Vaginal Misoprostol before Elective Caesarean Section for Preventing Neonatal Respiratory Morbidity

Original Article

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ABSTRACT

Background: Delivery by elective caesarean section at a gestational age of less than 39 weeks increases the risk of various respiratory morbidities in the newborn including respiratory distress syndrome. Prostaglandins are substances that have beneficial effects on the neonatal lungs as it promote surfactant secretion by inducing the catecholamine surge. However on clinical practice, the effectiveness of the antenatal prophylactic administration prostaglandin is still not clear.

Aim: This study aimed to evaluate the efficacy of vaginal Misoprostol before ECS in pregnant women with gestational age less than 38 weeks for preventing the occurrence of neonatal respiratory morbidity.

Materials and Methods: Study sample included 159 participants were randomly assigned into 2 groups: Group (A): misoprostol group who administered 1/2 tablet of Cytotec (R) 200 g one hour before elective caesarean section and Group (B): included women received no treatment before elective caesarean section**.**

Results: A significant decrease in respiratory rate among the Misoprostol group and decrease in neonatal respiratory morbidity especially RDS type 2, 3 and TTN, also misoprostol causes significant decrease in the rate of NICU admissions and none of the neonates required mechanical ventilation.

Conclusion: Prophylactic misoprostol before elective caesarean at a gestational age of less than 39 weeks reduces the rate of neonatal respiratory morbidity and may prevent neonatal RDS type 2 and 3.

Key Words: Elective caesarean section (ECS), prostaglandins, respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN)

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INTRODUCTION

Elective cesarean section (ECS) at a gestational age of less than 39 weeks is associated with 2-7 folds increased risk of respiratory morbidity, respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN) and persistent pulmonary hypertension of the newborn (PPHN), that is attributed to iatrogenic prematurity with surfactant deficiency[1].

The actions of antenatal corticosteroids relevant to RDS include their antiinflammatory actions and their remarkable role in the lung's maturity during gestation by producing surfactant and sodium channel functions improvement.

Administering antenatal corticosteroid to women at 34 to <37 weeks of gestation are effective at reducing the incidence of RDS[2].

However, caution should be implemented before wide-scale universal adoption of antenatal corticosteroid for pregnancies that are at risk of preterm birth at 34 to <37 weeks of gestation as it is unclear whether there are long-term effects. Concerns are present because of the presence of glucocorticoid receptors in the developing fetal brain which might thus be particularly vulnerable to antenatal corticosteroids and could lead to neurodevelopmental disorders. Thus, finding another antenatal prophylactic medication is crucial to reduce RDS among neonates delivered by ECS[3].

Prostaglandins are substances that have been successfully used for labor induction in the pregnant females and the E series being preferred over others due to the fact that they are more uteroselective. It was found that prostaglandin has beneficial effects on the neonatal lungs as it causes the reabsorption of lung fluid from the fetal lung and promotes surfactant secretion by inducing the catecholamine surge[4]. However on clinical practice, the effectiveness of the antenatal prophylactic administration prostaglandin on reducing the neonatal respiratory morbidity is still not clear.

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AIM OF THE STUDY

The aim of our study is to evaluate the efficacy of vaginal Misoprostol before elective cesarean section (ECS) in pregnant women with gestational age less than 38 weeks for preventing the occurrence of neonatal respiratory morbidity. In our study, the Misoprostol group received vaginal Misoprostol (1/2 tablet of Cytotec (R) 200 µg (manufactured by: Pfizer)) one hour before ECS while the control group received no treatment. All participants received Dexamethasone before the ECS.

PATIENTS AND METHODS

Study design: Randomized single blinded trial study (parallel group study with 1:1 randomization) conducted at gynecology department Al Shorouk General Hospital. Study approval: Before starting the study and in accordance with the local regulation followed, the protocol and all corresponding documents was declared for Ethical and Research approval by the ethical committee of OB/Gyn department, Al Azhar University for girls.

Study participants: A computer randomization table generated and held with second author (N.A), and 159 participants recruited subsequently from in-patient obstetric ward of the hospital at morning and scheduled for elective CS, they randomly assigned to intervention or non-intervention which sent by first author. Sample size calculation: Sample size calculated by G power 3.0.10 software according to the following formula: t-tests. Means: Difference between two independent means (two groups) Analysis: Input: Tail(s) = two ,effect size d = 0.5,α err prob = 0.05, Actual power = 0.90. Power (1-β err prob) = 0.9 Allocation ratio N2/N1 = 1 .Sample size group 1 = 70 Sample size group 2 = 70 Total sample size = 140 Actual power = 0.902966 . we consider 5% dropout, so we added 19 participants to the sample.

