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The Efficacy of Intrauterine Misoprostol during Cesarean section Plus intravenous Oxytocin In Prevention Of primary postpartum Hemorrhage (PPH)

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ABSTRACT

Background:The misoprostol tablet is very soluble and can be dissolved in 20 minutes when it is put under the tongue a pharmacokinetic study compared the absorption kinetics of oral, vaginal and sublingual routes of administration of misoprostol found that sublingual misoprostol has the shortest time to peak concentration, the highest peak concentration and the greatest bioavailability when compared to other routes.The aim of the present study was to to improve the management primary postpartum hemorrhage during and after elective cesarean section (CS). Patients and methods:This study was carried out on 46 cases admitted for elective CS at University Hospital. They divided into two groups regarding the protocol of treatment, was given oxytocin, 10 IU in 250 ml of Normal saline solution over 10 minutes was administered directly after opening the uterus.Misoprostol group was given 400 mcg misoprostol plus intra venous Oxytocin administered directly after opening the uterus. Results: There was statistical significantly between the two studied groups in hemoglobin and HCT postoperatively with higher level among intra venous oxytocin plus intra uterine misoprostol than intra venous oxytocin only group. But regarding preoperative hemoglobin and HCT, there was no statistically significant difference before and after treatment. Higher blood loss either intraoperative, postoperative and overall blood loss on intra venous oxytocin only group than intra venous oxytocin plus intra uterine misoprostol.There was statistical significantly decrease in both hemoglobin and HCT postoperatively in the two studied groups but this decrease was more among intra venous oxytocin only group than intra venous oxytocin plus intra uterine misoprostol. Conclusion:Intrauterine misoprostol combined with oxytocin infusion during caesarean section can minimise intraoperative blood loss, avoid postpartum haemorrhage, and reduce any additional uterotonic medication requirements.

Keywords:Cesarean section; Oxytocin; postpartum Hemorrhage

INTRODUCTION

Prevention of PPH in this group is important to safe maternal life. Oxytocin has been routinely used to prevent uterine atony and excessive uterine bleeding during CS. However, despite its effectiveness, 10-40% of cases need additional uterotonics to ensure good uterine contraction **(1,2).**

Misoprostol is a prostaglandin E1 analogue with good uterotonic properties and few adverse effects at therapeutic dose. It can be used oral, sublingual, buccal, rectal

and intrauterine. Besides, it can be used for termination of pregnancy in cases of missed or incomplete miscarriage **(3,4).**

In situations of preserved placenta, it can also have a role to play in the treatment of associated bleeding, which is often due to atony. In the field of gynaecology, misoprostol may be used for induction of cervical maturation prior to office gynaecological procedures. This could reduce the related pain caused by the transcervical passage of instruments **(5)**.

Therefore, the aim of this work is to improve the management primary postpartum hemorrhage during and after elective CS.

PATIENTS AND METHODS

The present study was prospective study in that 46 pregnant females were recruited for this study scheduled for elective cesarean section in the period from October 2019 to April 2020 that carried out in Obstetrics & Gynecology department of Zagazig University Hospital.

Inclusion criteria

Patients included in the study those:

1-Un-complicated pregnancy, gestational age of 37-40 completed weeks.

2- Had no hypersensitivity or contraindications to prostaglandins.

3- Had no history of coagulopathy. 4- Accepting to participate in the study.

The reasons for exclusion:

Women with anemia and placental abnormality (e.g placenta previa, placenta abruption).History of complications at previous pregnancy especially PPH. Maternal hypertension, current or previous history of heart disease, liver and renal disorders.

Operative design:

Eligible participants were randomly allocated into two equal groups.**Group A:** (23 patients): patients who receive intravenous infusion of 10 I.U oxytocin (Syntocinon 10 IU/1ml ampoule- Sandoz pharmaceutical-NDC 0078-0060-) diluted to 250ml of normal saline for 30 minute after delivery of the neonate.**Group B:** (23 patients): patients who received 400 µg misoprostol intrauterine plus oxytocinintravenousjust after cord clamping and delivery of the placenta (2 cytotec tablets each 200 µg –Pfizer-NDC 0025-1461).

The selected cases were subjected to full history taking Blood pressure measurement, examination, preoperative workup including: preoperative hemoglobin and hematocrit level within 24 hours before operation and coagulation profile to exclude any coagulopathy.

