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Prostaglandin E1 before Elective /Caesarean Section to Reduce Transient Tachypnea of the Newborn (TTN): A Randomized Control Trial

Noha H. Rabea[1], Noha A.S. Sakna[1], Hossam H. Ahmed[2] Marwa S. Sayed[1]

Obstetrics and Gynecology Department, Faculty of Medicine[1,2],

Ain Shams University[1], Cairo University[2]

Corresponding Author: Marwa Saber Sayed**, E-mail:** drmarwasnosi@gmail.com,

Mobile: +20 1115670205, **ORCID number:**0000-0001-8917-8814.

ABSTRACT

Aim of the study: This study aimed to determine the role of prostaglandin E1 on the reduction of the neonatal respiratory morbidity specially (TTN).

Study Design: This is a parallel, randomized placebo-controlled trial, comparing the use of misoprostol (Prostaglandin E_1) use in the form of misoprostol E_1 vaginal tablets with non-medicated similar vaginal tablet (placebo) to decrease the neonatal respiratory distress specially (TTN).

Results: This study included 300 cases with gestational age range between 38 weeks to less than 39 weeks. The included cases were classified into 2 groups: Study group included 150 cases, were given PG E1, control group: Included 150 cases, were given placebo.

Conclusion: We found one positive cases for TTN in the study group, and 3 positive cases for TTN in the control group. The results we got were insignificant. So, we suggest taking larger sample in the future studies.

Keywords: Prostaglandins, Cesarean section, Respiratory morbidity, Transient Tachypnia of Newborn.

INTRODUCTION

Neonatal respiratory distress is more common in preterm newborn than term newborn regardless the mode of delivery; however, it is higher after elective caesarean than after normal vaginal delivery [(1)].

Transient tachypnea of the newborn (TTN) is due to delayed resorption of pulmonary fluid, as a consequence of defective catecholamine surge [(2)], which are known to stimulate pulmonary fluid reabsorption through acting upon beta-adrenergic receptors in fetal lung, which are present later in gestation, thus, enabling surfactant secretion [(3)].

This catecholamines surge can be stimulated by prostaglandins given prior to caesarean section [(4)] as those who are born vaginally are found to have metabolic adaptation through higher catecholamine levels at birth. So, giving prostaglandins one hour before elective caesarean section after excluding those with contraindications to their use may help in this process [(5)].

In a previous similar prospective study of 36 women scheduled for an elective caesarean section beyond 38 weeks [(4)]18 women received intravaginal prostaglandin E2 tablets and 18 received placebo, there was one neonatal respiratory distress case in the control group, which was reported as transient tachypnea of the newborn with similar Apgar score at one and five minutes and no need to mechanical ventilation nor side effects related to treatment in either group, so no difference in respiratory outcome was reported.

The aim of the current study was to determine the role of prostaglandin E1 on the reduction of the neonatal respiratory morbidity specially (TTN).

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PATIENTS AND METHODS

Study Setting

This study was conducted in Ain Shams University Maternity Hospital (ASUMH) and Police Hospital- Nasr City and it started from November 2016 to July 2017.

Trial Design

Parallel, randomized placebo-controlled trial, comparing the use of Misoprostol (Prostaglandin E_1) in the form of Misoprostol E_1 vaginal tablets with non-medicated similar vaginal tablet (placebo) to decrease the neonatal respiratory distress specially (TTN).

Eligibility Criteria

Inclusion criteria

- Age: 18 years or more.
- Term pregnancy (38 - < 39 weeks).
- Pregnant women planned for elective transverse lower segment caesarean section with an indication.

Exclusion criteria

- Women with history of significant cardiac disease, D.M, eclampsia, pre-eclampsia, epilepsy, severe asthma, severe allergic condition, vascular disease, renal or hepatic disease.
- Women with contraindication to prostaglandins as glaucoma or known hypersensitivity to prostaglandins or specifically for misoprostol.
- Psychological problem or mental disease that renders the patient not able to understand the nature, scope, and sequences of the study.
- Pregnancies with known fetal malformation/s or chromosomal aberration.

INTERVENTION

Subjects

The population in this study was consisted of a sample of pregnant women between 38 - < 39 weeks gestation scheduled for elective caesareansection, selected according to inclusion and exclusion criteria, 300 cases were randomly assigned into two groups:

- The first group (Study Group) included 150 women and they were treated with Misoprostol (prostaglandin E_1).
- The second one (control Group) was consisted of 150 women and they were given placebo.

Misoprostol (Prostaglandin E1) containing vaginal tablet in the form of 200 microgram Misoprostol (Cytotec: Pfizer) administered about 60 minutes before scheduled caesarean section. Placebo was given in the form of non-prostaglandin E_1medicated vaginl tab. And it contained only the inactive ingredients (Hydrogenated castor oil, microcrystalline cellulose, crospovidone). They were synthesized with the help of Laboratories of Ain Shams Faculty of Pharmacy to be administered vaginally for the purpose of research.

Ethical considerations:

The study was done after approval of Research Ethical Committee, faculty of Medicine, Ain shams University and an informed written consent was taken from each participant.

