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Original Research Article

Four hundred micrograms buccal misoprostol versus five units intravenous oxytocin in prevention of postpartum hemorrhage in elective caesarean section, randomized controlled study

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ABSTRACT

Background: The number of studies has been increased about the use of misoprostol during caesarean delivery to prevent obstetric hemorrhage, but may be no study compare buccal misoprostol versus oxytocin in prevention of obstetric hemorrhage during and post cesarean section. Our study is done to compare buccal misoprostol 400 mcg versus oxytocin 5iu intravenous bolus in prevention of postpartum hemorrhage during and post elective cesarean section.
Methods: A prospective registered, double blinded, randomized controlled trial Operative list or emergency unit at Obstetrics and Gynecology Department, Women Health Hospital, Assiut university, Egypt, comparing 77 patients in each group after verbal consent.
Results: There was significant difference between both groups regarding total amount of blood loss (intra partum plus post-partum) 555.45±74.33 in oxytocin group versus522.6±88.76 in misoprostol group.
Conclusions: Buccal misoprostol is more effective than intravenous infusion of oxytocin in reducing blood loss during elective cesarean delivery. However, occurrence of temporary side effects such as fever and chills was more frequent with the use of misoprostol. Clinical trial.gov: NCT03676621.

Keywords: Elective caesarean section, Post-partum haemorrhage, Buccal misoprostol

INTRODUCTION

The rate of caesarean section has increased in both developed and developing countries it saw estimated in 2010 that cs rate was 32% in united states and 42% China which are both considerably higher than world health organization's recommended proportion of 10 to 15%.[1-3]

In devolving country like Egypt the rate reached to very higher level, to about 60% or more in some governorates. Caesarean section is a one of the major risk factors for post-partum hemorrhage.[4] The incidence of obstetric hemorrhage during caesarean section deliveries range from 1-11%.[5] post-partum hemorrhage at caesarean section occurs for many reasons, the most common one is atony during it or post operative.[4]

Prevention of intra operative hemorrhage or postpartum is one big category studied during last decade. Oxytocin is one of the main drug used to prevent post-partum hemorrhage during caesarean section and the recommended dose is 5 IU intravenous bolus injection.[6] In our country occasionally for long times oxytocin was not available, and also face some sort of problem of its

efficacy related to its storage. Misoprostol is a synthetic prostaglandin E1 analog that has been demonstrated to be an effective uterotonic agent in the third stage of labor and the immediate postpartum period.[7] Misoprostol is inexpensive and thermostable (thus does not require refrigeration like oxytocin), making it a cost-effective and powerful drug to use in the developing countries.[8]

When we compare misoprostol with oxytocin, misoprostol is recommended due to its cost, effectiveness stability, and low rate of side effects. Oxytocin must also be given by injection, while misprostol can be given orally or rectally for this use making it much more useful in areas where nurses and physicians are less available.[9] Misoprostol can be administered by various routes including the poorly studied buccal-space pathway (between gum and check on each side) where the dosage form is placed between gums and the inner lining of the cheek.[7] Placing misoprostol in the buccal space, does not interfere with the surgical field, and ensures a continuous plasma level of a potent uterotonic agent for a period of at least 5 hours, with lower response variability compared with vaginal and rectal routes of administration.[10] On the basis of these evidence our study is done to compare buccal misoprostol 400 mcg versus oxytovin 5 IU intravenous bolus in prevention of postpartum hemorrhage during and post elective caesarean section

METHODS

Trial design

The study was a single-center, open randomized, parallel, and registered clinical trial from 01 November 2018 to 20 September 2021.

Inclusion criteria

All legally adult pregnant women, above 18 years old, at term with singleton pregnancies booked for elective caesarean section accepting to participate in the study were included in the study**.**

Exclusion criteria

Medical disorders involving the heart, liver, kidney or brain, diabetes mellitus and hypertension, patients requiring blood transfusion due to anemia, risk factors for uterine atony e.g. macrosomia, polyhydramnios, multiple pregnancies, placenta previa or placental abruption, previous major obstetric haemorrhage (>1000 ml in previous deliveries), known fibroid or adenomyosis Severe preeclampsia, uterine anomalies, women who received anticoagulant therapy, blood disorders (e.g. coagulopathies , thrombocytopenia).

Indications of caesarean section

Repeated caesarean section (previous 2 cs or more). Previous one caesarean with oligohydramnios. previous one caesarean with contracted pelvis. previous one caesarean with malpresentation. previous one caesarean section with decreased fetal movement. primigravida with malpresentation. primigravida with contracted pelvis.

