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Role of Misoprostol (PGE 1) before Elective Caesarean Section in Decreasing Transient Tachypnea of the Newborn (TTN)

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Abstract

Background: Newborn respiratory distress occurs in about 7% of deliveries. The most common etiology of respiratory distress in newborns is TTN, which occurs in about five or six per 1,000 births.

Aim of Study: To evaluate the effect of Misoprostol (Prostaglandin E_1) when given to women undergoing caesarean section on decreasing the incidence of the neonatal respiratory distress assessed by neonatal catecholamines.

Patients and Methods: This study 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). We take 300 cases randomly distributed into two groups: The first group (group I) was included 150 women, were given Misoprostol (prostaglandin E_1), and the second one (group II) was consisted of 150 women, were given placebo.

Results: There was no significant difference between the study and the control groups regarding neonatal condition. Respiratory rate was significantly lower among study group than among control group. There was no significant difference between both groups as regard tachypnea, retractions and TTN. There was no complication to PE occurred in our current study as uterine hyperstimulation, uterine rupture or meconuim staining of liquor.

Conclusion: Administration of PG1 should be not more than one hour before delivery and under complete medical observation cover. We suggest involving only elective cases between 28 weeks to less than 39 weeks, any case with medical disorders or risk should be excluded.

Key Words: *Caesarean section – Misoprostol (PGE_1) – TTN.*

Introduction

CESAREAN delivery is the most common major surgical procedure performed on women worldwide and its rates continue to rise steadily in both developed and developing countries **[1]**.

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Neonatal respiratory distress occurs more in preterm newborn than term newborn, and whether born vaginally or through caesarean section, but in a higher percentage after elective caesarean than after normal vaginal delivery or emergency caesarean section **[2,3]**.

It is responsible for 30% of neonatal deaths **[4]** It has several subdivisions: One is the respiratory distress syndrome (RDS) which is called hyaline membrane disease, it can occur in about 1% of pregnancies as a result of a pathology in lung surfactant either qualitative or quantitative, and usually in preterm neonates **[5]**.

Another is transient tachypnea of the newborn (TTN) in which there is respiratory distress and increased respiratory rate due to delayed resorption of pulmonary fluid, as a result of defective catecholamine surge it occurs in about 11% of live births **[5,7]**.

In infants suffering from respiratory distress syndrome, adrenaline (epinephrine) and noradrenaline (norepinephrine) concentrations have been found to correlate with measures of illness severity. Extreme baseline catecholamine concentrations and a reduced noradrenaline response to opiate sedation are associated with subsequent mortality **[8]**.

Catecholamines can stimulate pulmonary fluid reabsorption through acting upon beta-adrenergic receptors in foetal lung which present more late in gestation, and thus enable the secretion of surfactant **[5]**.

This surge of catecholamines can be provoked through prostaglandins given before caesarean section to pregnant females, **[9]** as those who are born vaginally are found to be adapted metabolically through a higher catecholamine level at birth **[10]**.

So, prostaglandins may be given about one hour before an elective caesarean section after excluding the presence of contraindication to their use to decrease the neonatal respiratory diseases and thus, the number of children who suffered from bronchopulmonary dysplasia that occurs frequently in children who had previously TTN will diminish [5]. The prostaglandins in common use are misoprostol (prostaglandin E 1) and dinoprostone (prostaglandin E 2).

The aim of the current work was to evaluate the effect of Misoprostol (Prostaglandin E 1) when given to women undergoing caesarean section on decreasing the incidence of the neonatal respiratory distress assessed by neonatal catecholamines.

Patients and Methods

This study 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), conducted at El Hussein Hospital Al-Azhar University and Police Hospital starting from November 2019 to October 2021.

The population in this study consists of a sample of pregnant women between (38-<39) weeks gestation scheduled for elective caesarean section, selected according to inclusion and exclusion criteria, we take 300 cases randomly distributed into two groups: The first group (group I) was included 150 women, were given Misoprostol (prostaglandin E1), and The second one (group II) was consisted of 150 women, were given placebo.

Inclusion criteria: Age: 18 years or more, term pregnancy (38-<39 weeks), and Pregnant women planned for elective transverse lower segment caesarean section with an indication whether primigravida or previous section.

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 Glucoma 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, and pregnancies with known foetal malformation/s or chromosomal aberration.

Intervention:

Subjects:

The population in this study consists of a sample of full term pregnant women scheduled for elective caesarean section, selected according to inclusion and exclusion criteria, we take 300 cases randomly distributed into two groups: The first group (group I) was included 150 women, were given Misoprostol (prostaglandin E 1), and The second one (group II) was consisted of 150 women, were given placebo.