OUTCOMES

- ✓ **The primary outcome**
  - Incidence of TTN
- ✓ **Secondary outcomes**
  - Apgar score was reported at one and five minutes.
  - . The need of neonates for mechanical ventilation.
  - Percentage of neonates required admission into the intensive care unit.

- Fetal mortality in the studied population.

Sample Size Calculation:

Results of previous trial done by Motaz *et al*[6] was very poor regarding the statistical results due to very small sample size sample size was calculated according to the power of test during sampling when it reached >/=85 true rate with error or<l=15%sample size of 300 patients was considered sufficient for both groups And were randomly assigned using computer –generated random sequence in a ratio of 1:1 Allocation for each arm of the study.

Statistical Analysis

Statistical analysis of the present study was conducted, using the mean, standard deviation, independent t-test was used to compare between two groups in quantitative data, paired Student T-test was used to compare between related samples and chi square test and Fisher's Exact test were used to compare between groups in qualitative data by (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). p value of< 0.05 was considered significant.

RESULTS

There was no significant difference between the studied and control groups regarding demographic characteristics.

Table 1: Demographic characteristics among both groups

Variables		Study (N=150)	Control (N=150)	P
Age (years)	**Mean±SD**	28.4±2.9	28.1±2.7	^0.279
	Range	22.0–35.0	21.0–36.0	
BMI (kg/m^2)	**Mean±SD**	28.4±1.6	28.5±1.8	^0.660
	Range	25.2–32.2	25.1–32.7	
Parity (n, %)	**Primi**	53 (35.3%)	51 (34.0%)	#0.808
	Multi	97 (64.7%)	99 (66.0%)	
Previous CS (n, %)		24 (16.0%)	26 (17.3%)	#0.757

Independent t-test, #Chi square test, BMI: body mass index

There was no significant difference between the study and the control groups regarding neonatal condition (Table 2).

Table 2: Neonatal condition among both groups

Variables		Study(N=150)	Control(N=150)	P
APGAR 1	**Mean±SD**	8.2±0.6	8.1±0.6	^0.156
	Range	6.0–9.0	5.0–9.0	
APGAR 5	**Mean±SD**	8.9±0.6	8.8±0.6	^0.142
	Range	7.0–10.0	6.0–10.0	
NICU (n, %)		1 (0.7%)	2 (1.3%)	#0.624
Mortality		0 (0.0%)	0 (0.0%)	--

^Independent t-test, #Fisher's Exact test

Respiratory rate was significantly lower among the studied group than among the control group (Table 3).

Table 3: Respiratory rate (cycle/minute) among both groups

Measures	Study (N=150)	Control (N=150)	^P
Mean±SD	48.9±4.4	51.7±5.6	**<0.001***
Range	40.0–63.0	40.0–86.0	
Value of study over control			
Items	**Mean±SE**	**95% CI**	
Respiratory rate reduction	2.8±0.6	1.7–3.9	

^Independent t-test, *Significant, CI**:** confidence interval

There was no significant difference between both groups as regard tachypnea, retractions and TTN. Additionally, There was no complication to PE occurred in our current study as uterine hyperstimulation, uterine rupture or meconium staining of liquor (Table 4).

Table 4: Respiratory condition among the studied groups

Findings	Study (N=150)	Control (N=150)	#P	RR (95% CI)
Tachypnea RR>60.0	1 (0.7%)	3 (2.0%)	0.622	0.50 (0.03–3.19)
Retraction	0 (0.0%)	1 (0.7%)	1.000	--
TTN	1 (0.7%)	3 (2.0%)	0.622	0.50 (0.03–3.19)

#Fisher's Exact test, RR: Relative risk, CI**:** confidence interval

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DISCUSSION

Respiratory distress (RD) accounts for about 30% of neonatal deaths [(7)] with an onset occurring at birth or several hours after delivery [(8)].

The relative risk is inversely proportion with gestational age. TTN resulting from delayed reabsorption and clearance of alveolar fluid showed that post- delivery prostaglandin release distends lymphatic vessels, which remove lung fluid as pulmonary circulation increases with the initial fetal breath. Caesarean delivery without labor by passes this process and it was therefore a risk factor for TTN Surfactant deficiency may play a role in TTN [(6-9)].

Considering the rising rate of elective caesarean section in the last few years [(10)], TTN is estimated to be between five and six per 1,000 births [(11)].

The current study showed that the mean respiratory rate of the newborns in the misoprostol group was significantly lower than those of the control group; however, there were no significant differences between both groups as regards TTN, Apgar score (1 and 5 minutes), NICU admission, neonatal mortality, intercostal retraction or cases of respiratory rate > 60 per minute .Only one previous study addressed this issue, which was done by Singh et al[(4)]. who studied 36 women given either PGE2 or

placebo before elective C.S. between 36 and 38 weeks and their results agreed with the results of the current study.

There were no side-effects reported in the current study from the medications used.

The current study has the advantages of being the first study to use PGE1 for this purpose and recruiting large number of cases; however, the main limitation of the current study is being a single-center study.

CONCLUSION

PGE1 administration before elective C.S. performed between 38 and 39 weeks didn't improve TTN.

Further studies are needed in those with gestational age below 36 weeks.

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