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ORIGINAL RESEARCH

A Randomized comparison of 400µg and 600µg sublingual misoprostol doses prevention of post-partum haemorrhage after caesarean delivery

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ABSTRACT

Background: PPH may occur due to failure of uterine contraction after delivery and subsequently leading to loss of 500 ml or more blood during vaginal delivery and 1000 ml or more during caesarean delivery. Misoprostol is prostaglandin can be given by oral, vaginal, sub lingual and rectal route. Its dose may vary from 200 µg to 1000 µg. **Aim:** To compare the efficacy and side effects of 2 sublingual dose of Misoprostol for prevention of PPH. **Methodology:** The present observational study was conducted to compare the effectiveness of sublingual misoprostol 2 dose for prevention of post-partum haemorrhage in patient with caesarean delivery. A total 200 subjects were divided into 2 groups namely M400, and M600. M400 group was to receive 400ug of Misoprostol and M600 group was to receive 600ug of Misoprostol immediate after opening the peritoneum. **Result:** The lowest mean blood loss was seen in the patients who received 600µg in Sublingual Misoprostol group, followed by 400µg Sublingual Misoprostol group. 10.0% case in 400µg and 5.0% case in 600 µg Sublingual Misoprostol group total blood loss was >1000ml. There was significant lower duration of 3rd stage of labour in 600µg dose of Sublingual misoprostol. In 400µg Sublingual Misoprostol 5.0% cases needed one unit and 5.0% cases needed more than one unit blood transfusion. The increased incidence of side effects (like shivering, fever, Abdominal Pain, Nausea &vomiting, Hypotension and Tachycardia) with increase dose of sublingual misoprostol. **Conclusion:** The lower doses of misoprostol may be as effective as high doses. Clinical applications of low doses of sublingual misoprostol for the prevention of PPH should be further explored by large randomized trials comparing the effectiveness and the safety of low doses of sublingual misoprostol.

Keywords: misoprostol, postpartum haemorrhage, blood loss, uterotonic, fever

INTRODUCTION

Postpartum haemorrhage (PPH) is one of the most common obstetric maternal complications and is among the three most common etiologies of maternal death worldwide.[1] Its incidence is increasing and it affects 1–5% of all deliveries.[2,3] The risk of PPH is further increased in the presence of risk factors such as multiple pregnancy, polyhydramnios, grand multiparty, severe preeclampsia, prepartum haemorrhage, prolonged and obstructed labour, augmented labor, obesity, and anaemia.[4] It is a preventable complication and its prevention is considered to be vital and logistic means for bringing down maternal mortality rate and thus accepted as a key component of safe motherhood. Atony is the main cause of PPH and is responsible for about 80% of PPH events.[5]

Misoprostol, a synthetic prostaglandin with uterotonic properties, has been proposed as an alternative strategy for prevention of PPH in settings where oxytocin use is not feasible. It has important advantages over oxytocin, including the potential for oral administration and a long shelf life at room temperature.[6] Moreover, misoprostol can be administered sublingually, enabling a more rapid onset of action and greater bioavailability by avoiding

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first-pass metabolism.[7] These characteristics have led civil society organizations in Uganda to champion increased accessibility and use of misoprostol as a complementary drug to oxytocin in prevention of PPH.[8] Yet despite these advantages, sublingual misoprostol remains a second-line option to injectable uterotonics according to most recommending agencies because of insufficient or conflicting evidence about its efficacy in the active management of the third stage of labor.[9,10] Although prior studies have compared injectable oxytocin with misoprostol, the comparative efficacy of sublingual misoprostol versus oxytocin remains largely unknown because prior studies have focused on oral administration of misoprostol by less skilled birth attendants, evaluated oral as opposed to sublingual administration of misoprostol, or evaluated suboptimal doses of either oxytocin, other injectable uterotonics, or misoprostol.[11]

Because of conflicting and insufficient data of misoprostol,[12] despite of its lots of advantages, it remains second line to injectables uterotonic according to most recommending agencies.[10] Comparative benefit of sublingual misoprostol to that of oxytocin remains doubtful because of unavailability of many research articles and prior studies mostly compared oral or rectal misoprostol with oxytocin or have compared sub optimal dose of either misoprostol or oxytocin.[11]

