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EFFECT OF PRE-OPERATIVE SUB-LINGUAL MISOPROSTOL VERSUS INTRAVENOUS OXYTOCIN ON CAESAREAN OPERATION BLOOD LOSS

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ABSTRACT

***Background*: Caesarean operation remains the most common abdominal surgery in women and has immense benefits to both mother and baby when employed. Haemorrhage, however, remains the greatest challenge associated with its outcome.**
***Objective*: To compare the effectiveness of pre-operative sub-lingual misoprostol with intravenous oxytocin administered after delivery of the neonate in minimising blood loss at Caesarean operation**
Design: A prospective study.
***Results*: The mean blood loss was significantly lower in misoprostol group compared to oxytocin group (517.32mls versus 621.22mls; p = 0.005). The drop in haematocrit was significantly lower in misoprostol group than the oxytocin group, (400µg-misoprostol versus oxytocin: 1.88 versus 3.04; p=0.0001). Side effects of chills, shivering and pyrexia were noted more with the use of misoprostol.**
***Conclusion*: Pre-operative sub-lingual misoprostol is more effective than intravenous infusion of oxytocin in reducing blood loss at Caesarean section operation. However, occurrence of transient side effects of chills, shivering and pyrexia were noted more with use of misoprostol.**

INTRODUCTION

Caesarean operation remains the most commonly performed major abdominal operation in women in both affluent and low-income countries and the rates vary considerably between and within countries (1, 2). Global estimates have indicated a Caesarean delivery rate of 15% worldwide, ranging from 3.5% in Africa to 29.2% in Latin America and the Caribbean(3). These rates have continued to increase both in affluent and low-resource countries, including Nigeria (4). In the United States it has increased from about 21% in 1996 to 32% in 2007 (5). In Nigeria rates from 20.8 to 34.6% have been reported in tertiary institutions and private hospitals (6). Reasons for these increases include improved global awareness on benefits and safety of the procedure, increasing foetal survival compared to difficult vaginal deliveries and introduction of electronic foetal monitors (7). In addition diminishing proficiency in the arts of operative vaginal deliveries coupled with difficult referral system have made Caesarean delivery a preferred alternative even

in the less endowed settings of the less developed countries (8).

Many secondary healthcare institutions are located in rural and semi-urban communities in Nigeria and they undertake surgical procedures that include Caesarean deliveries to relieve parturient mothers in difficult labour or intervene to salvage a compromised foetus (4,9). Challenges against successful outcome are largely haemorrhage and sepsis, and these two have been largely expressed as major contributors to both Caesarean maternal morbidity and mortality (10). Challenge of sepsis is daily being relieved by novel provisions of antibacterial agents of increasing potency and coverage. However, challenge of haemorrhage has no alternative other than provision of blood. In rural and semi-urban Nigeria the blood banking services are far from being optimal sequel to malnutrition and blood borne diseases that make blood donation scarce (10). Alternative to overcoming haemorrhagic challenge, therefore, will be to employ strategies that will minimise blood loss at surgery. To achieve these oxytocic drugs, oxytocin (syntocinon or pitocin) and methyl-ergometrine (methergine), are conventionally employed parenterally during Caesarean operations. These oxytocics are available in Nigeria in many generic types of doubtful potencies. Syntocinon and methergine are rare brands and when available their potencies may not be optimal from poor storage practices and the humid hot environment. The lack of these effective oxytocics further compounds the ability of the surgeon to combat haemorrhagic challenge in poor-resource settings.

Misoprostol is an analogue of prostaglandin (15-deoxy-16-hydroxy-16-methyl-PGE1) and an H2-receptor agonist, marketed by Pfizer as cytotec and originally labeled for treating gastric ulcer and patients on non-steroidal anti-inflammatory drugs (NSAID) (11). It is prepared in tablets form and can be administered orally, sub-lingually, vaginally and rectally. It is used in obstetrics and gynaecology to induce or augment labour, or perform mid-trimester abortions. It is also employed to prevent and treat post-partum haemorrhage (12). Between 2005 and 2008 it became licensed for obstetric and gynaecologic uses by World Health Organisation (WHO) and in more than 50 countries, including Nigeria (13). It has been found to be a good alternative to oxytocin or methylergometrine in treating or preventing post-partum haemorrhage (12).

