	3.04	23	0.47	0.672
	after	3.09	23	0.60	
Total bilirubin	before	5.43	40	3.03	0.258
	after	4.82	40	4.72	
Direct bilirubin	before	0.46	29	0.16	0.123
	after	0.58	29	0.40	
AST	before	32.78	31	23.91	0.205
	after	48.55	31	84.26	
ALT	before	14.85	33	16.21	0.111
	after	19.36	33	18.48	

Discussion

Recent results reported on the use of acetaminophen in the treatment of PDA are highly promising, but adequately powered. The aim of this study is to collect consistent data on the efficacy and safety of intravenous acetaminophen for the treatment of PDA in preterm infants. Hemodynamically significant

PDA in preterm infants is better to be closed to decrease complications of PDA(Such as necrotizing enterocolitis, developing chronic lung disease in infants.), through pharmacotherapy, surgical, or catheter closure .Pharmacotherapy seems to be the therapy of choice because of its safety and effectiveness in treatment of PDA in preterm infants. Drugs like cyclooxygenase (COX) inhibitors, e.g., indomethacin and ibuprofen, were used for closure of PDA. acetaminophen is an alternative therapeutic approach for ductal closure through inhibition of prostaglandin synthetase activity. Although its efficacy in PDA closure has been approved.(10) acetaminophen seems to inhibit peroxidase segment of the enzyme prostaglandin synthetase, unlike NSAIDs that inhibit cyclooxygenase pathway of this enzyme.NSAIDs are associated with significant adverse effects, including peripheral vasoconstriction, gastrointestinal bleeding and perforation, renal failure, oliguria and impaired platelet aggregation. In premature infants, ibuprofen has been associated with inhibition of bilirubin glucuronidation in the liver and hyperbilirubinemia. These adverse effects emphasize the possible benefits of alternative treatment with acetaminophen for PDA management.(12)

We used acetaminophen as a first option in the treatment of PDA for 46 patients successfully without any contraindications. Our study showed that acetaminophen is effective in promoting ductal closure of PDA in preterm infants.. The rate of closure in acetaminophen therapy in 46 preterm neonates with mean gestational age 30.1 weeks was 82.6%. This was in agreement with other studies. El mashad et al 2017 showed. The rate of closure in acetaminophen therapy in 100 neonates (80%) was more or less similar to that after ibuprofen (77%) and indomethacin (81%) therapy.(10) Hammerman et al. reported that they used acetaminophen in five cases because of different contraindications and unresponsiveness to the treatment. At all cases, the ducts were closed and positive responses were observed to the acetaminophen treatment. These cases' gestational ages were 26–weeks, and birth weights were 720–1210 g. Times of initial treatment were 3–35 d.(22) Oncel et al. have reported eight cases who were unresponsive to ibuprofen, or ibuprofen was contraindicated and received acetaminophen for treatment of PDA. These cases' with median gestational age of 28.5 weeks, and median birth weights was median birth weight of 995 g.(23)

Treatment of acetaminophen was administered on an average of 3–7 d and only one of eight patients was unresponsiveness to the acetaminophen treatment. However, higher rate of PDA closure (> 95%) was reported by other investigators. In the study of Dash et al enteral acetaminophen showed a PDA closure rate of 100% and no hepatotoxicity was detected. This surprising high result about acetaminophen efficacy deviates from other studies' results, but it must be considered that this RCT evaluated patients showing a mean GA of 31.6 weeks, higher than neonates in other trials. With better response to pharmacological treatment.(24) PDA is known to be less responsive to cyclooxygenase inhibition in young preterm neonates due to higher expression of prostaglandin receptors in their PDA walls. H¨arkin et al demonstrated a faster PDA closure rate in acetaminophen group (95%) than in placebo group. The authors used a different drug dosage, administering 20 mg/kg of acetaminophen at 24 hours of life, followed by 7,5 mg/kg every 6 h for 4 days and the ductus closed at a mean of 177 hours of postnatal life in treated patients versus 338 hours in controls. However, GA influenced ductal closure; in fact, in extremely preterm infants (< 27 weeks' GA), acetaminophen did not show a significant effect; among

