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RANDOMIZED CONTROLLED TRIAL OF SUBLINGUAL AND RECTAL MISOPROSTOL ADMINISTRATION ON BLOOD LOSS AT ELECTIVE CAESAREAN SECTION

Omozuwa E.S[1] and Okonkwo C.A[2]

[1]Department of Obstetrics and Gynaecology, Stella Obasanjo Hospital, Benin City.
[2]Department of Obstetrics and Gynaecology, University of Benin Teaching Hospital Benin-City

ABSTRACT: *Background: Misoprostol is widely used in the prophylaxis and treatment of Postpartum Hemorrhage (PPH). However, there is paucity of information on its effect on the volume of blood loss with regard to the route of administration in patients undergoing elective caesarean section. Aim: This study compares the effect of sublingual versus rectal administrations of misoprostol on blood loss in subjects undergoing elective caesarean section. Methodology: An open-label controlled trial was conducted on 72 women undergoing elective caesarean section randomized either to receive 600 µg misoprostol rectally (36 subjects) or sublingually (36 subjects). Blood loss, Hemoglobin (Hb) concentration and Packed Cell Volume (PCV) where measured using Standard Techniques. These in addition to side effects of misoprostol were compared in both groups. Results were expressed as Mean ± S.D were analyzed using Student's t-test and Chi-square and p < 0.05 was considered statistically significant. RESULTS: Mean intraoperative blood loss was significantly less in the sublingual group compared to the rectal group (602.87±131.96 vs 705.83 ± 142.24 ml, p = 0.002. Mean postoperative Hb (g) was higher in the sublingual group 10.00 ± 1.13g/dl vs 9.63 ±0.76 g/dl, p = 0.463. Perioperative Hb fall was less in the sublingual group (1.17 ± 1.08 g/dl vs 1.49 ± 0.99 g/dl, p = 0.193.CONCLUSION: Study suggests that sublingual administration of misoprostol is more effective in reducing intraoperative blood loss at elective Caesarean than rectal administration.*

KEYWORDS: Misoprostol, PPH, Sublingual, Rectal, Caesarean Section

INTRODUCTION

Bleeding is still the major cause of morbidity and mortality in postpartum period. Every minute of every day, a woman dies in pregnancy or childbirth. A remarkable cause of daily maternal mortality is Obstetric haemorrhage and its successful treatment is a challenge for both the developed and developing world (Zhao and Peng, 1998). A myriad of interventions exist to treat postpartum hemorrhage (PPH), ranging from uterotonics and hemostatics to surgical and aortic compression devices (Prata and Weidert, 2016.)

The incidence of Post Partum Hemorrahage (PPH) has been reported to range from less than 5% to greater than10% (Stood and Kumar-Singh, 2012) and these figures remain at least 100 times higher in developing countries than in developed countries. PPH accounts for a quarter of the 55,000 annual maternal deaths in Nigeria (Jadesimi and Okonofua, 2006) and its prevention has been identified as key components of safe motherhood (Stood and Kumar-Singh, 2012)

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The government of Nigeria expressed an indication for wide spread assess to misoprostol in order to meet the Millennium Development Goal of reducing maternal mortality by 75% between 1990 and 2015 and this in addition to an improved access to emergency obstetric care (Jadesimi and Okonofua, 2006; WHO, 2003)

Although Oxytocin is routinely used to prevent uterine atony and excessive uterine bleeding during caesarean delivery, 10 – 40% of women still need additional uterotonic therapy (Stood and Kumar-Singh, 2012; Munn et al., 2001) and a readily available uterotonic drug is misoprostol. For instance Six percent of CS are accompanied with significant bleeding or more than 10% drop in haemoglobin level mandating blood transfusion, therefore, controlling blood loss during CS will prevent morbidity associated with blood transfusion. Oxytocin as a first line uterotonics as well as misoprostol are used for this purpose (Prendiville and Elbourne, 1989; Keirse *et al*., 1995)

In low-income countries, postpartum haemorrhage is a major cause of maternal death (Ronsman and Graham, 2006) and arguably the most preventable. Attempts to reduce deaths from postpartum haemorrhage have been complicated by the fact that many deaths occur out-of-hospital settings or too quickly for the patient to be transferred to a health facility. Furthermore, the prevention and treatment of PPH had depended mainly on injectable uterotonics, which are not readily available outside the health system (Knight, 2007; Ronsmans and Graham, 2006). For these reasons, the use of misoprostol to prevent or treat postpartum haemorrhage has attracted considerable attentions (Norman *et al*., 1991).

Misoprostol is a synthetic prostaglandin E_1 analogue which was originally marketed for treatment and prevention of non-steroidal anti-inflammatory drug-induced peptic ulcer (Monk and Clissold, 1987) was approved as lifesaver for obstetric hemorrhage in developing countries (Jadesimi and Okonofua, 2006). Its uterotonic properties and few adverse effects at therapeutic doses (Goldberg *et al*., 2001). has gained wide use for many obstetrics and gynaecological indications such as induction of labour and medical termination of pregnancy (Kulier *et al*., 2004; Fawole *et al*., 2008; Neilson *et al*., 2006; Menakaya *et al*., 2005)

The administration of misoprostol cuts across the oral, sublingual, vaginal and rectal routes and its freely absorbed in any of routes. Furthermore, its easy availability, relatively low cost, thermo stability, long shelf life, and ease of administration, appear to make it particularly suitable for use in low resource settings in the developing countries (Mun *et al*., 2001; Goldberg *et al*., 2001; WHO, 2007).

