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Dose and side effects of Misoprostol for prevention of PPH: A Randomized comparison of 3 sublingual doses

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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 cesarean 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 3 sublingual dose of Misoprostol for prevention of PPH.

Methodology: The present interventionstudy was conducted to compare the effectiveness of sublingual misoprostol 3 dose for prevention of post-partum haemorrhage in patient with caesarean delivery. A total 60 subjects were divided into 3 groups namely M400, M600, and M 800. M400 group received 400ug of sublingual Misoprostol, M600 group received 600ug of sublingual Misoprostol and M800 received 800 ug of sublingual Misoprostol immediately after opening the peritoneum.

Result: The lowest mean blood loss was seen in the patients who received 800µg Sublingual Misoprostol, followed by 600µg and 400µg Sublingual Misoprostol. In 10.0% case in 400µg and 5.0% case in 600 µg and 800 µg Sublingual Misoprostol group, total blood loss was >1000ml. There was significant lower duration of 3rd stage of labour in 800µg dose of Sublingual misoprostol in comparison to 400 ug& 600ug 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 was more with increased dose of sublingual misoprostol.

Conclusion: The lower doses of misoprostol may be as effective as high doses in term of total blood loss and loss of hematocrit level as there was no significant difference between 3 sublingual dosages of 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.

Keywords: misoprostol, postpartum hemorrhage, 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 labor, 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 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 injectablesuterotonic 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

This randomized trial was done to evaluate the efficacy & side effects of 3 dosage of sublingual misoprostol in preventing postpartum hemorrhage in patients who have had cesarean deliveries, this interventional trial was carried out in the Department of Obstetrics &Gynaecology at Lord Buddha Koshi Medical College and Hospital in Saharsha, Bihar, India, in cooperation with the department of pharmacology at RMCH, BareillyWomen 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 60 subjects were divided into 3 groups namely M400, M600, and M 800. M400 group received 400ug of sublingual Misoprostol, M600 group received 600ug of sublingual Misoprostol and M800 received 800 ug of sublingual Misoprostol immediately after opening the peritoneum. Total blood loss in the initial 24 hours was estimated by two methods. The first one was the measurement of the volume component of blood, which wasthe measurement of blood volume collected in a suction canister after the delivery of the baby. The second one was the mass component, which was estimated by measuring the blood-soaked under-buttock blood adsorbing pads, blood-soaked mops, blood-soaked gauze pieces and blood-soaked towels and sanitary pad used for the initial 24 hours of delivery. The weight of blood was determined by subtracting the dry weight of the adsorbing material from the wet weight of subsequent materials. Volume was determined on the basis that 1 gram is equivalent to 1 ml of blood. A 5 ml venous blood sample was collected from all the selected subjects for the measurement of haemoglobin and haematocrit value before and after 24 hours of the start of the procedure. Neonatal weight was measured soon after delivery and recorded. Blood was drawn up to 24 hours after birth, and its volume was noted. Adverse symptoms such as nausea, shivering, fever, hypotension, and tachycardia were evaluated in all patients, and the findings were documented.

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 One Way ANOVA 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, 15.0% in 400µg and 10.0% cases in 800µg in Sublingual Misoprostol group; But 10.0% case in 400µg Sublingual Misoprostol group and 5.0% case in 600 µg Sublingual Misoprostol and 800 µg Sublingual Misoprostol group total blood loss was >1000ml**[Figure 1]**.The lowest mean blood loss was seen in the patients who received 800µg in Sublingual Misoprostol group (397.00±234.23ml), followed by 600µg Sublingual Misoprostol group (452.00±306.62 ml), and 400µg Sublingual Misoprostol group (507.00±308.97 ml). The minimum blood loss was observed in 800µg Sublingual Misoprostol group and the maximum blood loss was in 400µg sublingual misoprostol group. On applying the One Way ANOVA test we noted that it was statistically insignificant ($p>0.05$)[**Table 1**]. When we compare the mean difference of total blood loss on

the given doses of Sublingual Misoprostol and our study noted that there was no statistically significant difference were in study groups [**Table 1**].

The mean ± SD decline in haemoglobin level loss after 24 hours of delivery was 1.50%±0.74% in 400µg sublingual misoprostol group, 1.31±0.63 in 600µg misoprostol group and 0.69±0.29 in 800µg misoprostol group. By using the paired t test we noted that there was significantly reduce the post-operative haemoglobin level loss in several groups in compare to pre-operative ($p<0.05$) [**Table 2**].The mean±SD decline in haematocrit level loss after 24 hours of delivery was 2.85%±1.31% in 400µg misoprostol group, 3 2.40±1.35% in 600µg misoprostol group and 2.15±0.99% in 800µg misoprostol group. By using the paired t test, we noted that there was significantly reduce the post-operative haematocrit level loss in several groups in compare to pre-operative ($p<0.05$) [**Table 2**].