Unfortunately, oxytocin needs to be kept cool, which limits its use in low- and middle-income countries, and, until recently, it was thought that only trained personnel could give intramuscular injections. Consequently, administration of misoprostol, a synthetic prostaglandin that has effects similar to those of oxytocin, has been proposed as an alternative way to prevent postpartum haemorrhage in resource-limited settings. Misoprostol is stable at room temperature, and because it can be given sublingually (beneath the tongue), it acts very quickly. However, the comparative efficacy of sublingual misoprostol and intramuscular oxytocin for the prevention of postpartum haemorrhage has not been established. A randomized controlled trial compares the outcomes of individuals assigned to different interventions through the play of chance. In a double-blinded trial, neither the researchers nor the participants know who is receiving which intervention. In this particular trial, double-blinding is achieved by giving a dummy (placebo) sublingual pill to the women assigned to the oxytocin group and a dummy injection to the women assigned to the misoprostol group, as well as their assigned treatments. A non-inferiority trial investigates whether one treatment is not worse than another treatment.

MATERIAL & METHODS

The present observational study was conducted to compare the effectiveness of sublingual misoprostol 2 dose for prevention of post-partum haemorrhage in patient with caesarean delivery. The study done in the Department of Pharmacology, Rama Medical College and Research Centre, Hapur, Uttar Pradesh, India. Women between ages 18-35 years, scheduled for primary caesarean delivery and with gestational age >34 weeks were enrolled in this study. Women discharged before 24 hours of delivery, history of PPH, history of Antepartum haemorrhage (APH), previous caesarean section, anaemia (Hb <10g/dl), pre-eclampsia/ HELLP syndrome, Polyhydramnios (Amniotic fluid index more than 24) and with infection were excluded from the study.

A total 200 subjects were divided into 2 groups namely M400and M 600. M400 group was to receive 400ug of Misoprostol and M600 was to receive 600 ug of Misoprostol immediate after opening the peritoneum. Total blood loss in 2 hours after was collected after draining all amniotic fluid in small tray and absorbed into sterile gauze. Blood collected in tray was measured using measuring cup and blood soaked in gauze was measured by its weight difference before and after soaking blood. Volume was determined on the basis that 1.05 gram is equivalent to 1 ml of blood. Neonatal weight was measured soon after delivery and recorded. Collection of blood was done up to 24 hours of delivery and its measurement is recorded. All patients were assessed for adverse effects such as nausea, shivering, fever, hypotension, and tachycardia, and the results were recorded.

Mean and standard deviation (±SD) were used to describe quantitative data meeting normal distribution. Continuous two independent groups were compared by parametric independent Paired t test or Independent Sample t test. Discrete (categorical) groups were compared by chi-square ($\chi 2$) test. p values less than 0.05 ($p<0.05$) was considered as statistically significant and $P\leq 0.01$ was considered as highly significant.

OBSERVATION & RESULTS

The total blood loss >500ml was recorded in the 35.0% cases in 600µg and 15.0% in 400µg in Sublingual Misoprostol group; But 10.0% case in 400µg Sublingual Misoprostol group and 5.0% case in 600µg Sublingual Misoprostol group total blood loss was >1000ml **[Figure 1]**. The results showed no significant difference in average blood loss between the two groups. The 400µg group had an average blood loss of 507.00ml (±308.97 SD), while the 600µg group had an average blood loss of 452.00ml (±306.62 SD). Statistical analysis revealed a t-value of 0.565 and a p-value of 0.575, indicating no statistically significant difference ($p>0.05$) between the two doses. This suggests that both doses of sublingual Misoprostol have similar effects on blood loss, and the higher dose does not provide additional benefits in this regard [**Table 1**].

Significant decreases in haemoglobin ($p<0.001$) and haematocrit ($p<0.001$) levels in both groups. No

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significant differences between the two dose groups in terms of haemoglobin (p=0.876 pre-op, p=0.095 post-op) and haematocrit (p=0.841 pre-op, p=0.172 post-op) levels. In 400µg group, Haemoglobin 10.12±1.33 (pre-op) to 8.61±1.46 (post-op), Haematocrit 33.90±3.96 (pre-op) to 31.05±3.73 (post-op). And in 600µg group, Haemoglobin 10.14±1.64 (pre-op) to 8.83±1.49 (post-op), Haematocrit 33.20±3.64 (pre-op) to 30.80±3.89 (post-op). These findings suggest that both doses of sublingual Misoprostol result in significant blood loss, but there is no significant difference in efficacy between the two doses [**Table 2**].