Although misoprostol has been extensively evaluated for prevention and treatment of postpartum haemorrhage following vaginal delivery, there have been a few studies evaluating its efficacy in reducing intraoperative blood loss at caesarean delivery.

Misoprostol in these studies has been administered by oral, buccal, sublingual routes and compared mostly with oxytocin administrated as IM/IV bolus, IV infusion, or intrauterine injection or with placebo. Though dose of misoprostol used in these trials are widely varied, most of them found misoprostol as effective (Vimala *et al*., 2006, Hamm *et al*., 2005; Lokugamage *et al*., 2001; Lapaire *et al*., 2006) as in one case more effective than oxytocin (Tang *et al.*, 2005)

Oral, buccal, vaginal, rectal and the sublingual routes have been used in different studies (Mun *et al* ., 2001; Zhao and Peng, 1998; Vimala *et al*., 2006). In most studies, sublingual route was

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considered probably as the best route owing to its better absorption and pharmacokinetic properties (WHO, 2010). While other studies have shown concern about its side effect therefore disagreeing with the above proposal (Chaudhuri *et al*., 2010; Lapaire *et al*., 2006).

While the various studies recognize the efficacy of misoprostol in decreasing intraoperative blood loss, there was no consensus on the most effective route of administrations of misoprostol. Furthermore, a dose-dependent side effects of chills, pyrexia, vomiting e.t.c have been reported as side effects of misoprostol (Gulmezoglu *et al*., 2002; Peyron *et al*., 1993) but no report on the relationship of side effects to the routes of administration of misoprostol.

Hence this study aimed at comparing the relative efficacy of the sublingual and rectal misoprostol in decreasing intraoperative blood loss viz a viz its side effects during caesarean delivery.

METHODOLOGY

Study Population

This prospective open-label parallel-group randomized controlled trial was conducted on 72 women undergoing caesarean section between the September 2017 and September 2018 in Central Hospital, Benin city. Benin is the capital of Edo state and it is an ancient cosmopolitan city in Edo south. The hospital serves as a major referral center to other 34 state hospital with Health Management Board and private hospitals in Edo State. It has 20 gynecological beds and 120 obstetric beds and conducts about 4200 deliveries every year. About 240 cases of Caesarean section are carried out yearly with a Caesarean section rate of 17.5 percent.

Sample Size Calculation

On the basis of previous studies, the mean blood loss with the use of Oxytocin during caesarean section is 500ml with a standard deviation of 213 and Misoprostol can reduce it by 20% (Mohammad *et al*., 2013). Considering 80% power and 5% error, sample size was calculated using the formula by John and Allen, 2011

$$N = n_1 + n_2 = \frac{2\sigma^2\left(Z_{\alpha/2} + Z_{1-\beta}\right)^2}{\delta^2}$$

$$= \frac{2\sigma^2\left(Z_{\alpha/2} + Z_{1-\beta}\right)^2}{\delta^2 = (x_1 - x_2)^2}$$

Where N = the required sample size

σ = standard deviation

$Z_{\alpha/2}$ = 1.96 (standard normal deviate)

$Z_{1-\beta}$ = Desired statistical power ($1 - \beta = 0.80$, $Z_{0.80} = 0.842$)

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Z_α = Standard normal deviate corresponding to the probability α

Z_β = Standard normal deviate corresponding to the probability β

x_1 and x_2 = Refers to the true (or population) means for treatments 1 and 2.

δ^2 = Refers to the true difference between these means $\delta = x_1 - x_2$

x_1 = Mean of group 1

x_2 = Mean of group 2

n_1 = Group 1

n_2 = Group 2

Substituting into the formula above, the minimum sample size for the study was:

$$= \frac{2(213)^2(1.96+0.842)^2}{100^2}$$

$$= \frac{2(45{,}369)(7.851204)}{100^2}$$

$$= \frac{712402.548}{10{,}000}$$

$$= 71.24$$

$$= 71.2$$

$$= \frac{71.2}{2}$$

$$= 35.6$$

$$\approx 36$$

The minimum sample size for each group was 36.

Thus 72 women at Central Hospital, Benin city undergoing elective Caesarean section were randomized either to receive 600 μg misoprostol rectally (36 subjects) or sublingually (36 subjects). Post Caesarean Section Blood loss, hemoglobin concentration, PCV and side effects such as shivering, pyrexia and vomiting were compared in both groups

Informed Consent/Ethical Consideration

Ethical approval was obtained from the Ethics and Research Committee Hospital Management Board Edo State. Informed consents were also obtained from all patients who participated in the study.