During Operation:

In the Oxytocin group:10 IU in 250 ml of Normal saline solution over 10 minutes was administered directly before opening the uterus.Maximum fluids were 500-1000 ml of isotonic solution

In the Misoprostol plus oxytocin intravenous group: 400 mcg misoprostol was administered directly in opening the uterus. Maximum fluids were 500-1000 ml of

isotonic solution.Postoperative:Postoperative crystalloids: 500 ml of Normal Saline, 500 ml of 5%Glucose and 500 ml of Ringer's Lactate solution.Recording of vital signs observing the am unt of bleeding.Uterine massage to ensure uterine contractility.

Estimating of blood loss:

Blood loss was estimated by preoperative hemoglobin level within 24 hours and 12 hours postoperative hemoglobin level was measured.The mathematical calculation in which the lost blood intraoperative was estimated by measuring the hematocrit level immediately after hospital admission and one hour postoperative in recovery room.

The blood loss was calculated according to the following formula:

$$\text{Actual Blood Loss} = \frac{[\text{Blood Volume X (Hct1-Hct2)}]}{\text{Hct1}}$$

Where: Blood volume = Body weight X 70 ml/Kg. Hct 1 is the initial pre-operative hematocrit.Hct 2 is the 1-hour post-operative hematocrit.

The uterine tone and size were assessed postoperatively, by using a hand resting on the fundus and palpating the anterior wall of the uterus.

The side effects of each drug as nausea, vomiting, shivering, pyrexia and headache or others were noted. The main outcome measures for each case in each group were registered in the patient input form.

Study outcomes:

Primary outcome measures was assessment of amount of intraoperative and postoperative blood loss. Secondary outcomes measures were the differences between pre and postoperative (24 h after CS) hemoglobin concentration and hematocrit values, the need for additional uterotonic drugs and incidence of side effects.

Statistical analysis:

Data analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0). According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD. Differences between quantitative independent multiple by ANOVA or Kruskal Wallis, P value was set at <0.05 for significant results &<0.001 for high significant result.

RESULTS

There was no statistically significant difference between the two studied groupsin age, BMI, gravidity, parity and gestational age**(Table 1)**. There was no statistically significant difference between the two studied groupsregarding indications of cesarean section**(Table 2)**.

There was statistically significant difference between the two studied groups regarding blood loss with higher blood loss either intraoperative, postoperative and overall blood loss on intra venous oxytocin only group than intra venous oxytocin

plus intra uterine misoprostol. There was statistical significantly between the two studied groups in hemoglobin and HCT postoperatively with higher level among intra venous oxytocin plus intra uterine misoprostol than intra venous oxytocin only group. But regarding preoperative hemoglobin and HCT, there was no statistically significant difference before and after treatment.there was statistical significantly decrease in both hemoglobin and HCT postoperatively in the two studied groups but this decrease was more among intra venous oxytocin only group than intra venous oxytocin plus intra uterine misoprostol**(Table 3)**.

There was no statistically significant difference between the two studied groups regarding need for additional ecbolic. There was no statistical significantly differences between the two studied groups regarding pre-operative and 24 hours postoperative pulse rate, systolic and diastolic blood pressure . This table shows that there was no statistically significant difference between the two studied groups regarding need for additional ecbolic. This table shows that there was no statistically significant difference between the two studied groups regarding need for blood transfusion**(Table 4)**.

there was statistically significant difference between the two studied groups regarding side effects of drugs with higher shivering among intra venous oxytocin plus intra uterine misoprostol than intra venous oxytocin only (47.9% versus 4.3%) while headache and vomiting were more common among intra venous oxytocin only than intra venous oxytocin plus intra uterine misoprostol (26.1% and 17.4% versus 13.1% and 8.6% respectively)**(Table 5)**.