No significant difference in haemoglobin level loss between the two doses (400µg: 1.50±0.74 vs 600µg: 1.31±0.63, t=0.902, p=0.373). No significant difference in haematocrit value loss between the two doses (400µg: 2.85±1.31 vs 600µg: 2.40±1.35, t=1.069, p=0.292). These findings suggest that both doses of sublingual Misoprostol result in similar blood loss, as measured by changes in haemoglobin and haematocrit levels. The study indicates that increasing the dose from 400µg to 600µg does not provide additional benefits in reducing blood loss **[Table 3]**.

In figure 2 we compare the average duration of 3rd stage of labour with different 2 doses of Sublingual misoprostol. The minimum average duration of 3rd stage of labour was 6.63±1.77 min in 600µg in Sublingual Misoprostol group and it was 7.12±1.31 min in 400µg in Sublingual Misoprostol group. By using the Independent Sample t test, we observed that there was significant deference in dose of Sublingual misoprostol on average duration of 3rd stage of labour($p<0.05$) [**Figure2**].

In 400µg Sublingual Misoprostol 10.0% cases and 5.0% cases needed additional use of other uterotonic drugs in 600 µg Sublingual Misoprostol [**Figure 4**]. In 400µg Sublingual Misoprostol 5.0% cases needed one unit and 5.0% cases needed more than one unit blood transfusion. While in case of 600µg Sublingual Misoprostol group 5.0% cases of needed one unit blood transfusion [**Figure3**].

This study compares the adverse drug reactions (ADRs) of sublingual Misoprostol at two different doses: 400µg (n=100) and 600µg (n=100). The results show a significant dose-dependent increase in ADRs. In the 600µg group, 10% of patients experienced fever, 15% experienced shivering, 15% experienced abdominal pain, 20% experienced nausea and vomiting, 5% experienced hypotension, and 10% experienced tachycardia. In contrast, the 400µg group reported significantly lower rates of ADRs, with 5% experiencing fever, shivering, nausea and vomiting, and tachycardia, and no cases of abdominal pain or hypotension. These findings suggest that the 600µg dose of sublingual Misoprostol is associated with a higher incidence of adverse effects, emphasizing the importance of careful dose selection to minimize risks. [**Table 4**].

Figure 1: Compare the >500ml and >1000ml blood loss with different 2 doses of Sublingual misoprostol