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Inclusion criteria

Subjects with the following criteria were included in the study: (i) booked women for antenatal care (ii) elective caesarean section, (iii) nulliparous (iv) primarous women

Exclusion criteria

Subjects with the following criteria were excluded from the study: (i) women with medical conditions such as haemoglobinopathies, pregnancy induced hypertension, HELLP syndrome, gestational diabetes, mothers with macrosomic fetus, sensitivity to prostaglandins, coagulation disorders, asthma, heart, lung and liver disease (ii) twin pregnancy (iii) two or more deliveries (iv) previous caesarean sections, (v) hemoglobin concentration < 10g/dl, (vi) women whose pregnancies were by Assisted Reproductive Technique (vii) women whose spinal anaesthesia failed (viii) women who developed complication during surgery (ix) women who declined consent.

Randomization

Subjects were randomly allocated using a computer-generated random table unto two misoprostol treatment groups: 600 μg of misoprostol per rectum rectally (n=36) and 600 μg of misoprostol sublingual (n=36). Post Caesarean Section Blood loss, hemoglobin concentration, PCV and side effects such as shivering, pyrexia and vomiting were compared in both groups.

Administration of Misoprostol

Misoprostol tablets (Pfizer) ^{Rx} with expiring date 2021 were obtained from the pharmacy department of central hospital Benin. The sachets containing misoprostol were opened in the operating theatre and nobody was blinded to the trial drug i.e. both the investigator and the patient were aware of the drug or treatment being given. In this situation, the criteria set out for the study were strictly followed. Observing the side effects of the trial drug using the correct devices, personnel and repeated measurements were ensured as much as possible.

Procedure for Caesarean Section

All the women had 30 i.u. oxytocin infusion at cord clamping which is routinely used in our centre. All the Caesarean section for the study were performed by consultants and senior registrars in the department including the investigators who performed a larger proportion of the procedures.

All the subjective elements from the outcome measures were removed as much as possible, such as estimating blood loss using the correct and accurate machines and instruments.

Spinal anesthesia was performed on each subject by a consultant anesthetist with the injection deposited between L4 and L5 interspace after preloading with normal saline with a gauge 25 spinal needle. The drug (misoprostol) i.e. 3 tablets (600μg) were placed in the patient's sublingual space or rectum just before the incision was made on the abdomen by the investigator or the anesthetists.

Caesarean sections were performed by Senior registrars and Consultants. Uterine incisions were low transverse type

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. All the women had an intravenous infusion of oxytocin 30 i.u. in 1000ml of normal saline solution commenced immediately after cord clamping up to the end of the operation. The placental was delivered by cord traction. Uterine incisions were closed in two layers with No. 1 polyglactin.

Rectus sheath was approximated with Nylon – 2 sutures. Skin was approximated with subcuticular closure.

Operation time was also recorded using the stop watch taken as the time incision was made on the abdomen to the time of the last stitch in the abdominal repair. The number of days spent in the ward after surgery i.e. the length of post-operative hospital stay was extracted from the follow-up records in the ward.

Measurement of blood loss

During the operation, an isolated suction was used for the evacuation of the amniotic fluid through a small incision over the uterus and another calibrated receiver connected to the suction machine was used to collect the blood loss at surgery separately. A standard mop measuring 30cm by 30 cm was used and weighed before and after surgery to determine their weight differences which was equivalent to the amount of blood in them. The weight of the surgeon gowns and drapes used for the patient were also determined before and after surgery to determine the amount of blood. Every gram increase in the patient's drapes and surgeon's gown weight including the standard mop were considered as 1ml of blood. These items added to the amount of blood collected in the calibrated suction receiver were calculated as the total amount of blood loss during surgery. postpartum hemorrhage was estimated blood loss greater than 1,000 ml. volume of blood suctioned intra operatively, weight of mops preoperatively, weight of mops postoperatively, weight of drapes pre and post operatively, weight of surgeons gowns pre and post operatively. All were summed up to be total blood loss at surgery.

Measurement of Hemoglobin Concentration and Packed Cell Volume

Pre-operative and postoperative packed cell volume and the haemoglobin/haematocrit were measured in both groups using standard laboratory techniques.

Perioperative fall in haemoglobin (Hb) in both groups were calculated from the preoperative haemoglobin level and 24 hours after the operation.

Measurement of Blood Pressure and Pulse Rate

Blood pressures and the pulse rates of the patient were measured using the Omron sphygmomanometer in both groups before the operation and repeated every 5 minutes during the procedure.

Side effects of misoprostol

The side effects of the drugs; shivering, pyrexia and vomiting were observed for their severity and frequency of occurrence and recorded up to 4 hours after the operation in the recovery room. For the pyrexia, patient temperature was measured orally and recorded at interval of 20, 40 and 60 minutes after the operation. Temperature above 38 degrees was considered as hyperpyrexia.

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Data analysis

Data entry and analysis was done using Statistical Package for the Social Sciences (SPSS) IBM Statistical Software data editor version 20 (SPSS Inc., Chicago IL USA). Results were presented as means, standard deviations frequencies and percentages. Statistical analysis of generated data was done using Student t-test and Chi-square test employed as appropriate. Effect confounding variables was checked by the use of logistic regression. Probability level of <0.05 was considered statistically significant.