Participants at the morning of the operation given information about the study aims and informed verbal consent taken.

Inclusion criteria: women aged 18 years or older, women with an uncomplicated pregnancy 36 -38ws weeks gestation, Women carrying a singleton fetus with no major anomalies., Gestational age confirmed with certain LMP or reliable early ultrasound measurement of crown-rump length.

Exclusion criteria: women with any medical disorders, fetal distress or demise, Women scheduled for emergency CS, women with any contraindication or sensitivity to prostaglandins.

Intervention: At the time of recruitment, all participants subjected to complete history taking, general and abdominal examination including number of previous miscarriages, number of previous CS, indication of current ECS and gestational age at delivery. All women received two intramuscular doses of 12 mg dexamethasone 12 hours apart, 48 hours before the scheduled time of ECS and two gram cephalosporin before induction of anaesthesia.

Eligible participants randomly assigned into two groups. Study sample including (159) participants where assignment into 2 groups, we consider 5% dropout, so we added 19 participants to the sample; group A misoprostol group (1/2 tab of cytotec 200 mg by Pfizer pharmaceutical) who received vaginal misoprostol 100 mcg one hour before ECS and group B including women didn't received misoprostol before ECS.

Continuous cardiotocographic monitoring carried out after misoprostol insertion to detect any evidence of uterine hyperstimulation and/or fetal distress.

The surgical and anesthetic team was stand by in a state of complete readiness for the CS from the time of misoprostol administration. The anesthetic and surgical techniques was standardized for all women. Spinal anesthesia used for all participants with preload of 500 ml saline and continuation of intravenous fluids throughout the operation. Regarding the surgical technique, all deliveries performed through a transverse lower uterine segment CS with delayed cord clamping (30 seconds after delivery). The same surgical team performed all the operations. All deliveries attended by a neonatology specialist, and details of the resuscitation at the operative theatre recorded in their files.

Study outcome: primary outcomes included rate of neonatal RD defined as RR>60 cycles per minute and/or signs of RD. Secondary outcomes included Apgar scores at 5 minutes. The respiratory rate of the newborn, the incidence of apnea, the incidence of TTN, the need for mechanical ventilation of the neonate either by ambu-bag resuscitator or endotracheal intubation . the incidence of admission to NICU, the duration of NICU stay and the neonatal mortality rate. Maternal haemoglobin level before CS as secondary outcome.

STATISTICAL ANALYSIS

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean and standard deviation. Significance of the obtained results was judged at the 5% level. The used tests were Chi-square test for categorical variables, to compare between different groups, Student t-test for normally quantitative variables, to compare between two studied groups and Mann Whitney test for abnormally quantitative variables, to compare between two studied groups.

RESULTS

Table 1: Demographic data of studied groups

	Group (A) (n=77)		Group (B) (n=82)		U	*P Value*
Age						
Min.-Max.	19-45		18-42		3077.50	0.893
Mean± S.D	30.54±5.608		30.46±6.559			
Weight						
Min.-Max.	60-102		57-167		t=0.173	0.863
Mean± S.D	79.84±10.521		80.20±14.611			
Height						
Min.-Max.	150-180		152-178		U=2515.00	0.266
Mean± S.D	162.71±6.452		161.74±6.652			
BMI						
Min.-Max.	24.03-36.89		20.44-67.75		t=1.033	0.303
Mean± S.D	30.03±2.976		30.78±5.427			
Gravidity						
≤2	26	33.8	36	43.9	X^2= 1.715	0.198
>2	51	66.2	46	56.1		
Parity						
≤2	56	75.7	59	76.6	X^2=0.019	1.000
>2	18	24.3	18	23.4		
Gestational age	Group (A) (n=77)		Group (B) (n=82)		U	P Value
Min.-Max.	37-38		37-38		2757.00	0.304
Mean± S.D	37.74±0.472		37.82±0.419			

*: Statistically significant at *P <0.05*

Table 2: Clinical history of studied groups

	Group (A) (n=77)		Group (B) (n=82)		Test of Sig.	*P Value*
	No.	%	No.	%		
Mode of Previous Deliveries						
No	3	3.9	5	6.1		
CS	71	92.2	75	91.5	X^2=0.653	0.721
CS and NVD	3	3.9	2	2.4		
Indication of CS						
Previous CS	74	96.1	77	93.9	X^2=2.952	0.556
Others	3	3.9	5	6.1		
History of medical illness						
No	71	92.2	75	91.5	X^2=0.029	1.000
Yes	6	7.8	7	8.5		
Surgical History						
No	69	89.6	67	81.7	X^2=2.005	0.181
Yes	8	10.4	15	18.3		
Bad Obstetric History					X^2=	
No	77	100	80	97.6	X^2=1.902	0.497
Yes	0	0	2	2.4		