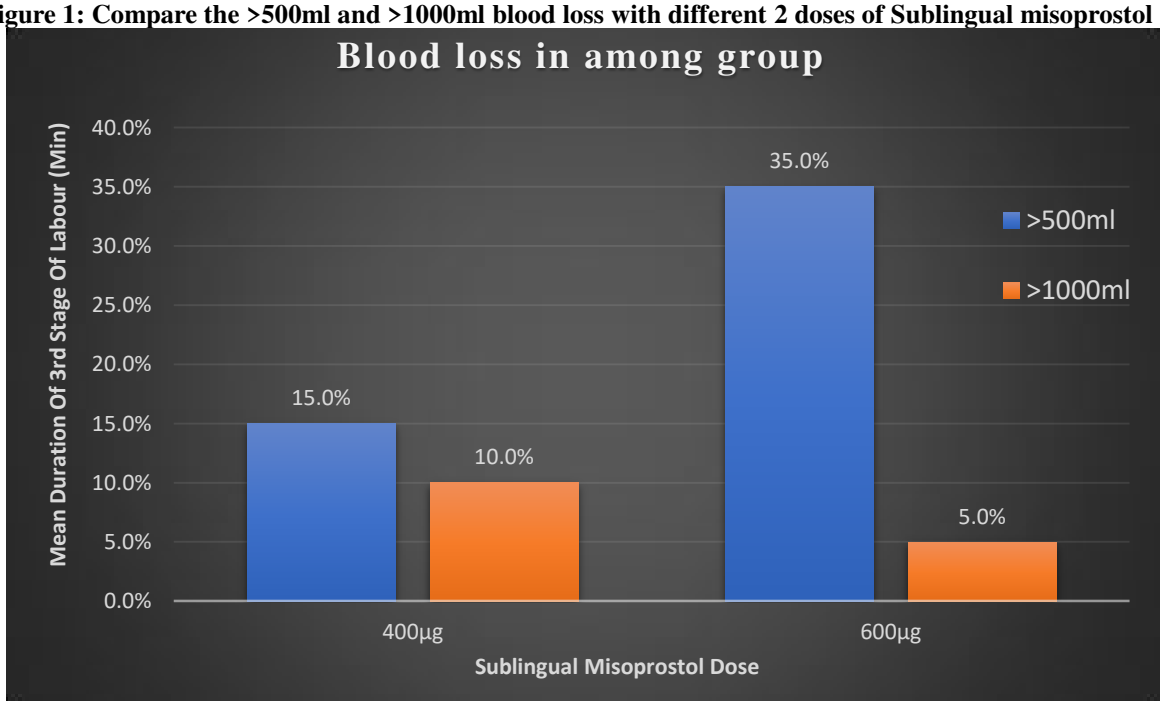

Table 1: Compare the total blood loss with different 2 doses of Sublingual misoprostol

Sublingual Misoprostol Dose	Average blood loss (ml)		t value	p vale
	Mean±SD	Mean±SD		
400µg vs 600µg	507.00±308.97	452.00±306.62	0.565	0.575

Independent Sample t test

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Table 2: Compare the total haemoglobin level loss and haematocrit value loss with different doses of Sublingual misoprostol.

Vairiables	Sublingual Misoprostol Dose	Frequency (n=200)	Pre-operative	Post-operative	P value*
Haemoglobin level loss	**400µg**	100	10.12±1.33	8.61±1.46	**<0.001**
	600µg	100	10.14±1.64	8.83±1.49	**<0.001**
Inter Group p value#			0.876	0.095	
Haematocrit value loss	**400µg**	100	33.90±3.96	31.05±3.73	**<0.001**
	600µg	100	33.20±3.64	30.80±3.89	**<0.001**
Inter Group p value#			0.841	0.172	

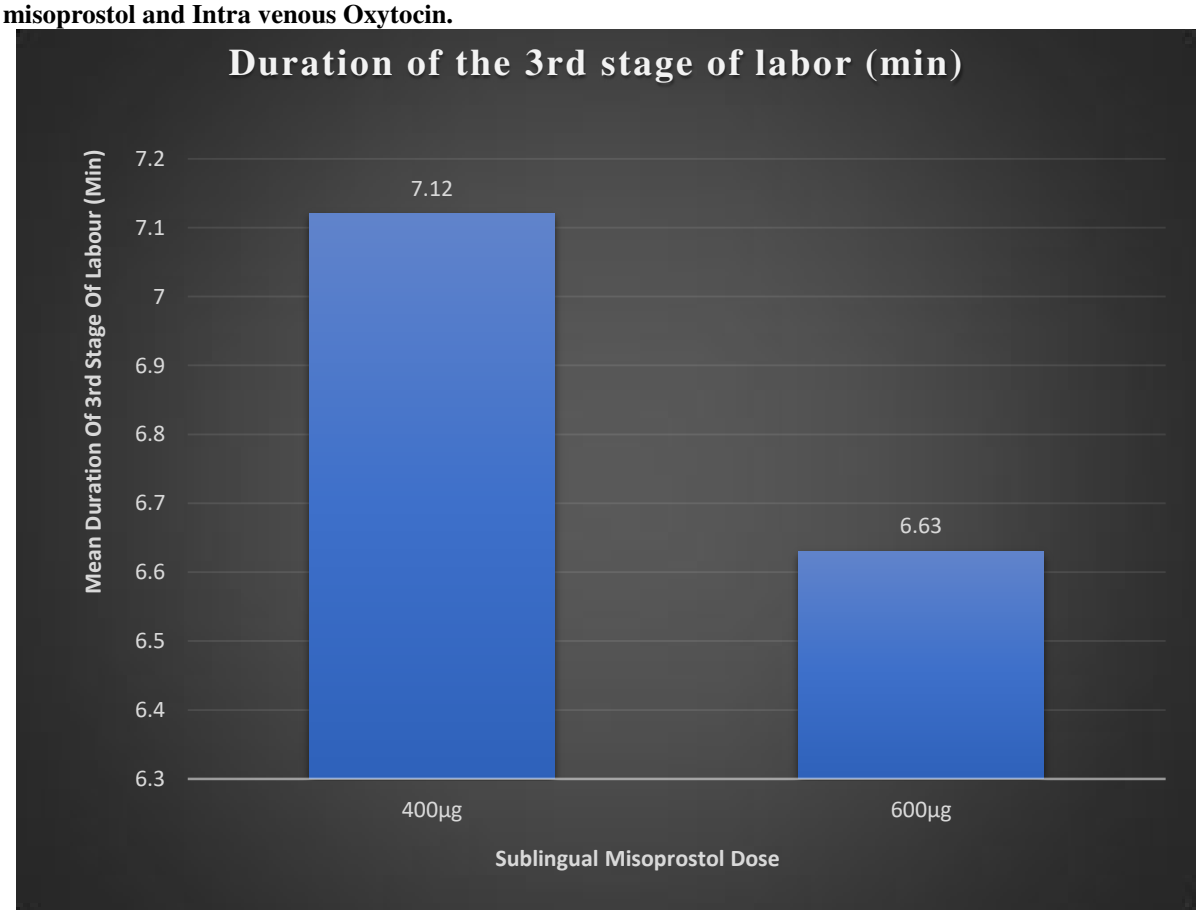
***Paired t test; #Independent Sample t test**