RESULTS

The characteristics of subjects in both groups of subjects with different routes of administration of misoprostol are shown in table 1. The intraoperative blood loss ranging between < 500 mls to > 1000 mls and the intraoperative hemoglobin concentration in both groups are shown in table 2. The mean intraoperative blood loss was significantly less (p=0.002) in the sublingual group (602.87 ± 131.96 mls) compared to the rectal group (705.83 ± 142.24 mls). The mean postoperative haemoglobin in Hb(g) was empirically higher (p = 0.463) in the sublingual group (10.00 ± 1.13g/dl) than the rectal group (9.83 ± 0.76g/dl). Similarly the perioperative haemoglobin (Hb) fall was less (p = 0.193) in the sublingual group (1.17 ± 1.08g/dl) compared to the rectal group (1.49 ± 0.99 g/dl) as shown in Table 2. The side effects of misoprostol administration in both groups is shown in table 3. Table 4 shows the logistic regression predicting the route of administration from predictor variables (cofounding variables). The odds ratio for perioperative haemoglobin is 1.576. Total blood loss is 0.995. Preoperative is 0.776 while duration of hospital stay 1.094. These indicate that when holding all other variables constant, the perioperative haemoglobin was more likely to affect sublingual route of administration than rectal route when compared to total blood loss.

The categories of surgeons that performed the surgeries viz a viz mean blood loss is shown in figure 1. There were more Senior Registrars [40 (55.6%)] than Consultants [32 (44.4%)] among the category of Surgeons that performed the surgery for the studied population; sublingual route: Consultants 17 (47.2%) and senior registrars 19 (52.8%). Rectal route: Consultants 15 (41.7%) and senior registrars 21 (58.3%). Mean blood loss for the senior registrar for the sublingual group was 633.68 ± 150.78ml. For the consultant in the sublingual group 568.74 ± 100.64. P = 0.141, not statistically significant. Mean blood loss for the senior registrar in the rectal group was 719.05 ± 154.75. For the consultants in the rectal group was 687.33 ± 125.44ml. P = 0.517 was not statistically significant.

Figure 2 represents a figure showing the blood loss in relation to sublingual vs rectal rouetes of misoprostol administration. The figure shows that the total blood loss (ml) from women with rectal route of administration was significantly higher (p = 0.002) than those with sublingual

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Table 5 shows correlation natrix of total blood loss with operative time, perioperative Hb and duration of hospital stay. Figures 3a-c shows scatter plot (regression graph) for estimated blood loss with (a) operating time (b) perioperative Hb (c) duration of hospital stay. There was a weak positive correlation; r = 0.004 and a fair positive correlation; r = 0.147 between total blood loss and operating time in sublingual and rectal route respectively. For each additional time of operation, the total blood loss of sublingual route increased by 0.057ml and rectal route by 2.241ml. The relationship between total blood loss and operating time was not statistically significant in both sublingual route (p=0.980) and rectal route (p=0.392) (Table 5, Figure 3a).

There was a strong positive correlation; r=0.582 and a moderate positive correlation; r = 0.392 between total blood loss and perioperative Hb change in sublingual and rectal respectively. The relationship between total blood loss and perioperative Hb changes was statistically significant in both groups; p < 0.0001 and p =0.018 for sublingual and rectal respectively (Table 5, Figure 3b). There was a moderate positive correlation; r = 0.492 and a fair positive correlation; r =0.094 between total blood loss and duration of hospital stay in sublingual and rectal respectively. The relationship between total blood loss and duration of hospital stay for sublingual was statistically significant (p = 0.002) and rectal was not statistically significant (p = 0.587).

Table I: Women profile and characteristics/indication for Caesarean section

Parameters	**Mean ± S.D**		***P.* value**	**Odds Ratio (OR)**	**95% CI**
	Sublingual misoprostol (n = 36)	**Rectal misoprostol (n = 36)**			
Maternal age (yrs)	28.36 ± 4.18	27.53 ± 3.87	0.383	–	–
Parity (mean)	0.42 ± 0.60	0.28 ± 0.45	0.274	–	–
Primiparous	23 (63.9)	26 (72.2)	0.613	0.681	0.2510 – 1.845
Multiparous	13 (36.1)	10 (27.8)	0.613	1.470	0.5420 – 3.985
Gestational age (wks)	38.31 ± 0.92	38.25 ± 0.87	0.794	–	–
Abnormal lie	17 (47.2)	14 (38.9)	0.3221	1.857	0.6931 – 4.976
Contracted pelvis	09 (25.0)	12 (33.3)	0.7717	0.8448	0.2702 – 2.641
Breech presentation	10 (27.8)	10 (27.8)	0.7717	1.184	0.3786 – 3.701

Abbreviations: CI, Confidence interval; SD, Standard deviation.