Study location

Operative list and emergency unit at obstetrics and gynecology department, women health hospital, Assiut university, Egypt.

Intervention

Verbal and written consent were obtained from all eligible women, then taking history and general and obstetric examination done for the patients. Investigations including ultrasonograghic fetal assessment, complete blood count, prothrombin time and concentration.

Randomization

The candidate women were divided into two groups. A computer generated random numerical table was used by an independent statistician to prepare sealed opaque envelopes containing a group assignment. Two groups of envelopes, corresponding to two study groups, were given to a third party (a nurse), who was unaware of the contents. The nurse distributed envelopes to patients, alternating between the groups. Patients assigned to group 1 received 5 IU oxytocin IV after delivery of the fetus+2 tabs placebo. Patients assigned to group 2 received 400 in the buccal space after anesthesia+IV saline infusion.

Procedure

All the towels were weighed before and after caesarean section and the difference were calculated, the amount of intraoperative blood loss was estimated in the suction apparatus in ml. A trained nurse was responsible for blood and amniotic fluid collection during surgery using two separate suction sets, as well as for weighing the surgical towels before and after surgery; all towels that were used were of the same size and weight and every 1 gm increase in weight was equated with 1-ml blood loss. The total amount of intra-operative blood loss was calculated. blood loss in suction apparatus plus weight difference of used towels. Second trained nurse was responsible for post-operative external blood loss measurement during the first 24 hours after surgery by weighing the soaked towels placed in the vulvar area. The post-operative blood loss was calculated (weight difference of towels placed in the vulvar area. The overall blood loss was calculated. Another blood picture was obtained 24 hours postoperative to detect changes in Hb level. The same nurse was responsible for follow up body temperature 2 hours after caesarean section (feverish if temperature is 38ºC or greater) and observation of the patient for nausea, vomiting, chills and diarrhea.

Outcomes

Primary outcomes

Involved estimation of intraoperative and postoperative blood loss for 24 hours (blood loss estimation started immediately following the skin incision)

Secondary outcomes

Changes in hemoglobin concentration (hemoglobin concentrations were measured 2 hours before surgery and 24 hours after surgery). Misoprostol-induced maternal adverse effects (postoperative nausea, vomiting, diarrhea, fever and chills need to use other uterotonic drugs (oxytocin or ergometrine). Need to do further surgical interventions (uterine artery ligation, hysterectomy or re-exploration of the patient) need for blood transfusion.

Sample size

Sample size was calculated based on the primary outcome (the amount of intraoperative blood loss during CS) based on the results of previous study, the mean blood loss with the use of IV oxytocin was 588.9 ml with a standard deviation of 96.3 ml.[11] Assuming that buccal misoprostol is more effective in reducing blood loss by 10% 77 participants in each group will have 95% power at 5% significance to detect such a difference, 77 women were include in each group taking in account a 10% drop-out rate (Epi-info: centers for disease control and prevention Atlanta, GA).

Statistical analysis

Data entry and analysis were carried out using Statistical Package of Social Sciences for windows (SPSS, Chicago, Illinois, USA) version 20 quantitative variables were presented in terms of mean±standard deviation and qualitative variables were expressed as frequency and percentage. Tests of significance (t test and Chi-square) were calculated significance level was set at $p<0.05$.

RESULTS

Base line data

Baseline data in study groups showed that there was non significance difference between study groups regarding to age, gestational age, parity, and numbers of previous CS ($p>0.05$). The most common parity in this study was P1,32.5% in group A (oxytocin group), 28.6% in group B (misoprostol group). The most common No. of CS was previous 1, 48.1% in group A (oxytocin group), 36.4% in group B (misoprostol group). The most common indication of CS was elective repeated CS (two or more CS), 29,9 % in group A (oxytocin group), 41,6% in group B (misoprostol group). Regarding duration of operation: the mean duration of operation was 44.346±6.68 (range from 32-60) minutes in group A (oxytocin group) versus 44.34±6.45 (range from 30-60) minutes in group B (misoprostol group) with no significant difference.

Table 1: Operative and post-operative data in the two studied groups (n=77).

