**MATERNAL CAESAREAN OUTCOMES FOLLOWING SUBLINGUAL MISOPROSTOL AS AN ADJUNCTIVE INTRAOPERATIVE UTEROTONIC**

**ABSTRACT**

**Background:** This study was aimed at evaluating the safety of adjunctive sublingual misoprostol in reducing intraoperative blood loss during caesarean section, with the objectives of determining the need for additional intraoperative oxytocic, need for postoperative blood transfusion and the side effect profile of the study medications when adjunctive sublingually administered misoprostol is used in preventing excessive blood loss at caesarean delivery.

**Methods:** This study involved one hundred and fifty-two gravidae at term, who were randomised into two trial arms (Misoprostol study arm or the Placebo study arm), having met the inclusion criteria and were scheduled for caesarean section. The misoprostol group received 400-ug of sublingual misoprostol. The control group received two sublingual placebo tablets. Both arms received 30 IU intravenous oxytocin. The primary outcome measure was the need for extra doses of oxytocic. The secondary outcome measures were the need for postoperative blood transfusion and side effect profile of the study medication. A *P* value =.05 was statistically significant.

**Results:** The sublingual misoprostol study arm had a lesser need to receive more oxytocics than the sublingual placebo study arm (11.8% vs 19.7 %), but this was not statistically significant (*P* = .18). The requirement for blood infusion was not statistically significant between the trial arms (*P* = .78), although fewer women were transfused in the misoprostol arm than in the placebo arm of the study (9.2 % vs 10.5%). All cases of shivering were seen in the misoprostol group (88.2 %), and this was statistically significant between the study groups, (*P* = .00).

**Conclusion:**Sublingually administered adjunctive misoprostol at a dose of 400 ug at caesarean birth did not considerably decrease the demand for extra doses of ecbolics, and blood transfusion following the surgery, but caused significant shivering.

*Keywords: Caesarean, misoprostol, oxytocin, outcomes.*

**1. INTRODUCTION**

Misoprostol use as an adjunct to oxytocin to prevent excessive intraoperative blood loss during abdominal delivery has been studied widely. Its use can be associated with outcomes that may be inimical to the particular patient the medication is prescribed to. This unwanted outcomes include; the need for extra doses of oxytocin during surgical birth, the need for intraoperative blood transfusion, and side effects of misoprostol.

Extra doses of oxytocin may expose the patient to undesirable effects such water intoxication, palpitation, abnormal cardiac rhythm, nausea, vomiting, and chest pain (Pakniat & Khezri, 2015). Other side effects experienced include headaches, respiratory distress, hypotension, and hypertension (Widmer et al., 2018; Zeng et al., 1951).If the dosage of misoprostol co-administered with oxytocin is right, the dose of oxytocin needed to bring about effective haemorrhage control at caesarean sections will be reduced. Thus, in essence, the patient is less likely to have the side effects of oxytocin.

It is well known that blood loss is inevitable during surgical birth; and it can subsequently lead to postpartum haemorrhage and its consequences. In the tropics because of the elevated environmental temperatures affecting oxytocin potency, misoprostol may be added to the oxytocic regimen used at abdominal delivery to reduce blood loss, especially for women with risk factors for primary postpartum haemorrhage. If haemorrhage is curtailed postpartum haemorrhage’s consequences will be avoided. These consequences are related to transmission of blood borne infections and blood transfusion reaction. In other words, adequate dosage of misoprostol adjunctively administered may decrease the need for blood transfusion.

Adjunctive misoprostol as an uterotonic is associated with side effects (Sood & Sanjay, 2012). These side effects are dose related. Several dosage of misoprostol have been tried in a bid to reduced blood loss at caesarean section. Smaller doses of misoprostol have been argued to have reduced its side effects such as shivering, fever, nausea and vomiting (Sood & Sanjay, 2012; Agarwal & Thakar, 2022). Using an appropriate dose of the prostaglandin will not only effectively limit haemorrhage at abdominal delivery, but will have lesser and tolerable side effect.

This study was aimed at evaluating the safety of adjunctive sublingual misoprostol in reducing intraoperative blood loss during caesarean section, with objectives of determining the need for additional intraoperative oxytocic, need for postoperative blood transfusion and the side effect profile of the study medications (nausea, vomiting, fever and shivering).