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Table 2: Blood loss and hemoglobin concentrations of the two groups of subjects with in misoprostol administration sublingually and rectally

	Mean ± SD		*P.* value	Odds Ratio (OR)	95% CI
	Sublingual misoprostol (n = 36)	Rectal misoprostol (n = 36)			
Estimated blood loss					
Total (ml)	602.87 ± 131.96	705.83 ± 142.24	0.002		
<500 ml	6 (16.7)	2 (5.6)	0.261	3.400	0.6373 – 18.140
500-1000 ml	30 (83.3)	33 (91.7)	0.476	0.455	0.1043 – 1.981
>1000 ml	0 (0.0)	1 (2.8)	0.314	0.324	0.0128 – 8.233
Blood transfusion	1 (2.8)	3 (8.3)	0.607	0.314	0.0311 – 3.176
Postoperative Hb (g/dl)	10.00 ± 1.13	9.83 ± 0.76	0.463		
Preoperative Hb (g/dl)	11.17 ± 1.03	11.32 ± 0.97	0.512		
Perioperative Hb (g/dl) [Preoperative – Postoperative (Hb)]	1.17 ± 1.08	1.49 ± 0.99	0.193		
Operating time (min)	52.92 ± 10.22	55.69 ± 9.34	0.233		

Table 3: Side effects of the drugs and duration of hospital stay

	Number (Percentage) (%)		*P.* value	Odds Ratio (OR)	95% CI
	Sublingual misoprostol (N = 36)	Rectal misoprostol (N = 36)			
Shivering	34 (94.4)	12 (33.3)	<0.0001	34.000	6.962 – 166.05
Pyrexia					
>38°C	2 (5.6)	1 (0.0)	0.555	2.059	0.178 – 23.787
Vomiting	6 (55.6)	4 (0.0)	0.496	1.600	0.411 – 6.234
Hospitalization period (days)	6.00 ± 0.72	6.06 ± 0.79	0.756	–	–

Abbreviations: CI, confidence interval; N = Number
[a] Values are number (percentage)

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Table 4: Logistic Regression Predicting Route of Administration from Predictor variables (cofounding variables)

Predictor	*B*	Wald χ^2	*P*. value	Odds Ratio (OR)	95% CI
Total Blood Loss (ml)	–0.005	3.478	0.062	0.995	0.989 – 1.000
Preoperative Hb (g/dl)	–0.253	0.444	0.505	0.776	0.368 – 1.635
Perioperative Hb (g/dl)	0.455	0.989	0.320	1.576	0.643 – 3.864
Side Effect					
Shivering	–3.601	16.63	<0.0001	0.027	0.005 – 0.154
Pyrexia	–0.909	0.226	0.634	0.403	0.010 – 17.026
[c]Vomiting					
Duration of Hospital stay	0.089	0.029	0.864	1.094	0.393 – 3.045

Abbreviations: CI, confidence interval
[c] Reference category

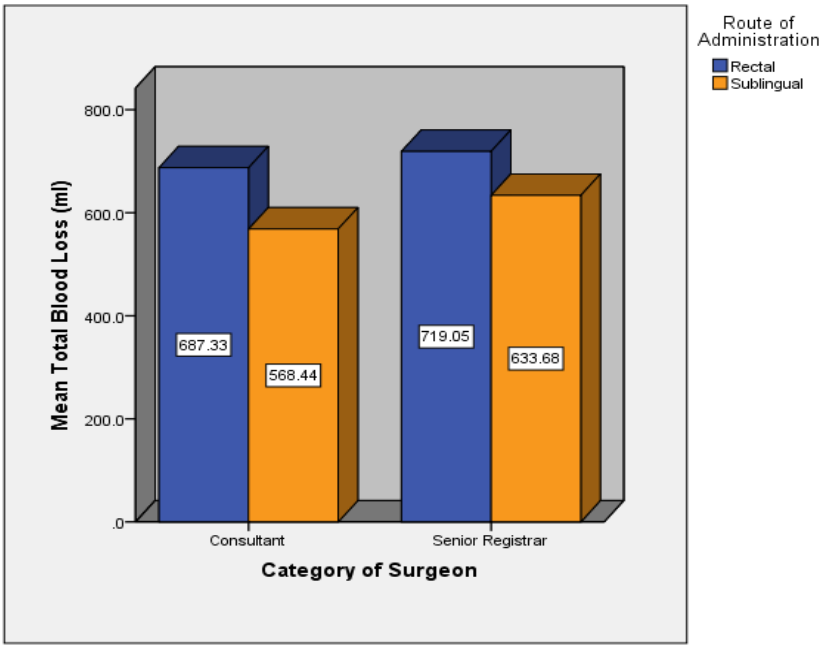

Figure 1: Category of Surgeon that performed surgery for the studied population

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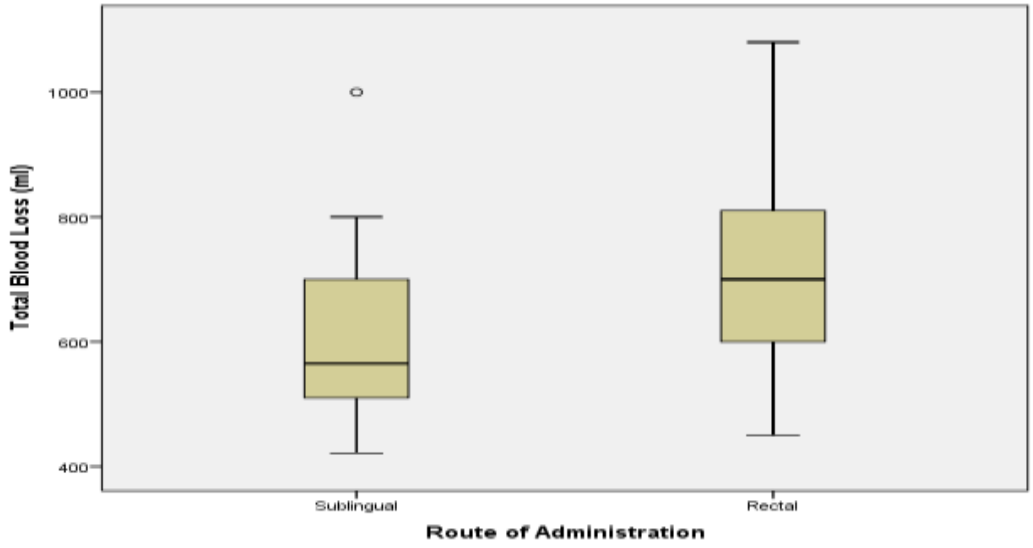