Variables		Groups				P value
		Group A		Group B		
		N	%	N	%	
Uterineatony	No	60	77.9	56	72.7	0.455 NS
	Yes	17	22.1	21	27.3	
Need for blood transfusion (number of units of packed RBCs)	No	74	96.1	76	98.7	0.311 NS
	1	3	3.9	1	1.3	
Need for further surgical interventions	No	76	98.7	76	98.7	0.368 NS
	Uterine artery ligation	1	1.3	0	0.0	
	IP drain insertion & uterine artery ligation	0	0.0	1	1.3	
Presence of intraoperative complications	No	76	98.7	75	97.4	0.605 NS
	Adhesions	0	0.0	1	1.3	
	Uterine artery injury	1	1.3	1	1.3	
Duration of hospital stay (days)	1	76	98.7	76	98.7	1.000 NS
	2	1	1.3	1	1.3	
	Range	1-2		1 -2		1.000 NS
	Mean±SD	1.01±0.114		1.01±0.114		

Values are presented as mean±SD or number (%), p value is significant if <0.05 and is calculated by Mann Whitney test for continuous variables and by Chi-square test for categorical variables.

Operative and post-operative data in the two studied groups

There was non-significance difference p>0.05) between both groups regarding to uterine atony, need for blood transfusion (Table 1).

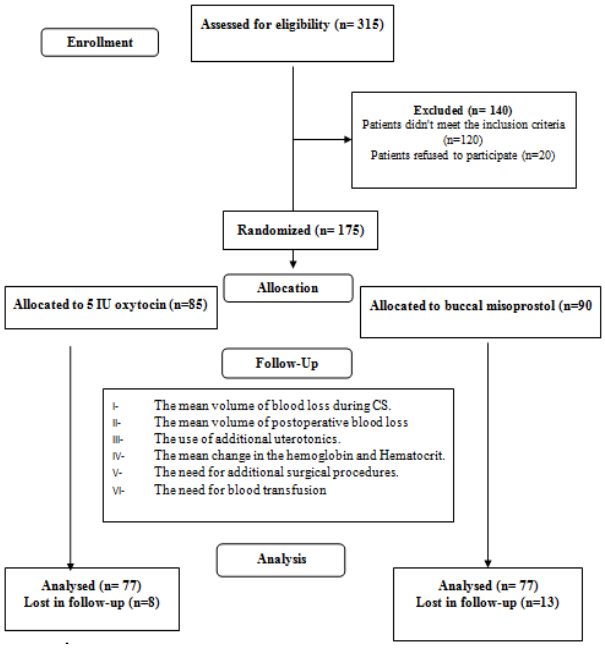

Figure 1: Methodology adapted in current investigation.

Need for other uterotonic drugs in the two studied groups

There was non-significance difference (p>0.05) between both groups regarding to need for intra-operative 10 IU oxytocin (Table 2).

Blood loss parameters in the two studied groups.

There was non-significance difference (p>0.05) between both groups regarding to amount of blood in suction apparatus (ml) and blood loss postoperative. There was a significant difference in weight of towels(gm)related to intra-operative blood loss and total blood loss (p<0.001) in both groups as (Table 3).

Laboratory data in the two studied groups

There is significant difference between both groups the level of HB decrease after operation in favor for buccal misoprostol (Table 4).

Side effects in the two studied groups

There was highly significance difference (p<0.001) between groups as regarding fever and chills with increased rates at group B (misoprostol group) (Table 5).

Table 2: Need for other uterotonic drugs in the two studied groups (n=77).

Items	Groups				P value*
	Group A		Group B		
	N	%	N	%	
10 IU oxytocin (intra operative)					
No	60	77.9	56	72.7	
Yes	17	22.1	21	27.3	0.455NS
Post-operative					
No	77	100.0	77	100.0	
Yes	0	0.0	0	0.0	-
P value**	<0.001		<0.001		
One amp. methergine (Intra operative)					
No	77	100.0	77	100.0	
Yes	0	0.0	0	0.0	-
2 tabs. of misoprostol post-operative					
No	77	100.0	77	100.0	
Yes	0	0.0	0	0.0	-

Values are presented as number (%), *p value is significant if <0.05 and is calculated by Mann Whitney test for continuous variables and **P value calculated by Chi-square test for continuous variables.

Table 3: Blood loss parameters in the two studied groups (n=77).

Parameters	Group A	Group B	P value*
Amount of blood in suction apparatus (ml)			
Range	150-400	100-400	0.072
Mean±SD	254.81±51.88	239.09±69.89	
Difference in weight of towels (gm)			
Range	150-350	100-310	0.009
Mean±SD	209.35±40.76	193.51±46.5	
Blood loss (ml), intra operative			
Range	270-650	250-660	0.020
Mean±SD	461.69±72.54	432.6±88.58	
Blood loss (ml), post operative			
Range	50-150	50 -150	0.129
Mean±SD	93.77±16.67	90±15.85	
P value**	<0.001**	<0.001**	
Total amount of blood loss (ml)			
Range	350-750	350-740	0.013
Mean±SD	555.45±74.33	522.6±88.76	

Values are presented as mean±SD, *p value is significant if <0.05 and is calculated by Mann Whitney test for continuous variables and **P value calculated by Chi-square test for continuous variables.