**2. METHODS**

**2.1 Study site**

This study was carried out at the Obstetrics and Gynaecology department of the Federal Medical Centre, Yenagoa, Bayelsa State, Nigeria. The study period was from 1st March to 30th December, 2024.

**2.2** **Study design**

Randomised controlled trial (superiority design).

**2.3 Inclusion criteria**

This included pregnant women at term (37+0 weeks to 41+6 weeks gestational age) for elective or non-elective caesarean sections and had risk factor for primary postpartum haemorrhage.

**2.4 Exclusion criteria**

This included those with: caesarean sections for dire emergencies (umbilical cord prolapse, suspected fetal distress and active antepartum haemorrhage), and caesarean section done under general anaesthesia. Gravid women with previous caesarean deliveries or other uterine surgeries, allergy to misoprostol use, known history of hepatic, renal and haematological disorders, fever (temperature ≥ 37.50c), pre-operative anaemia (pre-operative haematocrit level < 30 %) and eclampsia were excluded from the trial.

**2.5 Sample Size and Randomisation**

A sample size of 152 was gotten using the formula for calculating sample size for a superiority randomized controlled trial; as shown below:

 $n=\frac{2 X (Z\_{α}+ Z\_{в} )^{2} σ^{2}}{( μ\_{1}- μ\_{2 } - ẟ)^{2}}$

Where ‘n’ is the minimum sample size needed for the study, $Z\_{α}$ is the standard normal deviate at 95 % confidence level taken as 1.96 for a two-tail study, $Z\_{в}$ is the power of the study and power of 80 % (0.84) would be adopted for this study, $σ^{2}$ is the standard deviation of the mean in blood loss from a previous study (Ugwu et al.; 2014). An attrition rate of 20 % was put into consideration in arriving at the sample size. Eligible participants that were greater than or equals to 18 years of age at the point of obtaining informed written consent for abdominal birth (at the labour ward for emergency/urgent cases or at the antenatal ward for elective cases), were educated about the study.

The random allocation of the participants in this study was done using the WIN PEPI software. The WIN PEPI software was used to allocate numbers 1 to 152 randomly into two equal groups (A and B), hence generating a randomization list. After obtaining an informed consent from a participant, the participant was allocated to either group “A” or group “B”.

Firstly, every participant was requested by the researcher/research assistant(s) to pick a tag bearing a number from a box (Research ballot box). The box contained tags numbered from 1 to 152. Once a numbered tag was picked, that tag was not be replaced till the end of the research.

The researcher/research assistant(s) gave the numbered tag to a research clerk(s) (circulating theatre nurses) who in turn looked at the randomization list generated using the WIN PEPI software, and allocated the participants to either study group (‘A’ or ‘B’) corresponding to the number on the tag the participants had randomly picked.

**2.6 BLINDING**

Misoprostol tablets and the inactive tablets (placebo) were manufactured by a hospital’s pharmacist. The placebo tablets contained a starch base only, while the active tablets contained 200 ug of misoprostol each.

Both the active and inactive tablets had the same size, colour and smell. The misoprostol tablets and placebo tablets were packed in envelopes, which were sealed and labelled by the pharmacist.

Each envelope packed by the pharmacist contained three (3) active tablets (containing misoprostol) or three (3) placebo tablets.

Only the circulating theatre nurses held the randomization lists until the end of the trial. Their sole activity was to allocate participants to their randomly picked study groups.

In this research, each study participant received two sublingually administered tablets, either misoprostol tablets if in the misoprostol study group or placebo tablets if in the placebo study group.

**2.7 Data collection**

The research team comprised of the researcher, and ten research assistants. The caesarean sections were performed by at least a second year senior registrar, following standard lower uterine segment technique to avoid the bias of surgical skill.

At point of opening the parietal peritoneum at caesarean section, the anaesthetic nurse sublingually administered two tablets to the study participants, 400 ug misoprostol tablets to the misoprostol study arm or two placebo tablets (which contained a starch base) to the placebo study arm. The anaesthetist in charge of the surgery administered to all study participants, at the time of the clamping of the umbilical cord, 10 IU of intravenous bolus of oxytocin followed by an infusion of 20 IU of oxytocin in 500 ml of normal saline at a rate of twenty drops per minute which ran over eight hours. The oxytocin ampoules used in the study were of the same brand and batch.