Figure 2: A Box plot showing a graphical illustration of Estimated Blood Loss

Table 5: Correlation matrix of total blood loss with operative time, perioperative Hb and duration of hospital stay

Route of Administration			Total Blood Loss (ml)	Operating Time (mins)	Perioperative Hb (g/dl)	Duration of hospital stay (days)
Sublingual	Total Blood Loss (ml)	r	1	.004	.582**	.492**
		p		.980	.000	.002
	Operating Time (mins)	r	.004	1	-.205	.382*
		p	.980		.230	.021
	Perioperative Hb (g/dl)	r	.582**	-.205	1	.512**
		p	.000	.230		.001
	Duration of hospital stay (days)	r	. 492**	.382*	.512**	1
		p	.002	.021	.001	
Rectal	Total Blood Loss (ml)	r	1	.147	.392*	.094
		p		.392	.018	.587
	Operating Time (mins)	r	.147	1	.337*	.145
		p	.392		.045	.397
	Perioperative Hb (g/dl)	r	.392*	.337*	1	.233
		p	.018	.045		.171
	Duration of hospital stay (days)	r	.094	.145	.233	1
		p	.587	.397	.171	

r = Correlation Coefficient
p = Probability value
**. Correlation is significant at the 0.01 level (2-tailed). *. Correlation is significant at the 0.05 level (2-tailed).

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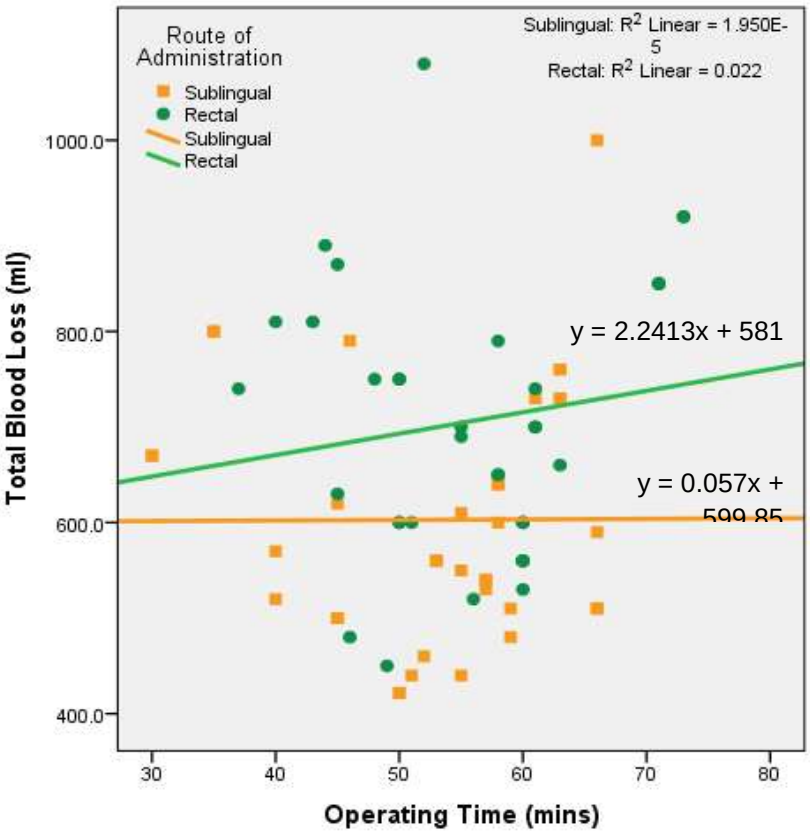
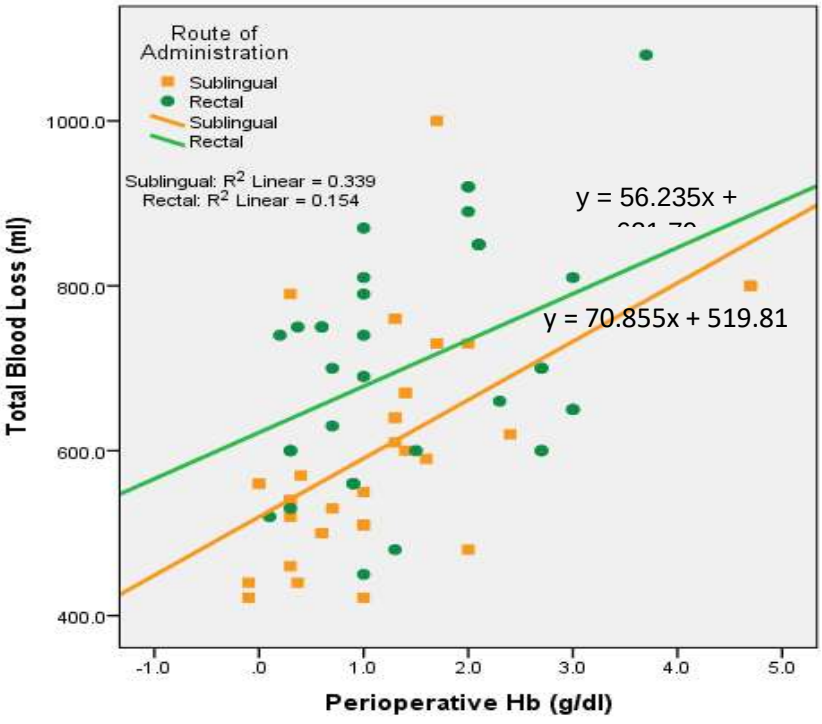