Neonatal outcome in the two studied groups

There was a non-significance difference between groups (p>0.05) regarding NICU admission and APGAR score (Table 6).

Table 4: Laboratory data in the two studied groups (n=77).

Parameters	Group A	Group B	P value*
Hb preoperative			
Range	8-14	8.7-13.8	0.951
Mean±SD	11.18±1.29	11.19±1.2	
Postoperative after 24 hours			
Range	8.2-12.5	8.2-12.5	0.292
Mean±SD	10.05±0.98	10.22±1.04	
P value**	<0.001	<0.001	
Change in Hb level			
Range	(-1.2)-2.6	(-1.8)-3.2	0.008
Mean±SD	1.13±0.60	0.977±0.639	
Hematocrit (%) pre-delivery			
Range	23 -43	25-48	0.163
Mean±SD	34.48±3.98	33.67±3.88	
Hematocrit (%) post-delivery			
Range	22.63-42.6	25-47.6	0.179
Mean±SD	34.28±4.03	33.47±3.89	
Change in hematocrit (%)			
Range	0-0.4	0-0.4	0.872
Mean±SD	0.203±0.201	0.197±0.201	

Values are presented as mean±SD, *p value is significant if <0.05 and is calculated by Mann Whitney test for continuous variables and **P value calculated by Chi-square test for continuous variables.

Table 5: Side effects in the two studied groups (n=77).

Parameters	Group A		Group B		P value*
	N	%	N	%	
Fever					
No	75	97.4	63	81.8	0.002
Yes	2	2.6	14	18.2	
Chills					
No	70	90.9	58	75.3	0.010
Yes	7	9.1	19	24.7	
Nausea					
No	60	77.9	64	83.1	0.416
Yes	17	22.1	13	16.9	
Vomiting					
No	59	76.6	66	85.7	0.149
Yes	18	23.4	11	14.3	
Diarrhea					
No	77	100.0	77	100.0	-
Yes	0	0.0	0	0.0	

Values are presented as number (%), *p value is significant if <0.05 and is calculated by Chi-square test for categorical variables.

DISCUSSION

Age

In the current study, mean age of presentation was 27.49±6.62years in oxytocin group and 27.31±5.44years in 400 µg buccal misoprostol group. These results corroborate the ideas of Othman and et al who suggested that mean age of oxytocin group was 25.87±4.41 years while that of sublingual misoprostol group was 25.38±5.48 years, explained by the fact that most women tend to have children during their most reproductive time frame.[12]

Gestational age

As regard gestational age (weeks), we reported that mean of gestational age was 38.19±1.37 weeks in oxytocin group and 37.94±1.8 in 400 µg buccal misoprostol group. These results are in agreement with subedi and et al which showed that gestational age (38.62±1.03 SD and 38.34±1.00 SD, p= 0.171) in both groups.[13]

Parity

Concerning of parity, 25 cases (32.5%) in oxytocin group and 22 cases (28.6%) 400 µg buccal misoprostol group had one parity. A similar pattern of results was obtained in kock and et al showed that para one women percent was 31.9%.[14]

Indication of CS

In this study, the indications for CS were Elective previous 2 CS or more 29.5%, previous 1plus oligohydramnios 16.9% and previous 1 CS plus contracted pelvis 20.8% in oxytocin group. While the indications for CS in 400 µg buccal misoprostol group

were Elective previous 2 CS or more, 41.6%, previous1 CS plus oligohydramnios 13.0%, and previous 1 CS plus contracted pelvis 14.3%. A possible explanation for this might be that in Egypt, 52% of women give birth by caesarean section according to the demographic and health survey.[15]

Outcomes

Operative time

Operative time (min) in oxytocin group, its mean was 44.34±6.68 min and in 400 μg buccal misoprostol group, its mean 44.1±6.45min. The same as in results by Othman and et al who found that operative time was (37.88±8.13 vs. 36.5±7.55) in sublingual misoprostol and oxytocin respectively.[11]

Uterine atony and blood transfusion

Majority of patients observed that no uterine atony occurred (77.9% vs. 72.7%) in oxytocin vs. 400 μg buccal misoprostol group. As regard need of blood transfusion, three women in oxytocin group and one woman only in 400 μg buccal misoprostol group were need 1 unit of packed RBCs. Our results go in line with the results by subedi and et al which founded that blood transfusion was 2 in oxytocin group versus no patient in misoprostol group.[13] While, Baskett et al reported no cases of transfusion need in their studies.[16]