The primary outcome measure was the need for extra doses of oxytocic. The secondary outcome measures were the need for postoperative blood transfusion and side effect profile of the study medication (nausea, vomiting, fever and shivering).

**2.8 Assessment of the need for additional intraoperative oxytocic**

After administering the study medications, the uterus was palpated for adequate uterine contraction after 10 minutes period. If the uterus was not tonically contracted as confirmed by the chief surgeon, an extra dose of 10 IU of oxytocin was given intravenously. A repeat of another 10 IU of intravenous oxytocin bolus was given after 10 minutes if there was still uterine atony. Intramuscular ergometrine at a dose of 0.5 mg was used as a secondary uterotonic agent, where there were no contraindications, after 10 minutes of administering the second additional 10 IU of intravenous oxytocin bolus.

In a bid to reduce the limitation brought about by the subjective assessment of the occurrence of uterine atony by the lead surgeon; the assistant surgeon and the perioperative nurse also palpated the uterus intra-operatively, and in concordance with the lead surgeon, confirmed the presence of uterine atony. Study participants who developed primary postpartum haemorrhage were treated using the standard management protocol for primary postpartum haemorrhage.

**2.9 Assessment of the need for post-operative blood transfusion**

The demand for transfusing blood was met when a study’s participant lost up to and above 1 litre of blood during the surgical delivery or she had a 48-hours postoperative packed cell volume < 24 %. Furthermore, 48-hours post-surgical packed cell volume ≥ 24 %, but < 30 % with symptoms of anaemia (such as dizziness, fainting spells or persistent headaches) was also an indication to transfuse blood.

**2.10 Assessment of the occurrence of side effects**

After the study intervention had been administered to four hours post-caesarean section, the investigator and or research assistants asked the study participants at one-hourly interval if they had experienced nausea, shivering or have vomited. A stat dose of intramuscular 600 mg paracetamol was administered to study participants that developed shivering. In other to assess the body temperature, an axillary mercury-in-glass thermometer was placed in the study participants’ axillae for three minutes by the investigator or research assistants. The axillary temperature was taken hourly from the end of surgery till 4-hours post-caesarean section. An axillary temperature of ≥ 37.50c was taken as pyrexia (Odinaka et al., 2016).

The axillary temperature was recorded in a temperature observation chart for a 4-hour postoperative observation period. A stat dose of intramuscular 600 mg paracetamol was administered to the study participants that developed fever.

**2.11 Data Analysis**

All data extracted were subjected to statistical analysis using the IBM SPSS version 25.0. Categorical variables were summarized in frequencies and proportions, and presented in figures and tables. Continuous variables were summarized in mean/standard deviations. The intention-to-treat (ITT) principle of analyzing randomized controlled trials (RCT) was deployed in analyzing the data from the study. Chi-square test and t-test were used as appropriate. A *P-*value = .05 was considered statistically significant.

**3. RESULTS**

One hundred and ninety-eight pregnant women were screened for the trial, out of which 152 pregnant women (76.8 %) who met the eligibility criteria were recruited into the trial. Equal number of them (76) were allocated randomly to both the Misoprostol study arm (Study arm “A”) and the Placebo arm (Study arm “B”).

**3.1 DEMOGRAPHIC/ MATERNAL CHARACTERISTICS OF PARTICIPANTS**

As depicted in Table 1, about three out of every ten participants were in the 30 - 34 years or the 35 -39 years age range, (31.6%) and (32.9 %) respectively. The 25 - 29 years age range, and then the 20 - 24 years age range, had the next highest number of study participants, (18.4 %) and (10.5 %), respectively. The proportion of participants in the greater than 40 years age range formed the least of the total number of participants (6.6 %). The mean ages for all the study participants was 32.59 ± 5.97 years. There was no statistically significant difference on comparing the study groups in terms of their age (*P* = .69).

Nulliparous patients formed the bulk of all study participants (46.1 %), this translated to a little under five participants out of every ten participants. The multiparous category for the participants’ parity had the second highest number of participants (33.6 %) followed by the primiparous category (15.1 %). About 5.3% of the study participants were grandmultiparous. There was no statistically significant dissimilarity between both trial arms as regards the participants’ parity (*P* = .80).