(a)



(b)

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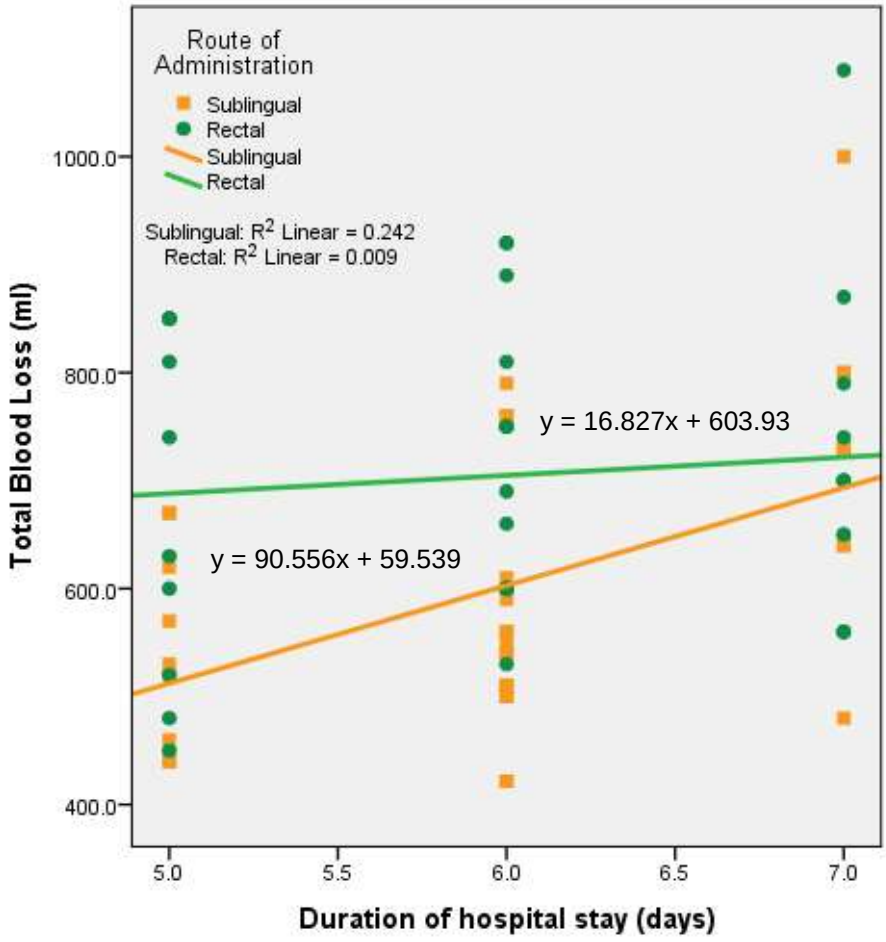

Figure 3c: Scatter plot (Regression graph) for estimated blood loss with (c) duration of hospital stay

DISCUSSION

Maternal mortality secondary to hemorrhage remains a major challenge in low-resource settings, because the intervention recommended for reducing it are neither available nor affordable; therefore increasing access to misoprostol – a synthetic prostaglandin E_1 analogue that is used for a range of obstetric and gynaecologic indications could play an important role (Shannon and Winikoff, 2004).

The effect of oral, sublingual and rectal misoprostol on postpartum haemorrhage in comparison with oxytocin has been documented (El-Refaey *et al*., 1997; Lam *et al*., 2004). Some studies showed that oral or sublingual misoprostol is more effective than oxytocin in preventing haemorrhage during caesarean section (Vimala *et al*., 2006; Hamm *et al*., 2005). While the role of misoprostol in the reduction of postpartum haemorrhage remains indisputable, its route of administration has been a subject of intense debate with regard to the most effective route of administration and the side effects (Vamala *et al*., 2006; Hamm *et al*., 2005; Lokugamage *et al*., 2001).