Misoprostol (Prostaglandin E 1) containing vaginal tablet in the form of Cytotec ® 200 microgram Misoprostol (manufactured by: Pfizer) administered about 60 minutes before scheduled caesarean section.

Placebo was given in the form of non Prostaglandin E1medicated vaginl tab. containing only the inactive ingredients (Hydrogenated castor oil, Microcrystalline cellulose, Crospovidone).

The participants were approached around the 36th week of gestation, to be given a handout explanation of the study details (information sheet) from the trained participating personnel and then written informed consents signed if agreed upon to be documented.

The treatment was brought by main investigator (not involved in selection of patients or their admission to the trial) and stored in independent premises in a refrigerator at a temperature of 2-8 degree centigrade on Celsius scale away from the usual medicine stored by authorized people, transported and given under supervision and another investigator who was indulged in the management of patients in study, had a receipt of all given study medications.

Detailed history taking and thorough clinical examination:

In the first visit planned, all women undergo full clinical examination after obtaining complete medical history from them. Each get a case record form (CRF1) and an interventional record (CRF2).

In the CRF1 the following data are recorded:

- Patient initials.
- Patient number according to the schedule of randomization.
- Age, height, weight, body mass index (BMI).
- Medical and surgical data, and any concomitant illness.

- Parity, gravidity, gestational age, and indication for caesarean section.
- Previous caesarean section.
- Drugs taken in the last month even if discontinued.
- Medications that won't be discontinued.
- Known allergies or any previous hypersensitivity reaction.
- Clinical examination including general examination, with pulse and blood pressure recording, and local obstetric examination including the Bishop score and cervical dilatation.
- Time from administration of the pessary to delivery of the foetus.
- Type of anaesthesia was used.

The Interventional record (case record form 2):

After preparing for elective caesarean section, vital signs assessed, the pessary given whether containing the misoprostol medication or placebo according to randomization, 1 hour or more later (and timing is recorded), women in the operating room, and the anaesthetic and surgical techniques were standardized. Regarding the anaethesia, the preload of 500ml crystalloids before spinal anathesia and continuation of the IV fluid and blood loss replacement. Regarding the surgical procedure, it had done according to the standard at Alazhar University including delayed cord clamping, the caesarian section and suturing continued as standard and managed as appropriate to the surgeon with continuous monitoring of vital signs and documentation of any abnormality. The study reports the neonatal outcome regarding the neonatal catecholamines of the newborn, respiratory distress, admission to the neonatal ICU, the length of stay in, the need for mechanical ventilation, any adverse event or mortality.

Statistical analysis:

All analysis was according to the principle of the intention-to-treat. Data was gathered, tabulated, coded by excel 2007 (Microsoft, Redmond, WA, USA). Then, data was analysed using SPSS version 19.0 computer software. Examination of the numerical values for normality, their expression as mean ± standard deviation, or median with interquartile range when appropriate was done after. On the other side, categorical variables was expressed as percentages. Between the groups, the continuous variables was compared using Student's (*t*) test, the categorical variables by Chi-square test or Fischer's exact test. When variables are not normally distributed, Whitney U test was used. All through, we are using the 5% level of significance.

Results

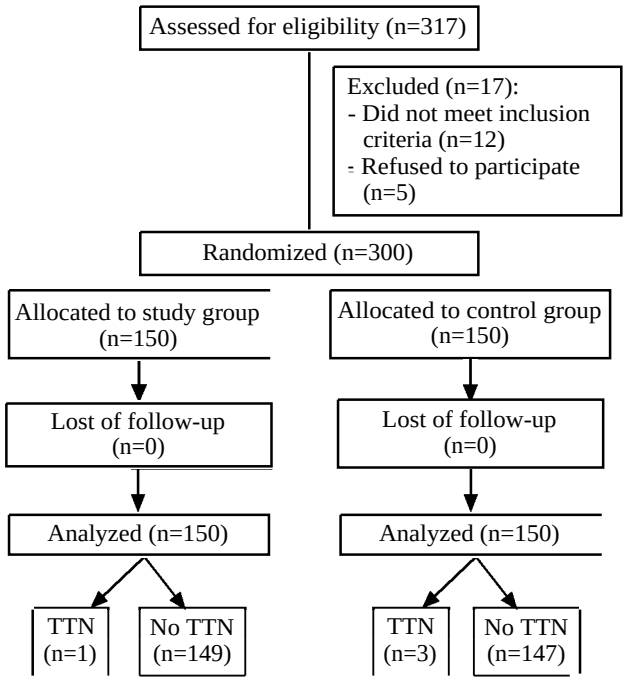

Fig. (1): Flow chart for the study.