Misoprostol when administered rectally or vaginally will take between 30 and 40 minutes to peak, will peak at 15 to 20 minutes when administered sub-lingual and five to ten minutes when given as oral solution (11, 12). Several studies that have compared misoprostol and oxytocin in our review showed that misoprostol was administered either rectally or vaginally and after delivery of the baby. A few that employed misoprostol sub-lingually also administered the drug after delivery of the baby. In these studies one would infer that optimal effect of misoprostol was not being employed at the time appropriate for desired result. Misoprostol when given sub-lingually at a time when the patient is being shifted from the ward to the operating room for surgery, would be peaking just before delivery or immediately after delivery of the baby.

The aim of this study was to compare the effectiveness of pre-operative sub-lingual misoprostol with intravenous oxytocin administered after delivery of the neonate in minimising blood loss at Caesarean operation.

MATERIALS AND METHODS

This prospective study was conducted between April 2009 and March 2011 at the Obstetrics and Gynaecology unit of Olabisi Onabanjo University Teaching Hospital, Sagamu, Nigeria. Sagamu is a semi-urban town 50 miles north of Lagos, Nigeria. The study was approved by the Hospital Ethics Committee in accordance with local research requirements in November 2008. Method and procedures were explained to prospective participating women before signing informed consent form.

One hundred women in labour or on admission for elective or emergency Caesarean delivery that have consented to be part of the study were randomly assigned to two groups. In one group each woman received two tablets of 400μgms tablet of misoprostol and in the other group each woman received 20 international units of oxytocin injection intravenously after the delivery of the neonate. In the misoprostol group the tablets were administered sub-lingually by the nurse while the woman was being shifted from labour ward to the operating room.

The population size determination was derived using sample size formula to compare two mean values; $n = \frac{2(Z_{1-\alpha}/2 + Z_{1-\beta})^2\sigma^2}{\rho^2}$

Where n is the minimum sample size required, Z is the standard normal deviate, α is the type 1 error, β is the type 2 error, σ is the standard deviation, and d is the standardised difference.

If $\alpha = 0.05$, $Z_{1-\alpha/2} = 1.96$, $\beta = 0.20$, power = 80%, $Z_{1-\beta} = 0.84$, $\sigma = 215$, and d=150; Therefore n = 32.049 per group.

Included in this study were women whose pregnancies were 34 weeks and above, primigravidae or nulliparae and multiparae with not more than five parous experiences. Excluded were women with previous Caesarean operation, ante-partum haemorrhage or related complications and history of ante-partum haemorrhage in previous or current pregnancy. Also excluded were women with previous

history of dilatation and curettage, deranged coagulation profile or platelet counts of less than 100×10^{-9} and women with history of allergy to prostaglandin or prostaglandin analogues. Women with hypertensive disorders associated with elevated liver enzymes, low platelets and elevated leucocytes dehydrogenase enzyme (LDH) were also excluded from this study.

The chief reason for Caesarean operation in woman with multiple complications was considered as indication for Caesarean delivery in this study.
The surgeries were performed under spinal analgesia and the surgical technique adopted was modification of Misgav-Ladach and traditional Pfannestiel procedures (1, 14, 15). During the course of surgery minor bleeders were cauterised with diathermy and major bleeders were ligated with sutures. All the surgeries were performed by consultant staff and post-fellowship senior registrars of the study team.
Blood loss at surgery was estimated by the gravimetric method; meticulous suctioning of blood into suction bottle from bleeding pool at operation sites and mopping with gauze towels. The liquor amni was also meticulously collected by suction into separate bottle. Cotton towels and gauzes were weighed as soon as discarded off operation site and operating drapes were weighed at the end of surgery. The known dry weights of towels, gauzes and drapes were subtracted from their wet weights and the difference in grammes equated to milliliter of blood, and this was added to blood volume in the suction bottle to estimate the total loss (16).