Just under two-fifth of the study participants were 37 weeks pregnant (36.8 %), and about one-third of the participants were of 38 weeks gestational age (30.3%). About 11.2 % of the women were post-date (41 weeks pregnant). Thirty-nine and forty weekers constituted a low number of the participants, 9.9 % and 11.8 %, respectively. As regards the participants’ gestational ages, there was no statistically significant dissimilarity between the misoprostol and the placebo study arms (*P* = .97).

**Table 1: Demographic/maternal characteristics of participants**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Characteristics** | **Total****N = 152 (%)** | **Study Groups** | **Test Statistics****(*P*-Value)** |
|  | **Sublingual Misoprostol****N = 76 (%)** | **Sublingual Placebo****N = 76 (%)** |
|  | **Age group** |  |  |  |  |
|  | 20 -24 years | 16 (10.5) | 7 (9.2) | 9 (11.8) | 2.20 (.69) |
|  | 25 - 29 years | 28 (18.4) | 13 (17.1) | 15 (19.7) |
|  | 30 - 34 years | 48 (31.6) | 28 (36.8) | 20 (26.3) |  |
|  | 35 - 39 years | 50 (32.9) | 24 (31.6) | 26 (34.2) |  |
|  | > 40 years | 10 (6.6) | 4 (5.3) | 6 (7.9) |  |
|  |  **Age in years – Mean ± SD** | 32.59 ± 5.97 | 32.22± 5.28 | 32.17 ± 5.77 |  |
|  |  |  |  |  |  |
|  | **Parity** |  |  |  |  |
|  | Nulliparous | 70 (46.1) | 36 (47.4) | 34 (44.7) | 0.96 (.80) |
|  | Primiparous | 23 (15.1) | 10 (13.2) | 13 (17.1) |
|  | Multiparous | 51 (33.6) | 25 (32.9) | 26 (34.2) |  |
|  | Grandmultiparous | 8 (5.3) | 5 (6.6) | 3 (3.9) |  |
|  | **Parity – Median (Range)** | 1.0 (1.0 – 4.0) | 1 (1.0 – 4.0)  | 1 (1.0 – 4.0) |  |
|  |  |  |  |  |  |
|  | **Gestational Age** |  |  |  |  |
|  | 37 weeks | 56 (36.8) | 27 (35.5) | 29 (38.2) | 0.50 (.97) |
|  | 38 weeks | 46 (30.3) | 22 (28.9) | 24 (31.6) |
|  | 39 weeks | 15 (9.9) | 8 (10.5) | 7 (9.2) |  |
|  | 40 weeks | 18 (11.8) | 10 (13.2) | 8 (10.5) |  |
|  | 41 weeks | 17 (11.2) | 9 (11.8) | 8 (10.5) |  |
|  | **Gestational Age in weeks \_ Mean ± SD** | 38.3 ± 1.36 | 38.3 ± 1.36 | 38.3 ± 1.36 |  |

**3.2 THE NEED FOR ADDITIONAL OXYTOCIC AND BLOOD TRANSFUSION**

Table 2 demonstrates the requirement for extra doses of intraoperative oxytocic and the exigency for postoperative administration of blood following abdominal delivery between the study groups. In terms of the need for additional intraoperative oxytocic, the sublingual misoprostol study arm had a lesser need to receive more oxytocics during caesarean birth than the sublingual placebo study arm (11.8% vs 19.7 %), respectively, but this was not statistically significant (*P* = .18). The requirement for blood infusion postoperatively, was not analytically dissimilar between the trial arms, (*P* = .78).

**Table 2: The need for additional oxytocic and blood transfusion**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Characteristics** | **Total****N = 152 (%)** | **Study Groups** | **Test Statistics****(*P* -Value)** |
|  | **Sublingual Misoprostol****N = 76 (%)** | **Sublingual Placebo****N = 76 (%)** |
|  | **Need For Additional Intraoperative Oxytocic** |  |  |
|  | Yes  | 24 (15.8) | 9 (11.8) | 15 (19.7) | 1.78 (.18) |
|  | No  | 128 (84.2) | 67 (88.2) | 61 (80.3) |
|  |  |  |  |  |  |
|  | **Need for Post-Operative Blood Transfusion** |  |  |
|  | Yes  | 15 (9.9) | 7 (9.2) | 8 (10.5) | 0.07 (.78) |
|  | No  | 137 (90.1) | 69 (90.8) | 68 (89.5) |

**3.3 SIDE EFFECT PROFILE OF THE STUDY MEDICATIONS**

Table 3 shows the side effect of the study medications in the sublingual misoprostol and sublingual placebo study groups. All cases of shivering were seen in the misoprostol group (88.2 %), and this was statistically significant, (*P* = .00). The occurrence of fever, nausea and vomiting were similar between both study groups.