Table 3: Compare the mean difference in average haemoglobin level loss and haematocrit value loss with different doses of Sublingual misoprostol.

Sublingual Misoprostol Dose	Haemoglobin level loss		t value	p value
	Mean±SD	Mean±SD		
400µg vs 600µg	1.50±0.74	1.31±0.63	0.902	0.373
Haematocrit value loss				
400µg vs 600µg	2.85±1.31	2.40±1.35	1.069	0.292

Independent Sample t test

Figure2: Compare the average duration of 3rd stage of labour with different doses of Sublingual misoprostol and Intra venous Oxytocin.



***Independent Sample t test; p value=0.007;**

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Figure3: Compare the need of additional use of other uterotonic drugs with different doses of Sublingual misoprostol and Intra venous Oxytocin.

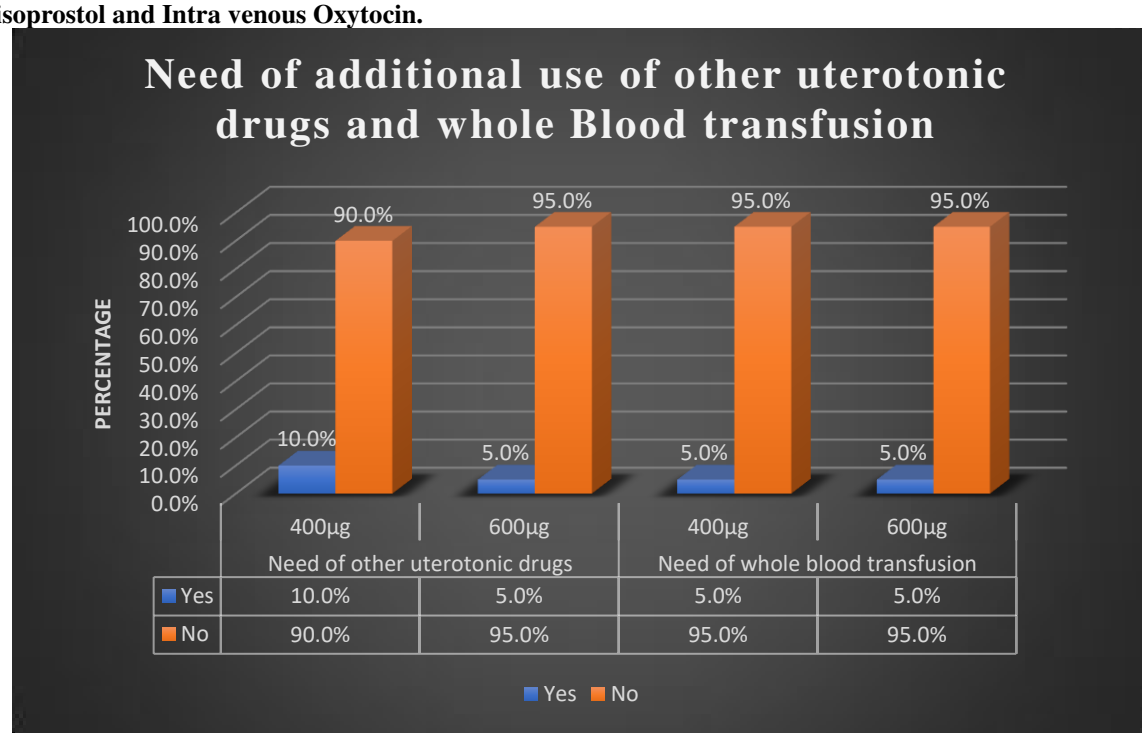

Table 4: Adverse drug reaction with different 2doses of Sublingual misoprostol

Adverse drug reaction	Sublingual Misoprostol Dose	
	400µg (n=100)	600µg (n=100)
Fever	5 (5.0%)	10 (10.0%)
Shivering	10 (10.0%)	15 (15.0%)
Abdominal Pain	0 (0.0%)	15 (15.0%)
Nausea and vomiting	5 (5.0%)	20 (20.0%)
Hypotension	0 (0.0%)	5 (5.0%)
Tachycardia	5 (5.0%)	10 (10.0%)