Postoperative loss of haemoglobin level in 800µg Sublingual Misoprostol Dose was significantly lower than the 400µg and 600µg Sublingual Misoprostol Dose ($p<0.05$). While Postoperative loss of Haematocrit value was insignificantly distributed in among 400µg, 600µg and 800µg Sublingual Misoprostol Dose ($p>0.05$)**[Table 3]**.

In figure 2 we compare the average duration of 3rd stage of labour with different 3 doses of Sublingual misoprostol. The minimum average duration of 3rd stage of labour was 5.55±1.77 min in 800µg in Sublingual Misoprostol group and it was 7.12±1.31 min in 400µg in Sublingual Misoprostol group. By using the One-Way ANOVA 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 & 800µg 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 600 & 800µg Sublingual Misoprostol group 5.0% cases of each groups needed one unit blood transfusion [**Figure3**].

The incidence of fever after delivery in 800µg sublingual misoprostol group was 20.0%, followed by 10.0% in 600µg sublingual misoprostol group and only 5.0% in 400µg sublingual misoprostol group. Out of 20 patients, 5 patients (25 .0%) in 800µg sublingual misoprostol group, 15.0% cases in 600µg sublingual misoprostol group and 10.0% cases in 400µg sublingual misoprostol group. We also noted that there increase the doses of sublingual misoprostol shows the more shivering adverse drug reaction. Abdominal Pain and Nausea &vomiting was common adverse reaction in higher dose of sublingual misoprostol groups. Hypotension was noted in 10.0% in 800µg sublingual misoprostol group and 5.0% patients in 600µg sublingual misoprostol group. There were no any patients showing the hypotension in 400µg sublingual misoprostol group. Tachycardia was observed in 15.0% patients in 800µg and 10.0% in 600µg sublingual misoprostol group, while there was no tachycardia in 400µg sublingual misoprostol group [**Table 4**].

Figure1:Compare the >500ml and >1000ml blood loss with different 3 doses of Sublingual misoprostol

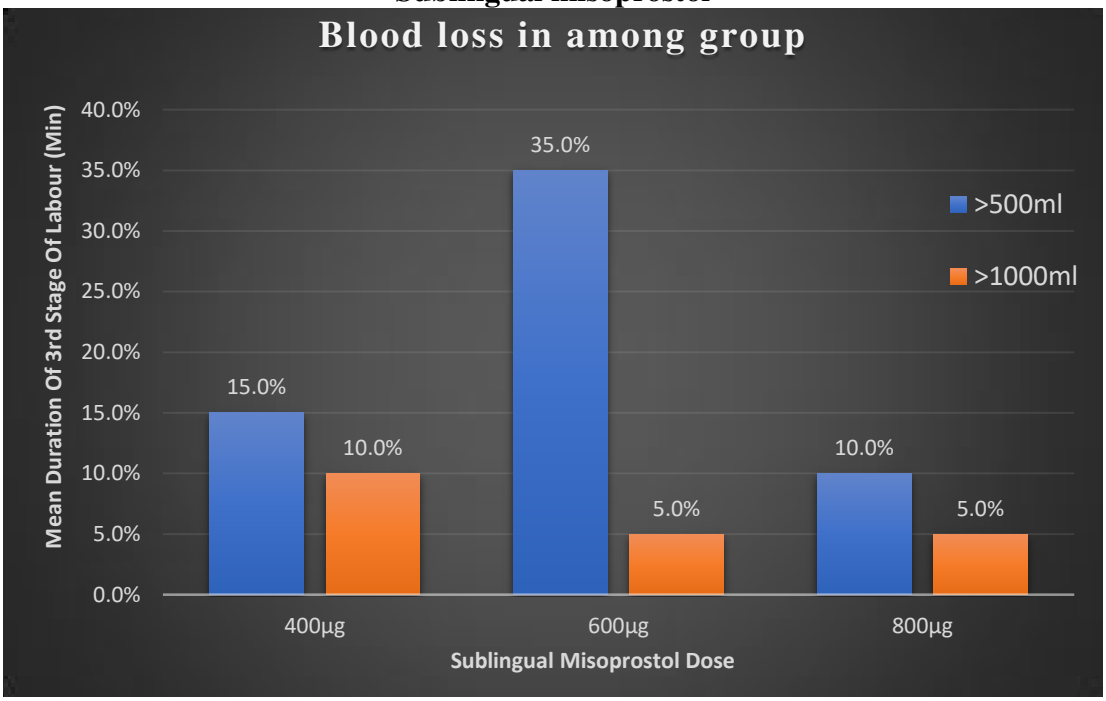


Table 1: Compare the total blood loss with different 3 doses of Sublingual misoprostol

