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Intravenous frusemide does not interact pharmacodynamically with acetaminophen in critically ill preterm neonates with patent ductus arteriosus

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Abstract. – OBJECTIVE: Evidence is controversial regarding the effect of concomitant frusemide with acetaminophen therapy in neonates with patent ductus arteriosus (PDA).

PATIENTS AND METHODS: Critically ill neonates diagnosed with hemodynamically significant PDA by echocardiography and receiving intravenous acetaminophen were recruited. Dosing regimens of frusemide, and acetaminophen, and the sizes of ductus arteriosus following treatment, were evaluated.

RESULTS: Fifty-one neonates were recruited. Forty-six (90.2%) had moderate-sized, and five (9.8%) had large-sized ductus arteriosus. Forty (78.4%) neonates had a successful closure. Twenty-four received concomitant frusemide with a median (range) cumulative dose of 3 (0.8-13) mg; duration of 2 (1-13) days; and a fraction of overlapping days with acetaminophen therapy of 0.4 (0.2-1). Twenty-one (87.5%) neonates that received frusemide had a successful ductal closure compared to 70.4% of those without ($p > 0.05$).

CONCLUSIONS: We did not observe any significant influence in the outcomes of acetaminophen therapy with concomitant frusemide in preterm neonates with PDA.

Key Words:
Paracetamol, Furosemide, PDA.

Introduction

Patent ductus arteriosus (PDA) is the second most common congenital heart disease with an incidence of 0.25 per 1000 newborns[1]. Spontaneous closure of ductus arteriosus occurs around 48 hours; but medical intervention is required if hemodynamically significant shunting of blood occurs from arterial to pulmonary system[2]. The first-line drugs for closing the ductus arteriosus are the inhibitors of prostaglandin synthesis (ibuprofen, indomethacin, and acetaminophen)[2]. Due to relatively better safety concerns, acetaminophen is preferred[3]. Frusemide is indicated in preterm neonates for treating respiratory distress syndrome, that is often observed concomitantly with PDA[4]. Frusemide was associated with the release of prostaglandin E2 resulting in vasodilation and inhibition of the closure of ductus arteriosus[5]. *In vivo* studies in the neonatal rats revealed that frusemide dilates the constricted ductus arteriosus and delays the closure of ductus arteriosus[6]. Neonatologists in US expressed a major concern for the development of PDA with diuretic use[7]. We carried out a study evaluating the association between clinical factors, and genetic polymorphisms with therapeutic response to acetaminophen in neonates with PDA. Here, we are presenting a separate analysis on the pharmacodynamic interaction of concomitant frusemide during acetaminophen therapy.

Patients and Methods

Study Design and Procedure

This was a prospective observational study carried out in the Neonatal Intensive Care Unit of Salmaniya Medical Complex, Ministry of Health (Manama, Kingdom of Bahrain) following the Ethics approval from AGU. Preterm neonates with hemodynamically significant PDA receiving intravenous acetaminophen at 15 mg/kg/dose every 6 hours were recruited. Demograph-

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ic details, frusemide dosage regimen, and follow-up echocardiographic findings were captured. Their gestational ages were classified as follows: extremely preterm (<28 weeks); very preterm (28 to <32 weeks); and late preterm (32 to <37 weeks). Birthweights were classified as follows: 1.5 to <2.5 kg – low; 1 to <1.5 kg – very low; and <1 kg – extremely low. The diameter of ductus arteriosus was classified as moderate-(1.5-3 mm) or large-sized (>3 mm).

Statistical Analysis

Chi-square test was used for evaluating the association of frusemide and successful closure of ductus arteriosus; and Kruskal-Wallis H test for numerical variables. Logistic regression analysis was performed with gestational age, birthweight, baseline size of ductus arteriosus, cumulative dose, duration, and fraction of days of frusemide therapy overlapping with acetaminophen as independent variables and the closure of ductus arteriosus as the dependent variable. Odds ratio (OR) [95% confidence intervals (CI)] was used as the effect estimate measure. SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY, USA; IBM Corp.) was used.

Results

Demographics and Overall Pharmacodynamic Outcomes

Fifty-one neonates were recruited, and their demographic characteristics are summarized in Table I. All the neonates were admitted with the provisional diagnosis of suspected sepsis on mechanical ventilation. Median (range) size of ductus arteriosus in the study population was 2.5 (1.5-4) mm. Forty-six (90.2%) had moderate, and five (9.8%) had large-sized ductus arteriosus. Thirty-seven (72.5%) neonates with moderate-sized, and three (27.5%) of large-sized ductus had successful closure (p=0.2).