The primary maternal outcome included blood loss at surgery, blood transfusion, length of surgery, needs for additional oxytocics, admission into intensive care unit or maternal death. Secondary maternal outcome included change in post-operative haematocrit, anaemia, post-operative pain and use of analgesia, fever, and wound infection.

Primary foetal outcome included Apgar scores at one and five minutes, admission into neonatal intensive care unit and perinatal death. Secondary foetal outcome included encephalopathy, necrotising entero-colitis and perinatal or neonatal death.

Data were analysed using SPSS version 15.0. Statistical analysis was performed using the Chi-square test for categorical variables and the two-tailed t-test for continuous variables. One-sample t test was used in finding the weighted mean difference (WMD) of mean blood loss and length of surgery. One-way analysis of variance was used to evaluate the difference in the means (MD) of multiple variables. The results are presented as mean, standard deviation and range, or as numbers and percentages, and p-value < 0.05 was considered statistically significant.

RESULTS

During the study period a total of one hundred pregnant or parturient women consented for the study, a group of fifty had 400μgms tablets of misoprostol and the other group of fifty had 20 international units of oxytocin administered intravenously after delivery of the neonate.

Table 1 shows the indications for Caesarean deliveries; foetal distress 33(33.0%) was the leading reason for Caesarean deliveries in both study groups, next to it was dystocic labour 23(23.0%) and then pre-eclampsia and other hypertensive disorders of pregnancy 20(20.0%).The least reason for Caesarean delivery in the study was pregnancies considered as precious, two (2.0%).

Table 2 demonstrates the descriptive statistics of data in both study groups. The ages of the women ranged from 18 to 40 years and the mean age was 29.30 ±5.21 years. The mean parity was 1.99 ±1.51, the range being from zero and four. At delivery the gestational ages of the pregnancies ranged from 34 and 41 weeks and the mean was 38.08 ±1.75 weeks. The means Apgar scores of the babies at first and five minutes were 7.60 ±1.11 and 9.27 ±0.79 respectively. The blood loss at surgery ranged from 285mls and 1080mls and the mean was 555.32 ±151.34mls. The duration of surgery ranged from 30 and 95minutes and the mean was 47.70 ±14.31 minutes. Seventy two cases (72.0%) were emergency Caesarean deliveries and 28 (28.0%) were elective Caesarean operations.

Table 3 demonstrates comparison of means of the primary outcome in both study groups. The table demonstrates that the differences in the means of length of surgery, length of hospitalisation and Apgar scores at five minutes between the study groups were not statistically significant. However differences in the means of blood loss, intra-operative requirements of oxytocics and pre-operative and post-operative haematocrit values were statistically significant.
Table 4 is the cross tabulation of occurrences of known side effects of misoprostol in the study groups.

In this study there was no maternal or perinatal mortality. There was also no observation of wound sepsis.

Table 1
Indications for Caesarean deliveries

Indication	Oxytocin Group	Misoprostol Group	Total	Percentage (%)
Severe Pregnancy induced hypertension/ Hypertensive disorders in pregnancy	7	13	20	20.0
Uncontrolled Diabetes Mellitus/ Gestational Diabetes Mellitus	1	0	1	1.0
Precious baby (Bad Obstetric history/ Pregnancy after infertility treatment)	1	1	2	2.0
Foetal Distress	18	15	33	33.0
Abnormal lie (Transverse lie/oblique lie)	2	1	3	3.0
Malpresentation (Face/brow)	3	2	5	5.0
Dystocia (Foeto-pelvic disproportion/ occipito-posterior/transverse arrest)	14	9	23	23.0
Foetal Macrosomia	1	2	3	3.0
Breech	2	4	6	6.0
Prolonged pregnancy	1	3	4	4.0
Total	50	50	100	100.0