*: Statistically significant at *P <0.05*

Table 3: CTG , maternal vital signs and maternal HB of studied groups

CTG finding	Group (A) (n=77)		Group (B) (n=82)		X^2	*P Value*
	No.	%	No.	%		
Not done	0	0	7	8.5		
Reactive	72	93.5	74	90.2	9.546	0.008*
Non-reactive or pathological	5	6.5	1	1.2		
Total	77	100	82	100		
Maternal pulse						
Min.-Max.	65-98		65-92		3142.50	0.960
Mean± S.D	81.04±6.822		81.02±6.668			
SBP						
Min.-Max.	100-140		100-140		3135.00	0.938
Mean± S.D	115.26±12.000		115.00±10.657			
DBP						
Min.-Max.	60-90		60-90			
Mean± S.D	73.26±7.293		72.32±7.420			
HB	Group (A) (n=77)		Group (B) (n=82)			
Before						
Min.-Max.	9.50-12.00		9.00-12.10		2934.50	0.419
Mean± S.D	10.79±0.811		10.87±0.851			
After						
Min.-Max.	9.00-11.90		8.60-11.80			
Mean± S.D	10.45±0.826		10.50±0.857			
P value						
HB deficit	0.34		0.37			

*: Statistically significant at *P <0.05*

Table 4: Neonatal outcome in studied groups

Birth Weight	Group (A) (n=77)	Group (B) (n=82)	U	*P Value*
Min.-Max.	2.50-4.20	2.50-4.00	2951.50	0.476
Mean± S.D	3.08±0.316	3.04±0.327		
APGAR Score (5 min)				
Min.-Max.	6-9	5-9	1936.50	<0.001*
Mean± S.D	8.26±0.880	7.38±1.311		
Neonatal RR	Group (A) (n=77)	Group (B) (n=82)	U	*P Value*
Min.-Max.	38-80	40-90	1784.50	<0.001*
Mean± S.D	54.91±9.751	63.60±11.661		

*: Statistically significant at *P <0.05*

Table 5: Neonatal respiratory morbidity NICU, the need for mechanical ventilation and morbidity among studied groups

Neonatal Respiratory morbidity	Group (A) (n=77)		Group (B) (n=82)		X^2	*P Value*
	No.	%	No.	%		
No	61	79.2	35	42.7		
Yes	16	20.8	47	57.3		
RD2	1	1.3	9	11.0	22.160	<0.001*
RD3	0	0	6	7.3		
TTN	15	19.5	32	39.0		
NICU Admission	Group (A) (n=77)		Group (B) (n=82)		X^2	*P Value*
	No.	%	No.	%		
No	69	89.6	56	68.3	10.735	0.002*
Yes	8	10.4	26	31.7		
Need for Mechanical Ventilation	Group (A) (n=77)		Group (B) (n=82)		X^2	*P Value*
	No.	%	No.	%		
No	77	100	74	90.2	7.910	0.007*
Yes	0	0	8	9.8		
Fetal Mortality	Group (A) (n=77)		Group (B) (n=82)		X^2	*P Value*
	No.	%	No.	%		
No	77	100	80	97.6	1.902	0.497
Yes	0	0	2	2.4		

*: Statistically significant at *P <0.05*

This table 5 showed increase in the number of neonatal respiratory morbidity NICU and the need for mechanical ventilation among the non-intervention group but no statistically significant differences as regards neonatal mortality due to respiratory morbidity

DISCUSSION

Delivery by elective caesarean section at a gestational age of less than 39 weeks increases the risk of various respiratory morbidities in the newborn including respiratory distress syndrome. Prostaglandins are substances that have beneficial effects on the neonatal lungs as it promote surfactant secretion by inducing the catecholamine surge. In the present study, we demonstrated that administration of Cytotec(R) 100 µg vaginally 60 minutes before ECS at 34 to 37 weeks' gestation significantly decreases the overall neonatal respiratory morbidity rate and severity.

Misoprostol administration one hour before ECS in our study causes significant decrease in neonatal respiratory morbidity especially RDS type 2, 3 and TTN, also it causes significant decrease in the rate of NICU admissions and none of the neonates required mechanical ventilation. Consequently this positively reflected on neonatal mortality rate.

In accordance with our findings, a previous study by Makhlouf *et al*.[4] indicated that patients administered Misoprostol in the form of Mesotac® 50 hour before ECS showed statistically significant decrease in neonatal apnea, respiratory distress, TTN and the need for intubation in comparison with the control group, such results are in accordance with our findings.