Table (1); Basic data of the studied groups (NO=23):

Variable	Group (A) No. (23)	Group (B) No. (23)	t-test	P
Age (years)				
mean ± SD	29.7±4.9	31.3±6.1	0.5	0.6
(range)	(19-38)	(20-41)		
BMI				
mean ± SD	28.4±4.6	28.6±5.7	0.4	0.7
(range)	(20-34)	(19-36)		
Gravidity				
mean ± SD	2.8±1.3	2.6±1.2	0.3	0.6
(range)	(1-4)	(1-5)		
Parity				
Nulliparous	9 (39.3%)	7 (30.4%)	0.7	0.9
Multiparous	14 (60.7%)	16 (69.6%)		
Gestational age (weeks)				
mean ± SD	38.7±2.2	38.1±2.1	0.5	0.6
(range)	(37-40)	(37-40)		

Table (2): Comparing indications of cesarean section between the two studied groups:

Indications of cesarean section	Group (A) No. (23) NO. (%)	Group (B) No. (23) NO. (%)	χ^2	P-value
Breech presentation	8 (43.8%)	6 (26.1%)	1.2	0.06
PROM	5 (21.7%)	3 (13.1%)		
Oligohydraminos	3 (13.1%)	4 (17.4%)		
Elderly primigravida	2 (8.7%)	3 (13.1%)		
CPD	2 (13.1%)	4 (17.4%)		
Primary infertility	1 (4.3%)	2 (8.7%)		
Prolonged labor	1 (4.3%)	1 (4.3%)		

Mean and standard deviation of blood loss, hemoglobin and HCT :Table (3) pre and post-operative in the two studied groups:

Blood loss	Group (A) No. (23)	Group (B) No. (23)	t-test	P
Intraoperative blood loss (ml) *mean ± SD (range)*	426.5±6.2 (380-450)	395.1±4.1 (365-415)	16.7	0.001**
Postoperative blood loss *mean ± SD (range)*	85.4±8.6 (67-100.2)	62.3±9.1 (40-75.8)	12.3	0.001**
Approximate total blood loss (ml) *mean ± SD (range)*	511.9±23.7 (447-550.5)	457.4±21.5 (405-490.2)	14.9	0.001**
Preoperative hemoglobin mean ± SD (range)	12.1±2.5 (10-14.5)	11.8±2.1 (9.8-14.6)	1.4	0.6
Postoperative hemoglobin mean ± SD (range)	9.9±0.7 (9.2-10.8)	10.1±0.8 (9.4-11.4)	2.5	0.04*
Preoperative HCT mean ± SD (range)	33.86±2.3 (29.8-36.7)	33.67±2.8 (29.8-35.9)	1.6	0.5
Postoperative HCT mean ± SD (range)	30.14±3.7 (26.2-33.8)	31.38±2.8 (28.4-35.4)	2.6	0.04*

Table (4): Mean and standard deviation of vital signs pre and post-operative and Need for additional ecbolic AND Need for blood transfusion in the two studied groups:

Vital signs	Group (A) No. (23)	Group (B) No. (23)	t-test	P
Preoperative Pulse rate *mean ± SD*	76.1±3.6	74.5±4.5	0.9	0.1
Postoperative Pulse rate *mean ± SD*	85.6±5	87.2±8.1	1.1	0.2
Preoperative systolic blood pressure *mean ± SD*	102.3±10.1	99.7±12.6	1.4	0.08
Postoperative Systolic blood pressure *mean ± SD*	133±1.7	134.5±1.6	1.7	0.06
Preoperative diastolic blood pressure *mean ± SD*	74.9±0.7	75.1±0.6	1.1	0.3
Postoperative diastolic blood pressure *mean ± SD*	86.4±0.5	87.1±0.8	1.2	0.07
Need for additional ecbolic	**Group (A) No(23) %**	**Group (B) No(23) %**	**test χ^2**	**P**
No	19 82.6	22 95.6	1.7	0.06
Yes	4 17.4	1 4.4		
Need for blood transfusion	**Group (A) No(23) %**	**Group (B) No(23) %**	**test χ^2**	**P**
No	20 86.9	22 95.6	0.6	0.9
Yes	3 13.1	1 4.4		

Table (5): Comparison between the two studied groups as regards side effects of drugs:

Side effects of drugs	Group (A) No(23) %	Group (B) No(23) %	test χ^2	P
No	9 39.1	6 26.1	3.8	0.03*
Shivering	4 17.4	11 47.9		
Vomiting	4 17.4	2 8.7		
Headache	4 17.4	3 13.1		
Dizziness	2 8.7	1 4.3		

DISCUSSION

Misoprostol binds myometrial cells to trigger extreme myometrial contractions that occur at the fundus near the corn and spread to the body of the uterus leading to tissue removal and decreases postpartum haemorrhage. We figured that inserting the tablets at uteri cornu was quick and easy to repair. It can aid the myometrial cells in their absorption **(6).**

This study included 46 women underwent caesarean section divided into two groups; group (A) 23 pregnant women who received intra venous oxytocin only and group (B) included the same number (23 pregnant women) received intra venous oxytocin plus intra uterine misoprostol for prevention of primary postpartum hemorrhage (PPH).We used misoprostol intrauterine route because in the case of a caesarean section, it was easy and easier to do than other routes such as oral, sublingual, buccal, or rectal. In addition, one may use spinal anaesthesia in all cases with less infection compared with the rectal route.