DISCUSSION

Misoprostol is an artificial analog of prostaglandin E1, which is approved for prevention of peptic ulcers according to pharmacopeia. It can also be used to treat atonic uterus and prevent PPH. In contrast to methylergonovine and carboprost, misoprostol is administrable for women with hypertension and asthma.[13]Misoprostol is preferred because it is easy to keep at room temperature, there is no need for an additional device to infuse it, and it has a low price in developing countries.'[14,15] However, misoprostol has limited side effects, for example fever, shivering, and nausea, which are transient.[16]

The present study is aimed tocompared the effect of various 2 dose of 400and 600µg of sublingual misoprostol in Ringer-lactate to reduce PPH and its adverse effects after cesarean delivery.**Sringamwong W et al**[17] also performed a randomised study of the optimal dose of misoprostol combined with oxytocin for preventing postpartum hemorrhage in cesarean section and concluded that either 400, 600 or 800 µg of misoprostol can prevent PPH similarly. However, the study prefers 400µg misoprostol because of minimization the side effects. While **Sood AK & Singh S**[18]conducted a prospective randomized placebo-controlled trial of the sublingual misoprostol to reduce blood loss at cesarean delivery and concluded that the sublingual misoprostol decreases intraoperative blood loss and the need for additional uterotonic agents at cesarean delivery.

Table 4: Compare the blood loss in various dose of Sublingual Misoprostol in our study withprevious studies

Sublingual Misoprostol Dose	Present study	Sringamwong W et al[17]	Leon W et al[19]
400µg	507.00±308.97	510.0 ml	--
600µg	452.00±306.62	465.7 ml	1000 ml

The lower mean blood loss was seen in the patients who received 600µg in Sublingual Misoprostol group, in compare to who received 400µg Sublingual Misoprostol group. Like our study **Sringamwong W**

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et al[17] also reported the mothers who received higher misoprostol dosage demonstrated lower blood loss. Each three different doses of misoprostol were supported by many prior literatures and all publication reported an effectiveness in reduction of PPH when combined with oxytocin.[20,21,22,23] Several comparison trails also summarized the positive impact of misoprostol 600 µg and 800 µg.[24,25] In 2020, **Alalfy Met al**[25] also published an efficacy of 400 µg of misoprostol in reduction of PPH.

The total blood loss >500ml was recorded in the 35.0% cases in 600µg and 15.0% in 400µg in Sublingual Misoprostol group; But 10.0% case in 400µg Sublingual Misoprostol group and 5.0% case in 600µg Sublingual Misoprostol group total blood loss was >1000ml. The lower blood loss was observed in 600µg Sublingual Misoprostol group in compare to 400µg sublingual misoprostol group. **Sringamwong W et al**[17] also reported thatin addition, intra-operative blood loss ≥500 ml occurred less frequently in patients receiving higher doses of misoprostol. There were 29.4%, 35.3% and 45.4% of the cases in the 800 µg, 600 µg and 400 µg misoprostol groups respectively. But another previous study **Leon W et al**[19] reported that the intra-operative blood loss ≥500 ml occurred less frequently in patients receiving 600µ of misoprostol (10.0%) in compare to 17.8% in patients receiving 800µ of misoprostol. These variations were due variation in study sample size, inclusion and exclusion criteria.

In present study we noted that in Hb and Hct values, however, minimization of intra-operative blood loss should be considered to stabilize a hemodynamic of the mothers who might have an un-discovery underlying health problem. In addition, post-operative Hb and Hct values changing can develop and stabilize within 24–48 h after acute hemorrhage,[26] and the timing of blood specimen collection might interfere with laboratory result.

When we compare the average duration of 3rd stage of labour with different 2 doses of Sublingual misoprostol. We noted that there was significant lower duration of 3rd stage of labour in 600µg dose of Sublingual misoprostol on average duration of 3rd stage of labour($p<0.05$). **Sharma T & Jaju PB**[27]concluded that the context of active management of 3rd grade labour.