Contrarily, a cochrane review study by Motaze *et al*.[5] indicated no significant difference in the respiratory outcomes after delivering Misoprostol; however, such controversies could be resulted from low quality of evidence caused by the small study sample of such studies and different Misoprostol dose. Additionally, Rabea *et al*.[6] indicated that patients administered Misoprostol in the form of Cytotec® 200 one hour before ECS showed no statistically significant differences in neonatal respiratory morbidity including tachypnea and TTN in comparison with the placebo group.

In the present study, Misoprostol administration one hour before ECS causes a significant increase in abnormal (non-reactive) CTG in comparison with the control group. CTG records changes in the fetal heart rate and their temporal relationship to uterine contraction. The increased incidence of abnormal CTG among the Misoprostol group that considered as side effects of Misoprostol as it causes some increased uterine muscle tone, it leads to transient fetal hypoxia, initiates catecholamine surge that relief the neonatal respiratory distress and decreases the neonatal respiratory morbidity.

In accordance with our findings, a previous study by Pevzner *et al*.[7] that studied the incidence of CTG abnormalities associated with misoprostol vaginal inserts during labor induction indicated that 17.3% of patients administered Misoprostol 100 mcg and 6.8% of patients administered Misoprostol 50 mcg showed abnormal CTG and uterine contractile abnormality including hyperstimulation, hypertonus and/or tachysystole.

Additionally, a recent study by Mlodawski *et al*.[8] indicated that the use of misoprostol vaginal insert 200 µg that release prostaglandins at a constant rate for 24 h in patients with an unriped cervix is associated with increased chance of abnormal neonatal intrapartum CTG trace.

There was a significant improvement of 5 min APGAR score among the Misoprostol group in comparison with the control group. ECS is usually associated with higher incidence of respiratory depression at birth and consequently low Apgar scores, administering Misoprostol one hour before ESC causes a significant improvement of APGAR and as it improves neonatal respiratory status.

In accordance with our findings, a previous study by Khairy *et al.*[9] that used Cytotec® vaginal tablet containing 200 mcg Misoprostol administered 60 minutes before scheduled caesarean section and indicated a highly statistical significant increase of APGAR-5 among the Misoprostol group in comparison with the control group.

In contrary with our finding, Rabea *et al*.[6] indicated no statistically significant difference between the Misoprostol group and the control group regarding APGAR-5 in comparison with the control group (8.9 ± 0.6 and 8.8 ± 0.6, respectively).

Misopostol can be used as prophylaxis of post-partum hemorrhage. Misoprostol administration one hour before ECS caused diminished HB loss but it was not significantly different in comparison with the control group. That could be attributed to the fact that we used very low dose low dose of Misoprostol (Cytotic (R) 100 mcg) that could exert a minimal effect as a prophylactic drug in preventing post-partum hemorrhage. As according to the WHO (2018)[10] recommendations, the therapeutic or preventive doses for post-partum haemorrhage are usually administered as 3 tablets (600mcg) or 4 tablets (800 mcg).

In the present study, we demonstrated that administration of Cytotec (R) 100 µg vaginally 60 minutes before ECS did not effect on the maternal vital signs in comparison with the control group.

In accordance with our finding, a previous study by Chanrachakul *et al*.[11] indicated that women who administered a 200 µg Cytotec (R) vaginally for labour induction did not show any changes in the maternal vital signs.

Regarding the implications for clinical practice, our study indicates the beneficial effects of the use of vaginal

Misoprostol (Cytotic(R) 100 mcg) one hour before scheduled ECS among pregnant women at their 34-38 weeks gestational age on improving the neonatal respiratory state.

The strengths of our study originated from its randomization and blinding of neonatologist that handle the newborn in addition it included a quiet large sample size.

The main limitation measuring the cord blood pH or catecholamine concentration studied in previous studies looks valuable outcomes but still it is considered as non-patient centered.

CONCLUSION

Prophylactic vaginal misoprostol before ECS at a gestational age of less than 39 weeks reduces the rate of neonatal respiratory morbidity and could be an efficient way to prevent neonatal RDS type 2 and 3 and TTN.

RECOMMENDATION

Misoprostol 100 µg can be administered vaginally to candidate pregnant women at a gestational age of less than 38 weeks before an ECS (after exclusion of any contraindication and thorough good history taking and clinical examination) in order to reduce the neonatal respiratory morbidity. Thus, decrease the duration of neonatal NICU admission and mortality.

Larger scale studies are recommended to compare the effect of Misoprostol on different gestational ages in order to show the most beneficial time for misoprostol administration.

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