In our study the statistical comparison between the two groups shows non-significant differences as regards maternal age, gravidity, parity, maternal BMI andGestational age.There was no statistically significant difference between the two groups as a distinct indication of CS.This in agree **with El rafaeyandRodeck(7) &Vimalaet al. (8)** revealed thatthere was no statistically significant difference in the indicator of caesarean section between the two groups surveyed.

In The current there was statistically significant difference between the two studied groups regarding blood loss with higher blood loss either intraoperative, postoperative and overall blood loss on intra venous oxytocin only group than intra venous oxytocin plus intra uterine misoprostol.The blood loss was estimated by preoperative hemoglobin level within 24 hours postoperative hemoglobin level was measured. The mathematical calculation in which the lost blood intraoperative wasestimated by measuring the hematocrit level immediately after hospital admission and one hour postoperative in recovery room. The amount of intraoperative blood loss in oxytocin group was 426.5±6.2 ml, Vs 395.1±4.1ml in misoprostol plus oxytocin group, 2h postoerative blood loss was 85.4±8.6 ml, Vs 62.3±91 ml, respectively.

When combined with 20IU oxytocin drip, (200µg) Sublingual misoprostol was found to be as effective as intravenous oxytocin (20IU) in prevention of postpartum hemorrhage following cesarean delivery with fewer side effects **(9).**

Also, **Vimalaet al. (8)**reported thatthe estimated mean blood loss during CS was significantly lower among women receiving sublingual misoprostol 400mg (819± 236ml) than among those receiving 20 i.u oxytocin (974± 285 ml, p = 0.004) soon after delivery of the neonate.

other study conductedtwo classes are sublingually issued either misoprostol 400 mg or i.v. Infusion of 20 i.u oxytocin soon after birth of the baby no substantial variations in the expected blood loss during surgery were found in both classes. In the misoprostol group the mean blood loss in the first 4 h after the surgery was slightly smaller than in the oIn our research there was a substantial statistical gap (P = 0.05)

between the two groups tested postoperatively in haemoglobin and HCT with higher levels of intravenous oxytocin + intrauterine misoprostol than intravenous oxytocin group alone. But there was no statistically meaningful increase in pre-operative haemoglobin and HCT before and after treatment) befor CS between both group. Hemoglobin level in oxytocin intravenous group befor CS was 12.1±2.5 versus 11.8±21inmisoprostolintrautrin plus oxytocin intravenous group, while after CS was 9.9±0.7 in misoprostol group Versus 10.1±0.8 in misoprostol plus oxytocin **(10).**

In **Vimalaet al. (8)**showedno difference in the pre- and post-delivery haemoglobin levels for the two classes. The mean haemoglobin loss for the misoprostol group was 0.4 gm / dl and for the oxytocin group was 0.6 gm / dl. In the oxytocin community there were more women who needed additional oxytocics who had reported blood loss of more than 1000 ml. This disparity however did not hit statistical significance.

In our study there was statistical significantly decrease in both hemoglobin and HCT postoperatively in the two studied groups but this decrease was more among intra venous oxytocin only group than intra venous oxytocin plus intra uterine misoprostol Hct value decreased significantly among both groups, manifested by the highly significant p value in comparison of pre and postoperative Hct in the two groups ($p \leq 0.05$). There was more loss in postoperative Hct value of oxytocin group 30.14±3.7 than misoprostol plus oxytocin intrauterine group 31.38±2.8 ($p \leq 0.05$). The present study showed that no statistically significant difference between the two studied groups regarding need for additional ecbolic.This in agreement with **Vimalaet al. (8)**revealed thatmisoprostol group 32% required extra ecbolics while in the oxytocin group 36% and p=0.673,