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.

There was no significant difference between study and control groups regarding demographic characteristics (Table 1).

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.

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

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.

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

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.

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

Discussion

Agreement with researcher:

Decades ago, it was suggested that poor respiratory outcomes in infants delivered by elective CS may be explained by delayed absorption of liquid in the lung due to lack of a catecholamine surge [7]. Studies in animals during spontaneous or oxytocin-induced labour show an association between an increase in plasma epinephrine and reduced production and increased absorption of lung liquid. It is known that prostaglandin E 2 stimulates production of surfactant in fetal lungs as term approaches [11]. Furthermore, the concentration of beta-adrenergic receptors in lung tissue is known to increase late in gestation, which might render the lungs more responsive to the effects of epinephrine [6]. Catecholamines thus promote surfactant secretion, [5] and stimulate reabsorption of lung fluid from the fetal lung [6]. This catecholamine surge can be stimulated by administering prostaglandins to the pregnant woman before delivery [9].

Disagreement with researcher:

There is no previous similar studies done in this trial except one done using PE 2 by Motaze et al., [12] there were 36 women in the one included study, 18 received intravaginal prostaglandin E 2 gel and 18 received placebo. One neonate in the control group developed respiratory distress, reported as transient tachypnoea of the newborn by the authors. None of the neonates required mechanical ventilation and the Apgar scores at one and five minutes where similar in both groups. Although no admissions to neonatal intensive care occurred, two neonates in the control group were admitted into special care. No further information was provided on the reasons for these admissions.

Outcomes indicating respiratory status did not differ significantly between intervention and control groups and there was no treatment-related side effects. Noradrenaline concentrations were significantly higher in the cord blood samples of the intervention group.

Full discussion:

Respiratory distress (RD) can occur in all newborns irrespective of gestational age or mode of delivery. It accounts for about 30% of neonatal deaths, [9] and can occur at birth or several hours after delivery [4,5]. Infants born by elective caesarean section (CS) delivery at term are at increased risk for developing respiratory disorders, compared with babies delivered per vagina [2] or by emergency CS, [3] the relative risk increasing with decreasing gestational age. The prevalence of deliveries by CS has been steadily increasing worldwide over the last few years [13].

A significant reduction in respiratory morbidity can be achieved if elective cesarean section is performed after 39 weeks of gestation [14].

TTN, which occurs in about five or six per 1,000 births [15] Newborns with TTN have a greater risk of developing asthma in childhood; in one study, this association was stronger in patients of lower socioeconomic status, nonwhite race, and males whose mothers did not have asthma [16]. TTN results from delayed reabsorption and clearance of alveolar fluid. Post-delivery prostaglandin release distends lymphatic vessels, which removes lung fluid as pulmonary circulation increases with the initial fetal breath. Cesarean delivery without labor bypasses this process and is therefore a risk

factor for TTN [17]. Surfactant deficiency may play a role in TTN.

Prostaglandins of the E series are preferred over the F series because they are more uteroselective [18]. The most widely used prostaglandins are misoprostol (prostaglandin E_1) and dinoprostone (prostaglandin E_2), which are available as oral tablets, vaginal tablets, pessaries or vaginal gels. For the purposes of cervical ripening and labor induction, prostaglandin E_2 starts acting in 10 minutes and results can be observed within 12 hours [19]. Prostaglandins can stimulate surfactant secretion and reduce lung fluid by provoking a catecholamine surge but it is unclear how early they have to be administered before CS in order to produce this effect. A randomized controlled trial found an increase in catecholamine levels in fetal blood in the intervention group compared with the placebo group, when prostaglandin E_2 was administered as intravaginal gel 60 minutes before CS [9]. Prostaglandins are not used in routine medical practice for the sole purpose of improving fetal respiratory outcomes. However, studies in animals have shown that when administered before CS, they accelerate fetal lung maturation and improve respiratory function after delivery [2].

A study evaluating metabolic adaptation in the newborn revealed that infants delivered per vagina showed high catecholamine levels at birth compared with infants born by CS under epidural or general anesthesia [20]. Prostaglandins can stimulate surfactant secretion and reduce lung fluid by provoking a catecholamine surge, [9] and therefore significantly reducing neonatal respiratory morbidity following a CS. This could eventually reduce long-term complications such as bronchopulmonary dysplasia,6 which results from prolonged ventilation in severe RDS and asthma, which develops more frequently in children aged zero to four years with a history of TTN [5]. It is important to collect and summarise evidence of the use of prostaglandins for improving fetal respiratory outcomes.