Pharmacodynamic Outcomes with Concomitant Frusemide Therapy

Twenty-four (47.1%) received concomitant frusemide. Median (range) cumulative dose and duration of frusemide therapy were 3 (0.8-13) mg and 2 (1-13) days. Median (range) overlap of frusemide with acetaminophen therapy was 2 (1-8) days. Fraction of days of acetaminophen course with concomitant frusemide therapy was 0.4 (0.2-1). No significant differences (p>0.05) were observed between the gestational age categories on the cumulative doses, total duration, and duration of overlap between frusemide and acetaminophen therapy (Figure 1). Twenty-two (91.7%) had moderate-sized, and two (8.3%) had large-sized ductus arteriosus. Twenty-one (87.5%) neonates had successful closure of ductus arteriosus. None of the variables significantly influenced the ductal closure in the logistic regression analysis. Eighty-seven percent of neonates with frusemide therapy had successful closure as against 70.4% (19/27) without frusemide therapy (p>0.05). After correcting for gestational-ages and birthweights, OR (95%

Table I. Summary of demographic characteristics of the study population (N=51).

Variables		Values
Gestational age (weeks)[$]		27.3 (2.3)
Gestational age category [n (%)]	Late preterm	3 (5.9)
	Very preterm	16 (31.4)
	Extreme preterm	32 (62.7)
Birthweight (kg) [$]		1 (0.3)
Birthweight category [n (%)]	Low	5 (9.8)
	Very low	15 (29.4)
	Extremely low	31 (60.8)
Male: Female (n)		24: 27
Length (cm)[$]		34.3 (4)
APGAR score[#]	1 min	6 (1-9)
	5 min	9 (2-10)
	10 min	9.5 (7-10)
Duration of ICU stay (days)[#]		46 (3-106)

[$]-Mean (SD); [#]-Median (range).

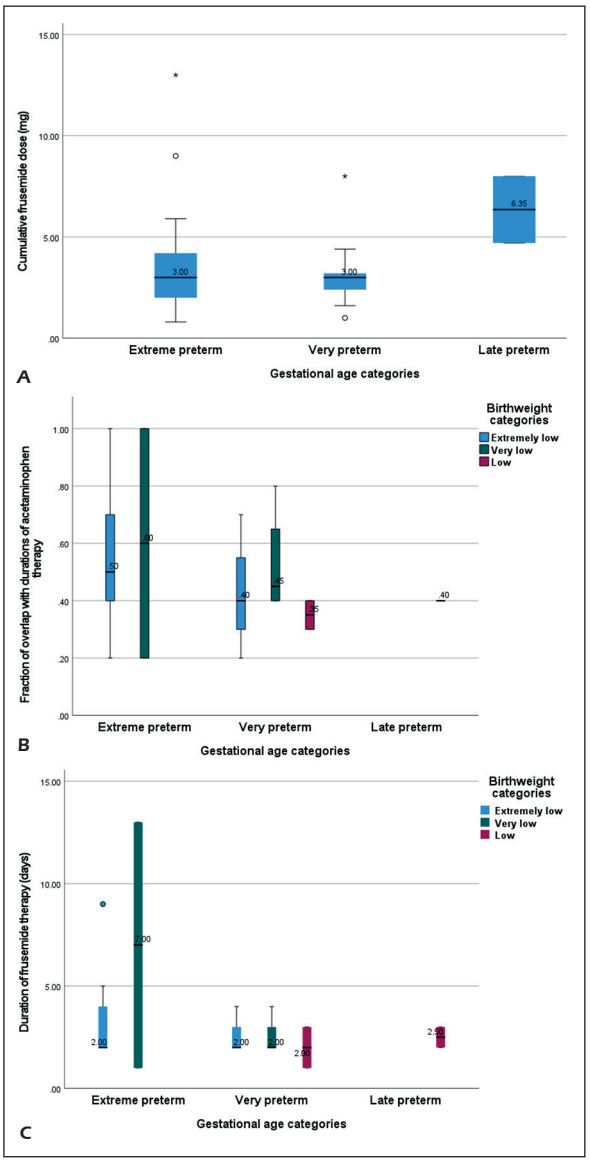

Figure 1. Gestational age-wise classifications doses and durations of frusemide therapy. The box and whisker plots reveal the median values and the variabilities observed in the cumulative doses **(A)**, fraction of overlap with acetaminophen **(B)**, and duration **(C)** of frusemide

CI) for ductal closure with frusemide use was 0.4 (0.09, 1.7).

Discussion

The first preliminary report evaluating the association of frusemide with PDA was from a study conducted in neonates with respiratory distress syndrome where frusemide was administered in 33 neonates and was compared to chlorothiazide[8]. The authors observed an incidence of PDA to an extent of 54% with frusemide as against 24% with chlorothiazide. However, this study was conducted 30 years ago and so the clinical relevance of this data in the contemporary world is uncertain. In a recent study from 43,576 very low birthweight neonates, the use of frusemide was associated with a decreased odd of requiring treatment for PDA (OR=0.72, 95% CI: 0.97, 0.79)[9]. Similarly, a study from France revealed that the 7.4% of their neonates with PDA were refractory to the medical treatment of which only 26.4% of this cohort received concomitant frusemide therapy[10]. We also did not observe any significant influence in the ductal closure with concomitant frusemide therapy in the present study.

Conclusions

Concomitant frusemide therapy does not significantly affect the pharmacodynamic outcomes following acetaminophen in neonates with PDA.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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