In a double-blind, non-inferiority, Multicenter study included 9348 women including Shatby Maternity Hospital concluded that intravenous oxytocin should be used when available, but 800 µg sublingualmisoprostol could be an effective first-line treatment alternative when oxytocin is not available**(11).**

Our study showed no statistically significant difference between the two studied groups regarding need for blood transfusion. There was statistically significant difference ($P \leq 0.05$) . between the two studied groups regarding side effects of drugs with higher shivering among intra venous oxytocin plus intra uterine misoprostol than intra venous oxytocin only (47.9% versus 4.3%) while headache and vomiting were more common among intra venous oxytocin only than intra venous oxytocin plus intra uterine misoprostol (26.1% and 17.4% versus 13.1% and 8.6% respectively).

According to Hofmeyr the incidence of side effects with misoprostol was dose-dependent and that efforts should be undertaken to establish the smallest effective and safe dose of the drug (**12**).

Shivering and pyrexia are common adverse effects of misoprostol use, occurring in 30% to 70% of cases **(13,14)**.

In our study, shivering were the pronounced side effects associated with misoprostol plus oxytocin group when compared to oxytocin. The number of women who experienced shivering was higher in the misoprostol group (11 cases representing

47.9% of the misoprostol group vs. 4 cases only representing 17.4% of the oxytocin group), this difference is considered highly significant as the P value was ≤0.05.

Intrauterine misoprostol efficacy was compared to placebo, and both groups got 10 IU oxytocin as an IV infusion**(15)**. The current research had a larger number of patients in each group compared with this research (120 vs. 100). Like our report, it covered full-term low-risk PPH women who witnessed CS whether or not labour had begun and omitted high-risk PPH patients.

In the present study there were no statistically significant differences between the two groups as regared intraoperative complications, and there was no any major complication, such as need for blood transfusion, surgical intervention for PPH and maternal mortality, in either group.Misoprostol has been used for more than a decade for prophylaxis and control of PPH. Many studies were done worlwide to compare between oxytocin and misoprostol as regards their role in prevention and management of postpartum hemorrhage and many studies were done to assess the effectiveness of the different routes of administration of misoprostol for prevention and control of PPH, but there is a lack of consensus about the optimum dose and the best route of administration.

The oral administration was assessed for the control of the third stage of labour in the distribution of caesarean products. Rectal misoprostol administration was explored and which successfully treated 7 PPH patients with 800 μg of rectal misoprostol following caesarean delivery (**16,17**).

Comparison was made between the two classes over the need for additional uterotonics, lack of haemoglobin and hematocrit levels, and the adverse effects. Results revealed that the use of intrauterine misoprostol reduced the need for additional uterotonics by 50%, reducing the depletion of haemoglobin and decreasing the amount of hematocrit by 39.6% and 40.6% respectively (**18**)

In a study conducted in China intrauterine administered misoprostol was found to be effective in reducing blood loss intra-operatively and after 2 hours of the cesarean section with no adversereactions In this randomised trial 180 cases were randomly allocated to three classes of hospital-patients who underwent elective caesarean section and were at risk for postpartum haemorrhage, 800 microgm misoprostol intrauterine administration group, 20 IU IV group oxytocin infusion and 600 microgm group Misoprostol oral administration, with 60 cases in each category.

Including our blood loss and mediation research medication side effectswere observed during the operation and within the first 2 hours after operation. Comparison between groups based primarily on blood loss calculation, decrease in levels of haemoglobin/hematocrit 2 hours after surgery, need to add other uterotonics and drug adverse effects. Effects revealed that blood loss of the misoprostol group intraoperatively and 2 hours after surgery was slightly smaller than that of the oxytocin group (P= 0.01), and no adverse reactions were observed in two groups. (**19**).

Misoprostol provides many benefits over oxytocin or ergometrine including that it has a long shelf life, is safe at room temperature, is light sensitive, needs no special storage or transport requirements, is orally active and can be given to patients

with hypertension. These benefits of misoprostol make it an important replacement agent to be used in third stage laboratory management of atonic postpartum hemorrhage **(20).**

CONCLUSION

Intrauterine misoprostol combined with oxytocin infusion during caesarean section can minimize intraoperative blood loss, avoid postpartum haemorrhage, and reduce any additional utero-tonic medication requirements. A mild side effect, such as shivering, was detected and spontaneously subsided.

No Conflict of interest.

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