**Table 3: Side effect profile of the study medications**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Characteristics** | **Total****N = 152 (%)** | **Study Groups** | **Test Statistics****(*P* - Value)** |
|  | **Sublingual Misoprostol****N = 76 (%)** | **Sublingual Placebo****N = 76 (%)** |
|  | **Shivering** |  |  |  |  |
|  | Yes  | 67 (44.1) | 67 (88.2) | 0 (0.0) | 119.81 (.00\*) |
|  | No  | 85 (55.9) | 9 (11.8) | 76 (100.0) |
|  |  |  |  |  |  |
|  | **Fever** |  |  |  |  |
|  | Yes  | 5 (3.3) | 2 (2.6) | 3 (3.9) | .20 (.64) |
|  | No  | 147 (96.7) | 74 (97.4) | 73 (96.1) |
|  |  |  |  |  |  |
|  | **Nausea** |  |  |  |  |
|  | Yes  | 11 (7.2) | 6 (7.9) | 5 (6.6) | .98 (.74) |
|  | No  | 141 (92.8) | 70 (92.1) | 71 (93.4) |
|  |  |  |  |  |  |
|  | **Vomiting** |  |  |  |  |
|  | Yes  | 6 (3.9) | 5 (6.6) | 1 (1.3) | .77 (.96) |
|  | No  | 146 (96.1) | 71 (93.4) | 75 (98.7) |

\*Statistically significant

**DISCUSSION**

The dose of misoprostolin lowering bleeding at surgical delivery is important (Sweed et al., 2019).If given in high doses, the side effect(s) of misoprostol are expected. These side effects can be really discomforting for the parturient, sometimes life threatening (uterine rupture), and troubling for the obstetric team. Nonetheless, too little administered dose of misoprostol may make the uterotonic effect of the drug non-existent when trying to curtail blood loss at surgical births (Sweed et al., 2019).

A majority of the participants in this research were of low parity. This finding is in keeping with that of other studies (Akpan et al., 2021; Nayak et al., 2017; Karya et al., 2021; Kumari et al., 2016). A possible reason may be that, in the locality where this study was done, the nulliparous and primiparous women, unlike the multiparae, tend to book for antenatal care. There is a common belief, and from primary researcher’s observations, that multiparous women in Southern Nigeria, especially grandmultiparous women, feel “experienced” concerning the events of pregnancy and labour. Therefore, they do not make themselves available for hospitalised care. Contraception may also play a role in this present work having low parity participants. The need to keep family size small due to economic hardship and lifestyle modernization may make women seek modern methods of preventing conception or illegally abortions.

The mean gestational age for the abdominal deliveries in this study (38.3 ±1.36 weeks) is similar to those of other studies (Ugwu et al., 2014; Sallam & Shady, 2018). Also, Maged et al., 2019; Afkham et al., 2022 and Sitaula et al., 2016, had gravid women with similar gestational ages participate in their studies.A good number of women would enter into labour after 38 weeks gestation, so elective caesarean sections are usually planned for 38 weeks in most hospitals in Nigeria. However, this finding differed from a study by Akpan et al., 2021, which had a mean gestational age of 31.6 ± 4.3 at delivery. Akpan et al., 2021 study involved women with placenta praevia. Consequently, it is expected that many of the women did not get to term, since they may have early warning bleeds, which may be torrentially, usually occurring around 32 to 34 weeks gestational age (Wagner, 2013).

As regards the demand for additional intra-surgical ecbolics on either the oxytocin alone or the misoprostol-oxytocin arms, it was noticed that in the works of Ugwu et al., 2014; Sood et al., 2012; and Agarwal & Thakar, 2022 as well as Sallam & Shady, 2018and Mohamed & Mohammed, 2021, the exigency for more oxytocics was higher on both arms of their studies than in this present work. This occurrence may be due to the fact that only the lead operator determined the need for extra doses of ecbolics. This may be an assessment bias. This present study reduced this bias by having the perioperative nurse and assistant surgeon palpate the uterus for its tonicity. So, in essence, a consensus with the primary surgeon was met before extra doses of uterotonics was administered. Therefore, intra-observer error/ judgment as regards assessing uterine tone was reduced.