In this study a randomized placebo-controlled study that was carried out in Al-Azhar University Hospitals (Al-Husein), and Police Hospital. There were 300 participants, 150 in the intervention and 150 in the control group. Participants were pregnant women at term with an indication for elective caesarean section (ECS). Excluded from the study were: pregnancies with known fetal malformation/s or chromosomal aberration, presence of absolute contraindications for use of prostaglandin E_1 vaginal tablets, for example, history of adverse reactions to prostaglandin preparations, C.S before 38 weeks' gestation and failure to obtain informed consent. The study compared 2mg of prostaglandin E1 tablets with placebo (K-Y jelly) when administered as intravaginal tablets 60 minutes prior to ECS. The aim of the study was to asses the reduction of TTN in the prostaglandin E_1 group than the placebo group. Other outcomes assessed included Apgar score at one and five minutes, neonatal respiratory distress, admission into a neonatal special care, arterial and venous pH measurements.

The study authors used non-parametric tests (Mann-Whitney-Wilcoxon test and Fisher's exact test) to compare both groups. *p*-values were reported we found 3 positive cases in control group VS 1 positive case in study group and it looks like insignificant results actually its recommended to take a much bigger sample next trial.

In our study Respiratory condition was non-significantly better among study group than among control group. But respiratory rate was significantly lower among study group than among control group.

Conclusion:

The study included in this trial involved only PE 1 vaginal tab and had a small sample size, the results was in significant. Therefore furthermore studies with more large number should be done.

Administration of PG1 should be not more than one hour before delivery and under complete medical observation cover.

We suggest involving only elective cases between 28 weeks to less than 39 weeks, any case with medical disorders or risk should be excluded.

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(الروستجلاندين E_1) قبل إجراء عملية قيصرية اختيارية ودورها فى خفض نسبة حدوث تسرع التنفس المؤقت عند الأطفال حديثى الولادة

خلفية الدراسة : تحدث الضائقة التنفسية لدى الوليد فى حوالى ٧٪ من الولادات. المسببات الأكثر شيوعاً لضائقة الجهاز التنفسى عند الأطفال حديثى الولادة هو تسرع النفس العابر عند الوليد، والذى يحدث فى حوالى خمسة أو ستة من كل ١٠٠٠ ولادة.

الهدف من الدراسة : تقييم تأثير الميزوبروستول (بروستاغلاندين E_1) عند إعطائه للنساء اللواتى يخضعن لعملية قيصرية على إنقاص وقوع الضائقة التنفسية الوليدية التى تم تقييمها بواسطة الكاتيكولامينات الوليدية.

المرضى وطرق الدراسة : هذه الدراسة عبارة عن تجربة موازية عشوائية مضبوطة وهمى تقارن استخدام الميزوبروستول (بروستاغلاندين E_1) على شكل أقراص مهبلية ميسوبروستول E_1 مع قرص مهبلى مماثل غير علاجى (الدواء الوهمى) لتقليل الضائقة التنفسية للولدان خاصة (تسرع النفس العابر لحديثى الولادة). أخذنا ٣٠٠ حالة موزعة بشكل عشوائى على مجموعتين: المجموعة الأولى (المجموعة الأولى) ضمت ١٥٠ امرأة، أعطيت الميزوبروستول (البروستاغلاندين E_1)، والثانية المجموعة الثانية كانت تتكون من ١٥٠ امرأة، أعطيت العلاج الوهمى.

نتائج الدراسة : لم يكن هناك فرق معتد به بين الدراسة ومجموعات الضبط فيما يتعلق بحالة الولدان. كان معدل التنفس أقل بشكل ملحوظ بين مجموعة الدراسة منه بين مجموعة التحكم. لم يكن هناك فرق كبير بين المجموعتين فيما يتعلق بتسرع التنفس، والتراجع، وتسرع النفس العابر لحديثى الولادة. ليم تكن هناك أى مضاعفات لـ PE حدثت في دراستنا الحالية مثل فرط تحفيز الرحم أو تمزق الرحم أو تلطيخ العقى للخمور.

الاستنتاج : لا ينبغى أن يكون إعطاء البروستاغلاندين E_1 أكثر من ساعة واحدة قبل الولادة وتحت غطاء كا مل للمراقبة الطبية. نقترح تضمين الحالات الاختيارية فقط بين ٢٨ أسبوعاً إلى أقل من ٣٩ أسبوعاً، وينبغى استبعاد أى حالة بها اضطرابات طبية أو مخاطر.