Surgical interventions

According to need for further surgical interventions one patient need uterine artery ligation in oxytocin group and one patient need I.P drain insertion & uterine artery ligation in 400 μg buccal misoprostol group. A study by (Bellad et al reported that a woman in their misoprostol group underwent bilateral uterine artery ligation due to atony, whereas another woman in the oxytocin group underwent hysterectomy.[17]

Additional uterotonic

In the current study, administration of 10 IU oxytocin (intraoperative and postoperative), we reported that, in oxytocin group it was estimated (22.1% vs. 0%) and in 400 μg buccal misoprostol group it was estimated (27.3 vs. 0%). A similar pattern of results was obtained in Subedi et al founded that no patients in oxytocin group and one patient in 400 μg buccal misoprostol group received additional uterotonics post-delivery.[13]

Blood loss

In oxytocin group its mean was 555.45±74.33 and in 400 μg buccal misoprostol group its mean was 522.6±88.76 with significant difference. This comes in agreement with another study by Othman et al.[12] That reported the overall estimated mean blood loss was significantly lower in the misoprostol group (490.75±159.90 ml) compared to the oxytocin group (601.08±299.49 ml, p=0.025). Shrestha, et al reported that there was a difference between misoprostol and oxytocin groups in terms of >500 ml blood loss (p=0.012) stated that rectal misoprostol was as effective as intravenous oxytocin, and it could be useful to use as an uterotonic agent at the third stage of labor.[18]

Change in HB and HCT

From the result of change in Hb level, we reported that; in oxytocin group it estimated mean of 1.13±0.60 and in 400 μg buccal misoprostol group it estimated mean of 0.977±0.639. There is significant difference between both groups the level of HB decrease after operation in favor for buccal misoprostol. There was no incidence of PPH (peripartum fall in Hb of 10%) in both the groups. There was no significant difference between two groups regarding decrease in Hct post-partum. Al-Sawaf et al found no difference in 200 μg sublingual misoprostol, 5 IU intramuscular oxytocin and control groups in terms of postpartum hemoglobin and hematocrit values.[19] Atukunda et al explained that postpartum hemoglobin changes were similar in the 600 μg sublingual misoprostol+1 ml placebo injection and 10 IU intramuscular oxytocin sublingual placebo groups.[20] Kaudel et al showed that in Nepal 108 women, 54 in each group, group A (600 μg oral misoprostol) and group B (10 U intramuscular oxytocin) were studied ,the mean change in Hb level in misoprostol group was 0.56+0.35 gm/dl as compared to 0.46+0.29 gm/dl in oxytocin group, which was statistically insignificant (p=0.222).[21] It was explained by (Smitha that additional uterotonic requirements are associated with increased bleeding, but the use of different clinical protocols (interventions, methods, and techniques) in management of bleeding affected the need for additional uterotonics.[22]

Side effects

In our study, we can see that fever was 2.6% versus 18.2%, chills were 9.1% versus 24.7%, nausea was 22.1% versus 16.9% and vomiting was 23.4% versus 14.3% in comparing oxytocin group versus 400 μg buccal misoprostol group. No patients in any of the groups had permanent side effect from this intervention By contrast to Hamm and colleagues' conclusion that a misoprostol dose above 200 μg placed in the buccal space would increase the adverse effects of the drug.[23] No major adverse events were observed in the present study, pharmacokinetic studies have shown that the buccal application of misoprostol has a pattern of increased uterine contractility and a tone similar to vaginal application but with a low area under the curve and minor adverse events.[24] Subedi et al also supported our results with his colleagues who found that the only secondary outcome which was statistically significant was shivering, more in misoprostol group than in oxytocin group (19 and 1 respectively, p≤0.001). Neonatal outcome: finally, we can see that NICU admission, were

6.5% versus 5.2% in comparing oxytocin versus misoprostol groups. 10 APGAR score were 44.2% and 51.9% for the oxytocin and misoprostol groups. A study Osoti et al suggests that even though administration of misoprostol increases the passes of meconium in the fetus.[25]

CONCLUSION

Buccal misoprostol is more effective than intravenous infusion of oxytocin in reducing blood loss during caesarean delivery. However, occurrence of temporary side effects such as fever and chills were more frequent with the use of misoprostol, neonatal adverse effect is less even at higher doses.

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