Interestingly, the request for extra dose of ecbolics was lower in Kumari et al., 2016 trial when put side by side with this present work. This is so because in the former study 200 ug of rectal misoprostol was used as against 400 ug of sublingual misoprostol used in this present trial.

The exigency for supplementary dose of ecbolics intraoperatively was analytically similar between the adjunctive misoprostol arm and the oxytocin alone arm of this study, although the participants in the prostaglandin arm required lesser doses of extra uterotonic. In other researches, more doses of oxytocin were given to parturients in the standard arm than in the experimental arm, and this was statistically significant.(Sood & Sanjay, 2012; Agarwal & Thakar 2022; Ugwu et al.,2014; Sallam & Shady, 2018) This discrepancy as seen between this present work and that of other works could be explained by the fact that in this present research, as explained earlier, the lead surgeon, assistant surgeon and the theatre scrub nurse palpated the uterus for normal tonicity and in concordance declared whether or not extra doses of oxytocin should be given.

One of the implication of having a reduced, but non-significant need for additional oxytocic in this study may mean that the sample size of this study may have to be increased in a subsequent study or a multi-centred study performed, so that the carried out analysis in this present work may become statistically/mathematically significant. Another implication is that, in clinical practice this observed finding may be important enough to warrant attention, and cause a modification in uterotonic therapy regimen following caesarean birth, despite not reaching statistically significance.

The exigency for transfusing blood in both study groups of this present trial is low when compared to that of Sallam & Shady, 2018 study, because the blood loss was more at surgery in the latter study. This discrepancy could be traced to the use of visual assessment of haemorrhage in the Sallam & Shady, 2018 study. The reverse was the case when this current study was compared with Ugwu et al., 2014 study,where lesser amount of blood loss in both arms of their trial caused a lower demand for postoperative blood administration.

Sood & Sanjay, 2012 trial which compared 400 ug sublingual misoprostol-20 IU oxytocin combination to 20 IU of oxytocin alone, had similar amount of intraoperative blood loss with this current work, but the requirement for blood administration was lower. This is explained by the use of other indications for blood administration, other than intraoperative blood loss greater than one litre, in this present research. Other indications as stated in this current study were postoperative packed cell volume level less than 24 %, packed cell volume greater than or equals to 24 %, but less than 30 % in the presence of the symptoms of anaemia.

There was no appreciable dissimilarity in the requirement for blood administration after surgery between both investigative arms of this study, but the misoprostol arm had a lesser need for postoperative blood transfusion. This result is similar to those of Ugwu et al., 2014 and Sood & Sanjay, 2012, but incongruous with the findings of Agarwal & Thakar, 2022; and Nayak et al., 2017studies. The Nayak et al., 2017 study did show that misoprostol group had lesser demand for blood transfusion, and it was statistically significant. The disparity between Nayak et al., 2017 work and that of this present trial may be due to the fact that in Nayak et al., 2017 work, the amount of caesarean blood loss was quantified up to 2-hours post-surgery. This extra- two hours of blood loss assessment was added to the intraoperative haemorrhage. In this present study, the quantity of blood loss was assessed only during the surgery. In the Agarwal & Thakar, 2022 study, intraoperative blood loss may have been overestimated because of the use of Bourke and Smith formula. It stands to reason that the more the amount of haemorrhage at caesarean delivery, the higher the need for blood transfusion.