Sublingual Misoprostol Dose	Average blood loss (ml)		t value	p value
	Mean±SD	Mean±SD		
400µg vs 600µg	507.00±308.97	452.00±306.62	0.565	0.575
400µg vs 800µg	507.00±308.97	397.00±234.23	1.269	0.212
600µg vs 800µg	452.00±306.62	397.00±234.23	0.637	0.528

Independent Sample t test

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

Vairiables	Sublingual Misoprostol Dose	Frequency (n=60)	Pre-operative	Post-operative	P value*
Haemoglobin level loss	**400µg**	20	10.12±1.33	8.61±1.46	**<0.001**
	600µg	20	10.14±1.64	8.83±1.49	**<0.001**
	800µg	20	10.35±1.70	9.66±1.77	**<0.001**
Inter Group p value#			0.876	0.095	
Haematocrit value loss	**400µg**	20	33.90±3.96	31.05±3.73	**<0.001**
	600µg	20	33.20±3.64	30.80±3.89	**<0.001**
	800µg	20	33.30±4.52	31.15±4.43	**<0.001**
Inter Group p value#			0.841	0.172	

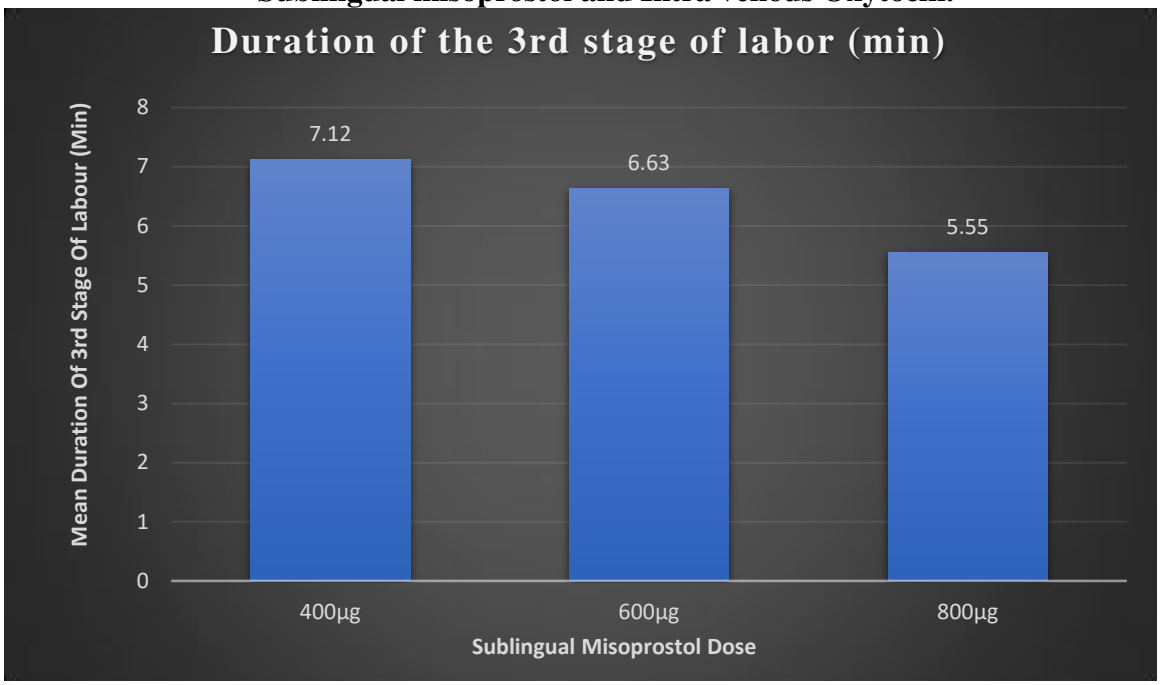
***Paired t test; # One Way ANOVA test**

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 vale
	Mean±SD	Mean±SD		
400µg vs 600µg	1.50±0.74	1.31±0.63	0.902	0.373
400µg vs 800µg	1.50±0.74	0.69±0.29	4.612	**<0.001**
600µg vs 800µg	1.31±0.63	0.69±0.29	4.012	**<0.00.1**
Haematocrit value loss				
400µg vs 600µg	2.85±1.31	2.40±1.35	1.069	0.292
400µg vs 800µg	2.85±1.31	2.15±0.99	1.909	0.064
600µg vs 800µg	2.40±1.35	2.15±0.99	0.667	0.509