In 400µg Sublingual Misoprostol 10.0% cases and 5.0% cases needed additional use of other uterotonic drugs in 600µg Sublingual Misoprostol. **Mukta M & Sahay PB**[28] reported the additional need for uterotonic drugs to be higher in the misoprostol group (22%). **Abd Allah WAE et al**[29] reported that13.0% patients in misoprostol group who need to additional uterotonic drugs.

In 400µg Sublingual Misoprostol 5.0% cases needed one unit and 5.0% cases needed more than one unit blood transfusion. While in case of 600µg Sublingual Misoprostol group 5.0% cases needed one unit blood transfusion. **Pakniat H et al**[30]reported that the total bleeding was significantly lower in sublingual misoprostol as compared to the tranexamic acid group. **Ahmed AA et al**[31]reported that the administration of misoprostol 400mcg through intrauterine route appears to be less effective in reducing blood loss during and after CS. **Nahar K et al**[32]stated that the sublingual misoprostol at 200 µg with its thermostability may be an effective alternative to intramuscular oxytocin in active management of third stage of labor. **Vodouhe MV et al**[33]reported that the 600 µg of misoprostol dose by sublingual route is also as effective as oxytocin in the prevention of postpartum haemorrhage without significant side effects.

The common side effect of misoprostol is pyrexia that is defined as an un-explained asymptomatic raising of body temperature. Although pyrexia is self-limited and usually mild degree, rarely in severe form of hyperthermia, mother usually expresses uncomfortable and anxious.[34] This experience will delay timing of maternal and child first contact after birth. This study reported high rate of pyrexia in all groups (52–62%) when compared to prior studies in variable doses of misoprostol.[24,34] However, previous randomized study trail in 2018 demonstrated pyrexia in 66.7% of 800 µg intrauterine misoprostol that slightly increased than the recent study.[20] The high percentage of pyrexia related to high dosage of misoprostol which similar to systematic review in 2019.[24] Nausea and vomiting were also mentioned in the prior literatures of various misoprostol dosage in 0.8–23%.[24,35]

Our study noted that the increased incidence of side effects (like shivering, fever, Abdominal Pain, Nausea &vomiting, Hypotension and Tachycardia) with increase dose of sublingual misoprostol. Which is similar to that reported in the literature by **Acharya G et al,**[36] **Hamm J et al**[37]and **Vimala N et al**[38]. Dose of misoprostol in various studies has ranged from 200 to 800 mcg reported by **Acharya G et al,**[36] **Zhao Y et al,**[39] **Lokugamage AU et al,**[40] **Hamm J et al,**[37]and**Vimala N et al**[38]. As the side effects are dose related, a dose of 400 mcg was chosen in the present study to minimize maternal adverse effects with optimal therapeutic benefit. **Hofmeyr GJ et al**[41] reported that the, 400 mcg of misoprostol was found to be safer than 600 mcg and just as effective. **Sood AK & Singh S**[18]alsoreported that the shivering, pyrexia, nausea vomiting, and diarrhea are common adverse effects of misoprostol and are dose related.

LIMITATION

The present study was conducted at single centre and not double-blinded. Furthermore, the sample size in each group was small.

CONCLUSION

In conclusion, our findings advocate that lower doses of misoprostol may be as effective as high doses in term of total blood loss and loss of hematocrit level.

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Study results suggests that 600µg sublingual misoprostol is more effective in preventing the fall in hemoglobin level in compare to 400µg sublingual misoprostol. Clinical applications of low doses of sublingual misoprostol for the prevention of PPH should be further explored by large randomized trials comparing the effectiveness and the safety of low doses of sublingual misoprostol. Nevertheless, in undeveloped countries like India and areas without appropriate hospital care and educated midwives, without proper cold-chain facilities misoprostol is a suitable alternative to prevent PPH.

In low-income countries, maternal anemia compounds the problem of PPH, and therefore administration of sublingual misoprostol at delivery of the anterior shoulder could reduce maternal morbidity and mortality. Avoiding the intravenous or intramuscular route allows easier administration, and this could lead to widespread acceptance of active management of the third stage of labor. Any attempt to keep blood loss less than 100 mL would be a substantial intervention in low-resource settings where most women are anemic, and a blood loss of even 500 mL may have adverse effects.

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