As regards the side effect profile of the study medications, in this present study, there were more cases of shivering (88.2 %) in the misoprostol-oxytocin combination group than that in Sood & Sanjay, 2012 (21.1 %), Rekha & Latha, 2014 (24 %), Agarwal & Thakar, 2022 (62.3 %), and Sallam & Shady, 2018 (37.8 %) trials. The possible explanation may be that the adverse effects were assessed up to 4-hours after surgery in this present study. Thus, within this period more women would have been observed to develop side effects such as shivering than in other studies. Another reason may be the employment of 1-hourly assessment for shivering in the participants of this present work. This offered timely observation and documentation of the occurrence of shivering in this research. Also, the misoprostol-oxytocin arm in this current work had a higher number of shivering cases than noticed in Karya et al., 2021 (7 %) and Kumari et al., 2016 (9 %) works. This disparity may be due to the administration of misoprostol via the rectal route in the latter studies. It obvious from this research and the above studies that shivering tend to feature more with sublingual administration of misoprostol than rectal misoprostol. This may be due to the proximity of the sublingual route to the thermoregulatory centres of the brain, unlike the rectal route. The incidence of nausea and vomiting may be generally low and of similar incidence whichever the route, sublingual or rectal, because misoprostol overall has a protective effect on the gastrointestinal system.

The oral, buccal, and sublingual routes of misoprostol administration are associated with more and severe untoward effect of the drug than the rectal and vaginal routes. Women have been found to experience more fever and shivering on taking sublingual misoprostol.

There was no case of fever in this present study, unlike in the investigative arm of the following studies (Kumari et al., 2016; Sallam & Shady, 2018; Rekha& Latha, 2014). This difference again can be said to result from a 4-hour observation period after surgery in this current research. The other studies had a longer period of observation. Therefore, pyrexia appears to occur after 4-hours of misoprostol administration.

This study demonstrated that shivering as an adverse effect of misoprostol occurred only in the misoprostol-oxytocin arm of the trial than in the oxytocin alone arm. This was the same finding as was seen in Rekha & Latha, 2014 study. Other studies (Kumari et al., 2016; Sallam & Shady, 2018; Mohamed & Mohammed, 2021) showed that shivering also occurred in the oxytocin alone arm of their research. This disparity between this finding in these studies and that of this present work may be due to the larger sample sizes in the former.

 Nonetheless, fever, nausea and vomiting occurrences were similar between both study groups in the current research. This same finding was reported by Sood & Sanjay, 2012 and Rekha & Latha, 2014 (with the exception of the occurrence of fever).

**CONCLUSION**

Sublingually administered adjunctive misoprostol at a dose of 400 ug to intravenous oxytocin at caesarean birth did not considerably decrease the demand for extra doses of ecbolics, and blood transfusion following the surgery, but caused significant shivering.

From the findings of this research, it is suggested that a large multicenter study, with a larger sample size, may need to be done in order to further validate this research’s findings.

**DISCLAIMER (ARTIFICIAL INTELLIGENCE)**

Authors hereby declare that NO generated AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

**ACKNOWLEDGEMENTS**

We appreciate the staff of the department of Obstetrics and Gynaecology, Federal Medical Centre, Yenagoa for creating a conducive environment for this study to be carried out. We acknowledge the financial contributions of Lovstar Academy and PIO Pharmacy, Old PDP road, Yenagoa, Bayelsa, towards this trial.

**COMPETING INTERESTS**

Authors have declared that no competing interest exists.

**AUTHORS’ CONTRIBUTIONS**

Author A\* designed the study, wrote the protocol and first draft of the manuscript, and managed the literature searches. ‘Author B’ and ‘Author C’ prove read and corrected the protocol and the first draft of manuscript. ‘Author D’ and ‘Author E’ were involved in the data analysis. ‘Authors A\*, and ‘Authors A’, collected data, and also performed the data analysis. ‘Author A’ wrote the final manuscript. All authors read and approved the final manuscript.

**CONSENT**

Written informed consent was secured from all participants after explaining the aim and objectives of the study, procedure and potential risks.

**ETHICAL APPROVAL**

All authors declare that the study was approved by the ethical committee of the Federal Medical Centre, Yenagoa with application form number – FMCY/REC/ECC/2022/JULY/477, and the study have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

**REFERENCES**

Afkham, M.S; Hashemnejad, M; Saeieh; et al. (2022). Prophylactic effect of rectal and sublingual misoprostol on postpartum haemorrhage in mothers with pre-eclampsia following caesarean surgery: a double randomised controlled trial. Annals of Medicine and Surgery, 80:104175.

Agarwal, S & Thakar, N.D. (2022). Sublingual misoprostol to reduce blood loss at caesarean delivery. International Journal of Reproduction, Contraception and Obstetrics and Gynecology, 11(1):95-99.