Table 2
Descriptive statistics of the study groups

Description	Group	N	Mean	Std. Deviation	95% CI Lower bound	95% CI Upper bound	Minimum	Maximum
Age of women	Oxytoc	50	28.72	.71	27.29	30.15	21	40
	misoprostol	50	29.88	.76	28.35	31.41	18	40
	Total	100	29.30	.52	28.27	30.33	18	40
Parity of women	Oxytoc	50	1.96	.22	1.51	2.41	0	4
	misoprostol	50	2.02	.20	1.61	2.43	0	4
	Total	100	1.99	.15	1.69	2.29	0	4
Gestational age at delivery	Oxytoc	50	38.04	.24	37.55	38.53	34	41
	misoprostol	50	38.12	.25	37.61	38.63	34	41
	Total	100	38.08	.17	37.73	38.43	34	41
length of surgery	Oxytoc	50	46.60	1.83	42.91	50.29	30	80
	misoprostol	50	48.80	2.20	44.38	53.22	30	95
	Total	100	47.70	1.43	44.86	50.54	30	95
blood loss at surgery	Oxytoc	50	621.22	22.74	575.51	666.93	420	1080
	misoprostol	50	489.42	15.19	458.89	519.95	285	786
	Total	100	555.32	15.13	525.29	585.35	285	1080
intra-operative oxytocin requirement	Oxytoc	50	589.00	153.76	280.00	898.00	0	3800
	misoprostol	50	.00	.00	–.00	.00	0	0
	Total	100	294.0	82.02	131.76	457.24	0	3800

intra-operative ergometrine requirement	Oxytoc	50	210.00	35.25	139.15	280.85	0	500
	misoprostol	50	30.00	16.96	– 4.09	64.09	0	500
	Total	100	120.00	21.46	77.42	162.58	0	500
pre-op and post-op difference in haematocrit	Oxytoc	50	3.04	.19	2.65	3.43	1	6
	misoprostol	50	1.88	.14	1.58	2.18	0	3
	Total	100	2.46	.13	2.19	2.73	0	6
Apgar score at one minute	Oxytoc	50	7.58	.16	7.24	7.92	5	9
	misoprostol	50	7.62	.14	7.33	7.91	5	9
	Total	100	7.60	.11	7.38	7.82	5	9
Apgar score at five minutes	Oxytoc	50	9.26	.11	9.03	9.49	7	10
	misoprostol	50	9.22	.11	9.06	9.50	7	10
	Total	100	9.27	.08	9.11	9.43	7	10
length of hospitalisation	Oxytoc	50	5.28	.13	5.02	5.54	4	7
	misoprostol	50	5.42	.12	5.16	5.68	4	7
	Total	100	5.35	.09	5.17	5.53	4	7

Table 3

Comparison of means of intravenous oxytocin versus sub-lingual misoprostol

Variable	Mean values of study groups		Diff of mean	Std Error	Signif	95% CI	
	IV Oxytoc	Sub-ling Misopro				Lower Bound	Upper Bound
Age of women	28.72	29.88	-1.16	1.06	.525	-3.69	1.37
Parity of women	1.96	2.02	-.06	.30	.979	-.79	.67
Gestational age at delivery	38.04	38.12	-.08	.35	.972	.91	.75
Blood loss at Surgery	621.22	489.42	131.80	27.35	.000	65.18	198.42
Intra-operative methyl-ergometrine requirement	210.00	30.00	180.00	37.81	.000	90.47	269.53
Intra-operative oxytocin requirement	589.00	0.00	589.00	153.76	.001	208.88	969.12
Pre-operative and post-operative difference in haematocrit	3.04	1.88	1.160	243	.000	.58	1.74
Length of surgery	46.60	48.80	-2.20	2.88	.948	-9.04	4.64
Length of hospitalisation	5.28	5.42	-1.40	.184	.728	-58	.30
Apgar score at 5 minutes	9.28	9.22	.02	.164	.815	-.41	.37

Table 4
Cross tabulation of Frequency of known misoprostol side effects in the study groups

Side Effect	Study Group		Pearson Chi-Square
	Oxytocin group n=50	misoprostol group n=50(%)	
Severe abdominal pain	2(4%)	5(10%)	.073
Pyrexia	3(6%)	8(16%)	.108
Chills	2(4%)	6(12%)	.135