these, 4 preterms (50%) required PDA ligation.(25) Le et al(1) agree with the idea that acetaminophen seems to be a good alternative in PDA treatment and should be considered, in case of ibuprofen contraindication, before ligation. The author also recommends performing other trials because two studies published on 2013 found low iv acetaminophen success rate in small groups of patients (n = 29 and n = 3Roofthooft et al (26)had disappointing results with PDA closure after iv acetaminophen treatment with a low success rate of only 17%. This could be due to a late start of acetaminophen administration in their study (median of 14 days). But El Kuffash et al (27)evaluated late treatment with iv acetaminophen beyond the 2nd week of life which became effective in PDA closure, avoiding PDA ligation. Anyway, more studies are needed to confirm the role of acetaminophen late administration. acetaminophen efficacy becomes greater when started in the first week of life and this may be related to the higher prostaglandin circulating levels during early postnatal life; Regarding the caution of hepatotoxicity of acetaminophen in neonates, we found that there was no significant change in AST, ALT, albumin, total and direct bilirubin serum levels in 46 patients after treatment with high dose iv acetaminophen(20 mg/kg Q6h for 4 days)with P > 0.05. No adverse effects or signs of hepatotoxicity such as Jaundice,yellowish sclera and hepatomegaly have been described as a result showing that early iv acetaminophen accelerates PDA closure without relevant side effects.The liver size and clinical examination of the 46 infants during and after treatment were normal.This result was in agreement with Jacqz-Aigrain et al (21)who reported that neonates tend to suffer less from the hepatotoxic effects of acetaminophen than do older children. Hammerman et al. reported that acetaminophen could offer important therapeutic advantages over NSAID (e.g., indomethacin and ibuprofen) as acetaminophen has no peripheral vasoconstrictive effect, so it can be given to infants with clinical contraindications to NSAIDs [8]. Yurttutan et al 2013(28) Treated Six preterm infants with median gestational age of 28.5 weeks and median birth weight of 1260 g and time of initial treatment was 5.5 day used oral acetaminophen as the first choice. The closure rate (83.3%) and reopening rate (20%).In their cases during and after the treatment, liver function tests were measured in normal ranges in all cases. Allegaert et al 2008(29) performed retrospective analysis at least suggest that a higher daily dose compared with the registered dose is also well tolerated and can therefore be considered for dose finding studies. In conclusion, this retrospective study on hepatic tolerance provides evidence for safe administration of iv acetaminophen in neonates. Future studies should focus on dose-findings and pharmacodynamics of this formulation in this population. This can be explained by the metabolism of acetaminophen that changes with age. In adults, the majority of acetaminophen is conjugated with glucuronic acid and, to a lesser extent, with sulfate. Hepatic glucuronidation is relatively immature at birth. The sulfate conjugate predominates in preterm infants, newborns, and young infants.(10) With maturation, these clearance pathways for acetaminophen change. The usual adult ratio of 2:1 glucuronide to sulfate conjugates of acetaminophen is achieved by 12 years of age.(30) Our result was in contrast with Anderson et al (31)who reported hepatotoxicity in term neonates, but it occurred after 3 days of excessive acetaminophen intake. Moreover, Alan et al (13)reported elevated liver transaminases in two out of three preterm neonates treated for PDA.In the review of Tan and Baral (32)among n = 88 treated patients, = 6showed transitory liver enzymes elevation. Bardanzellu et al 2017 (2)reported analysis on 16 reviews investigating the role of acetaminophen in PDA treatment shows that most authors support the efficacy

of this drug in ductal closure, becoming comparable to NSAIDs with inconstant transient lower side effects (in terms of elevation of liver enzymes) instead of GI bleeding, oliguria, and hyperbilirubinemia showed after ibuprofen therapy However, an appropriated monitoring in order to early detect acetaminophen toxicity is recommended. All these authors agree with the possibility of using acetaminophen in case of ibuprofen or indomethacin contraindications and/or failure.GI bleeding was significantly more observed in the indomethacin group followed by the ibuprofen group.

In our study bleeding tendency and GI complication did not detect. GI bleeding never seen that went with the results of other investigators. A safer profile in terms of gastrointestinal bleeding and hyperbilirubinemia after acetaminophen administration instead of ibuprofen has been described by Evans(5) and Terrin et al(33) In contrast to our results. Dash et al(24) reported striking high intestinal bleeding rate in the acetaminophen group (26.3%) The high intestinal bleeding rate in their study may be related to high osmolality of acetaminophen used in their study. PDA is thought to decrease lung compliance via an increase in pulmonary circulation and resultant increased lung water and pulmonary edema. In our study 39 cases cured in first course of acetaminophen administration and improved signs and symptoms due to PDA. PDA closure improves dynamic compliance and increases tidal volume in preterm neonates receiving mechanical ventilation. Clinicians usually increase ventilator settings in PDA to address the poor compliance; this finding may explain how a PDA could increase the risk of BPD.(10) This can explain a significant decrease in ventilator setting in our patients with PDA closure than those with failure of PDA closure.

Conclusion

The goal of the studies on PDA management would be to perform an individualized therapy, choosing the for each of the patient characteristics, which could be the most effective as much as possible, personalized, and with the lowest side effects. acetaminophen is as effective as indomethacin and ibuprofen in closure of PDA in preterm neonates with less side effects than both. Our data suggest that acetaminophen is an effective and safe therapeutic without hepatotoxicity side effects option for PDA closure. Our results support previous reports that proposed the use of acetaminophen as an alternative treatment for PDA. Between the available drugs for PDA treatment, acetaminophen seems to be a promising alternative and most authors agree with the necessity of more trials to establish the safer dose in preterms and its efficacy. If acetaminophen is shown to be effective in a large series, because of low risk of side effects, low cost it may be an advantageous alternative at PDA treatment.

However, non-well designed trials about proper acetaminophen dosing or large randomized controlled trials (RCT) on short and long-term safety

Abbreviations

PDA Patent ductus arteriosus

LFT Liver function test

LA Left atrium

LV Left ventricle

I.V Intravenous

COX inhibitors Cyclooxygenase inhibitors

Declarations

Ethics approval and consent to participate: All procedures performed in this study were in accordance with the ethical standards of the “Research Ethics Committee of Shiraz University of Medical Sciences” and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. **This study was submitted to and** approved by the “Research Ethics Committee of Shiraz University of Medical Sciences” with Ethics code IR.SUMS.MED.REC.1395.68

Consent for publication: This manuscript does not contain any personal data, and the consent for publication is applicable.

Ethical approval and consent to participate: The study was explained for the patients or guardians and informed consent forms were signed by them.

Availability of Data and Materials: We state that the data used and/or analyzed during the current study are **available from the corresponding author on reasonable request.** Data sharing is applicable to this article and datasets were generated and analyzed during the current study and data sharing is allowed.

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FA: Sample collection and data preparation, manuscript preparation

HM : Design, analysis, statistics and manuscript preparation

M.R.E: Data collection and Drafting, analysis

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NM: critical revision and manuscript preparation

HA: drafting

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Competing interest:

The authors declare that they have no competing interests

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