Akpan, U; Asibong, U; Arogundade, K; et al. (2021). Effectiveness of Pre-operative Rectal Misoprostol in Reducing Blood Loss during Caesarean section for Placenta Previa and Manual Removal of Retained Placenta: A Parallel Placebo-Controlled Study. Open Access Maced. Journal of Medical Science, 9(B):161-166.

Karya, U; Maheshwari, S & Rani, A. (2021). Uterotonic effect of rectal misoprostol of intraoperative and postoperative blood loss in caesarean delivery. International Journal of Reproduction, Contraception, Obstetrics and Gynecology, 10(4):1415-1420.

Kumari, K.A; Swathi, E & Saranu, S. (2016). Impact of preoperative 200 ug (P/R) per rectal misoprostol on blood loss during and after caesarean delivery. International Archives of Integrated Medicine, 3(6):49-58.

Maged, A; Fawzi, T; Shalaby, M; et al. (2019). A randomised controlled trial of the safety and efficacy of preoperative rectal misoprostol on preoperative and postoperative blood loss at elective caesarean delivery. International Journal of Gynaecology and Obstetrics, 147:102-107.

Mohamed, A.M & Mohammed, A.H. (2021). Impact of preoperative Rectal versus Intraoperative Sublingual misoprostol on Blood loss during Caesarean section: A randomised controlled trial. Thai Journal of Obstetrics and Gynecology, 29(1):48-52.

Nayak, L; Pradhank, K & Mishra, S. (2017). Role of 400 ug intraoperative sublingual misoprostol for reduction of caesarean section blood loss. Journal of Evidence Based Medicine and Healthcare, 4(10), 573-577.

Odinaka, K.K; Nwolisa, E.C; Alfred, I.C; et al. (2016). Can axillary temperature reliably screen for fever in under 5 children? Tropical Journal of Medical Research, 19: 145-151.

Pakniat, H & Khezri, M.B. (2015). The effect of combined oxytocin-misoprostol versus oxytocin and misoprostol alone in reducing blood loss at Caesarean delivery: a prospective randomised double –blind study. Journal of Obstetrics and Gynaecology of India, 65:376-381.

Sallam, H.F & Shady, N.W. (2018) Adjunctive sublingual misoprostol for secondary prevention of postpartum haemorrhage during caesarean delivery: double blind placebo randomized controlled trial. International Journal of Reproduction, Contraception, Obstetrics and Gynecology, 7(2):495-502.

Sitaula, S; Uprety, D.K; Thakur, A; et al. (2016). Impact of preoperative rectal misoprostol on blood loss during and after elective caesarean delivery. A Randomised Controlled Trial. Nepal Journal of Obstetrics and Gynaecology, 22(2):41-44.

Sood, A.K & Sanjay, S. (2012). Sublingual Misoprostol to Reduce Blood Loss at Caesarean Delivery. The Journal of Obstetrics and Gyecology of India, 62(2):162-167.

Sweed, M; El-Said, M; Abou –Gamrah, A; et al. (2019). Comparison between 200 ug, 400ug and 600 ug rectal misoprostol before caesarean section. A randomized clinical trial. Journal of Obstetrics and Gynaecology Research, 45(3): 585-591.

Rekha, P & Latha, K. (2014). Sublingual misoprostol to reduce blood loss at Caesarean section. International Journal of Modern Research and Reviews, 2(10):444-446.

Ugwu, I.A; Enabor, O.O, Adeyemi, A.B; et al. (2014). Sublingual misoprostol to decrease blood loss after caesarean delivery. A randomized controlled trial. Journal of Obstetrics and Gynaecology, 34:407-411.

Wagner, S.A. (2013). Third-Trimester vaginal bleeding. In: A.H Decherney, L Nathan, N Laufer & A.S Roman (Eds). Current Diagnosis and Treatment, Obstetrics and Gynaecology (11th ed; pp.314). Cenveo Publisher Services, Byrdhill Road Richmond, VA 23228, US.

Widmer, M; Piaggio, G; Nguyen, T.M.H; et al. (2018). Heat-stable carbetocin versus oxytocin to prevent hemorrhage after vaginal birth. The New England Journal of Medicine, 379: 743-752.

Zeng, Y; Zhang, Y; Zhen, M; et al. (2022). Side effect of oxytocin in postpartum haemorrhage: a systematic review and meta-analysis. American Journal of Translational Research, 15; 14(3):1934-1951.