DISCUSSION

The mean length of surgery in this study of 47.70 ±14.31 minutes, and perhaps in our practice, is significantly longer than 40 minutes as found by Hofmayer and colleagues (1), (WMD= 7.70 95% CI 4.86 – 10.54, p < 0.0001). Modification of Misgav Ladach-Pfannestiel technique as employed in this study has the merits of being quicker to perform than the traditional Pfannestiel. The patients also suffer less post-operative pain and recovery of physiologic function is faster (15). Probable explanation for this difference might be less sophistication in our area of practice compared to studies considered in the meta-analysis by Hofmayer and his team. This mean length of surgery may also explain a significantly higher mean blood loss, 555.32 ±151.34mls (WMD= 55.32, 95% CI 25.29 – 85.35, p<0.0001). However as much as 1000mls of blood is permissible without compromise in an otherwise stable woman (17).

Several studies have demonstrated comparable efficacy between misoprostol and oxytocin in preventing post-partum haemorrhage (18, 19). In majority of these studies misoprostol was employed either vaginally or rectally, and was administered after delivery of the baby.

This study demonstrated that misoprostol when administered sub-lingual 15 to 20 minutes before the baby is delivered is more effective than oxytocin in minimising blood loss at Caesarean operations, (oxytocin versus 400μg-misoprostol; MD 131.80, 95% CI 65.18 – 198.42, p < 0.0001).

Misoprostol will take between 30 to 60 minutes to peak when applied vaginally or rectally, 20 to 30 minutes when administered sub-lingual and when ingested as a solution effect will peak in about ten minutes (20, 21). It would therefore be inferred that in previous studies misoprostol was not being utilised at periods of its maximal effect on uterine activities. This pharmacokinetics informed our employing misprostol sub-lingual and administering it about 15 to 20 minutes before the anticipated delivery.

A similar study in Ibadan Nigeria, a comparable environment, found no significant difference in blood loss between oxytocin and sub-lingual misoprostol at Caesarean operation (22). In the study misoprostol was also administered sub-lingually but after delivery of the baby. In addition, the study considered pre-operative and four hour post-operative difference in haematocrit, a period considered rather short for meaningful reflection of haemodynamic change following moderate to severe blood loss. In this study the difference in haematocrit was between the pre-operative and 24-hour post-operative values. However, this study compared with findings of Vimala and his group in India (23) that demonstrated significant reduction in blood loss in sub-lingual misoprostol group than the intravenous oxytocin group (819mla versus 974mls, p=0.004).

In this study misoprostol at a dose of 400μg was found to be more effective than 20IU of intravenous oxytocin at reducing blood loss at Caesarean operation. Preoperative sub-lingual misoprostol at dose of 400μg was also found to be superior to oxytocin in maintaining the uterine tonus after delivery of the baby as expressed in the extra μg of methyl-ergometrine or mililitre of oxytocin administered intra-operatively to keep the uterus contracted and prevent further blood loss; methyl-ergometrine , (oxytocin versus 400μg-misoprostol; MD 180.00, 95% CI 90.47 – 269.53, p < 0.0001), oxytocin, (oxytocin versus 400μg-misoprostol; MD 589.00, 95% CI 208.88 – 969.12, p = 0.001).

Effectiveness of misoprostol, when administered sub-lingually and pre-operativly, was further expressed in the difference between the pre-operative and 24-hour post-operative haematocrit values, oxytocin versus misoprostol; MD 1.16, 95% CI .58 – 1.74, p < 0.0001. Use of misoprostol in treating or preventing post-partum haemorrhage is limited by side effects such as fever, chills, nausea, headaches, abdominal cramps and pain and these occur more commonly at doses of 800μg or more (11, 20, 24). In this study few side effects of severe abdominal pain, fever and chills were observed more in the misoprostol group than the oxytocin group (Table 4). The differences were, however, not statistically significant.

In conclusion, this study has shown that pre-operative sub-lingual misoprostol, at a dose of 400μg, is more effective in reducing blood loss at Caesarean operations than 20IU intravenous oxytocin. It can be recommended as alternative, or adjunct, to oxytocin in poor-resource settings.

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