Print ISSN: ISSN 2053-406X, Online ISSN: ISSN 2053-4078

In this study the subjects who had sublingual administration of misoprostol had less blood loss than their counterparts who had rectal misoprostol and this finding is consistent with other studies (Vamala *et al*., 2006; Zhao *et al*., 1993; Widmer *et al*., 2001). Sublingual misoprostol has been observed to be more effective than intravenous infusion of oxytocin in reducing blood loss during and after cesarean delivery (Othman et al., 2016). However, it is at variance with other other studies (Hamm *et al*., 2005; Acharya *et al*., 2001; Nisa *et al*., 2009). which noted that there was no difference in blood loss between both groups. Variations in observations are attributable to the method of collection and calculation of blood loss during caesarean section. For instance in this study attempts were made at making sure all blood loss during surgery were objectively accounted for by calculating the difference between the total weights of abdominal mops, surgeons gowns and drapes post operatively and pre operatively. This was in addition to the conventional blood loss estimation from the volume of blood in the calibrated suction jar.

Despite the difference in blood loss, the hemoglobin concentrations in both groups were essentially the same. The relatively more fall in Hemoglobin concentration in the rectal group compared to the sublingual group was empirical, however for subjects who have lower normal hemoglobin concentration the sublingual administration of misoprostol may be superior the rectal administration to forestall post-partum hemorrhage. Further statistical analysis in which postoperative Hb was used as one of the determinant of the perioperative Hb fall in the correlation matrix (table 5) of the predictive variables comparing the two routes of misoprostol administration also buttress the fact that there was more blood loss with the rectal group as compared with the sublingual group.

Perioperative haemoglobin difference was another method with which the blood loss could be determined. This is essentially the difference in the haemoglobin concentration pre and postoperatively. In a similar manner the perioperative haemoglobin was noted to be more reduced in the sublingual groups, though not statistically significant. This is similar to the findings in the previous studies (Fekih *et al*., 2009; Acharya *et al*., 2001). These similar results were due to the fact that most of the previous studies were conducted in a tertiary care centres on low risk patients for postpartum haemorrhage.

In this study, the odds ratio for perioperative haemoglobin was 1.576 and total blood was 0.995. This indicates that when all other variables were held constant, the perioperative haemoglobin was more likely to affect sublingual route of administration than the rectal route when compared with respect to the total blood loss. The study also show that there was a strong positive correlation; $r = 0.582$ and a moderate positive correlation $r = 0.392$ between total blood loss and perioperative haemoglobin change in the sublingual and rectal group respectively. The relationship between total blood loss and perioperative haemoglobin changes was statistically significant in both groups ($p < 0.0001$ and $p = 0.0189$ for sublingual and rectal respectively).

The surgeon's skills and expertise have been considered as factors that could influence blood loss during the surgical operations carried out in this study. Therefore, surgeons up to 5 years and beyond in clinical practice with good surgical skills performed all the Caesarean sections for the women used in the study. In the light of this, the blood loss in the 2 groups were not significantly affected by the cadre of surgeons that performed the Caesarean section. These findings were comparable with the results of similar studies (Hogberg, 2003; Fenton, 2003; Okunofua and Dumont, 2001)

Print ISSN: ISSN 2053-406X, Online ISSN: ISSN 2053-4078

In the strength of the above considerations, the distribution of blood loss amongst the categories of surgeons with respect to the route of administration confirmed that the sublingual route of misoprostol administration reduced intraoperative blood loss better than the rectal route.

Blood loss for the senior registrar in the sublingual group was 633.68 ± 150.78ml while for the rectal group was 719.05 ± 154.75 ml, (p = 0.141). Likewise for the consultants in the sublingual group was 568.14 ± 100.64ml and for the rectal group 687.33 ± 125.44 ml (p = 0.517).

Shivering pyrexia and vomiting are notable side effects associated with the use of misoprostol. Shivering compared to pyrexia and vomiting was significantly noted with the sublingual group. This can be explained with the fact that sublingual route tends to have better systemic absorption than the rectal route. These side effects however were noted to be transient and dose dependent. These findings corroborates with other studies (Vimala *et al*., 2006; Owonikoko *et* al., 2011). These side effects were temporary and caused no serious damage nor required a specific treatment and noted not to affect the period of hospitalization in both groups.

Different routes of administration and dose of misoprostol have been used in different studies, sublingual and rectal routes were chosen because they avoid oral intake, does not disrupt operative field and the drugs were administered just before incision was made on the abdomen considering the time of onset of action of misoprostol which in the previous studies was not put into consideration. The routes also ensure continuous plasma level of a potent uterotonic agent over a prolonged period.

In this study, regression analysis revealed a correlation of blood loss, operating time (r = 0.004, p = 0.950), perioperative haemoglobin (r = 0.582, p = 0.001) and duration of hospital stay (r = 0.492, p = 0.002) in the sublingual groups when compared with the rectal groups. Sublingual route therefore, tends to have more of the predictive attributes than that of the rectal route.

CONCLUSION

Sublingual route of administration of misoprostol is more effective in reducing intraoperative blood loss at Caesarean delivery than rectal route.

Limitations of study: The sample size was small and the subjects studied were essentially low risk.

Future planning:

Further studies need to be conducted on high risk cases under strict randomised controlled trial with a larger sample size.

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Conflicting interest

Authors have declared that no conflicting interest exists.

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