Independent Sample t test

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



***One Way ANOVA; p value=0.007;**

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

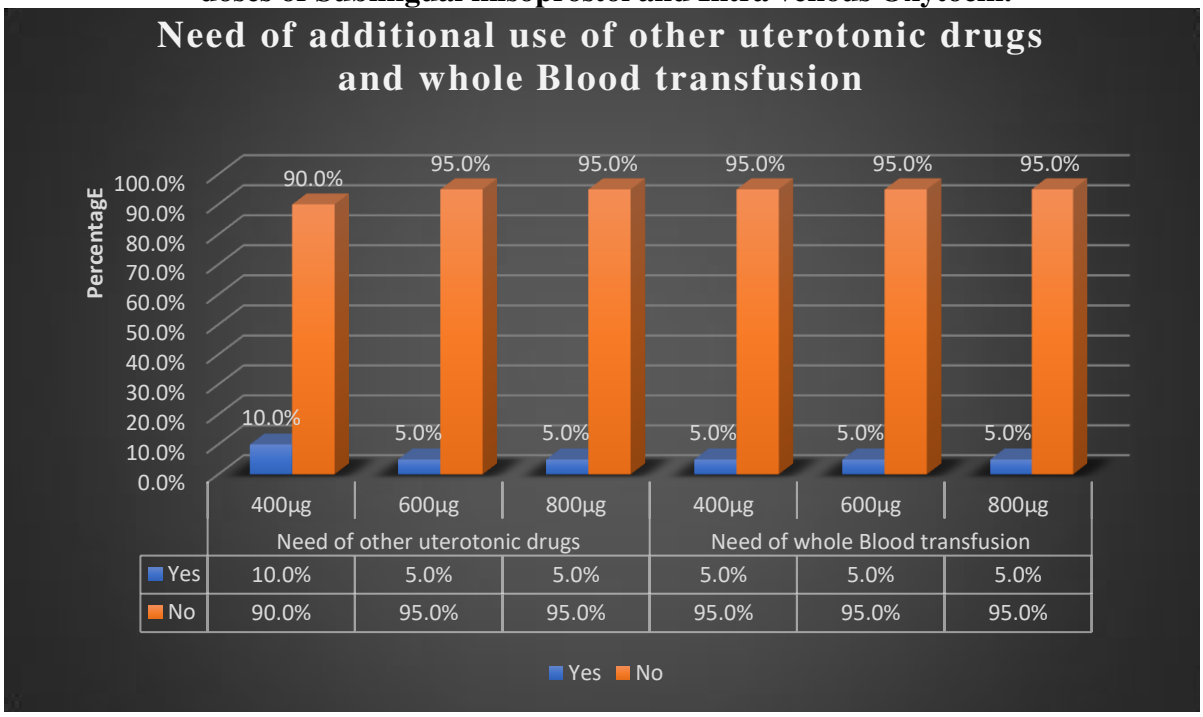


Table 4: Adverse drug reaction with different 3 doses of Sublingual misoprostol

Adverse drug reaction	Sublingual Misoprostol Dose		
	400µg (n=20)	600µg (n=20)	800µg (n=20)
Fever	1 (5.0%)	2 (10.0%)	4(20.0%)
Shivering	2 (10.0%)	3 (15.0%)	5 (25.0%)
Abdominal Pain	0 (0.0%)	3 (15.0%)	5 (25.0%)
Nausea and vomiting	1 (5.0%)	4 (20.0%)	3 (15.0%)
Hypotension	0 (0.0%)	1 (5.0%)	2 (10.0%)
Tachycardia	1 (5.0%)	2 (10.0%)	3 (15.0%)

DISCUSSION

Misoprostol is an artificial analogue 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 three different dosage of sublingual misoprostol (i.e. 400ug, 600ug and 800µg) 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
800µg	397.00±234.23	441.1 ml	1150 ml

The lowest mean blood loss was seen in the patients who received 800µg in Sublingual Misoprostol group, followed by 600µg Sublingual Misoprostol group and 400µg Sublingual Misoprostol group. Like our study **Sringamwong W 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, **AlalfyM et 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, 15.0% in 400µg and 10.0% cases in 800µg in Sublingual Misoprostol group; But 10.0% case in 400µg Sublingual Misoprostol group and 5.0% case in 600 µg Sublingual Misoprostol and 800 µg Sublingual Misoprostol group total blood loss was >1000ml. The minimum blood loss was observed in 800µg Sublingual Misoprostol group and the maximum blood loss was in 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 was due variation in study sample size, inclusion and exclusion criteria.

In the present study, we noted that however, minimizing intraoperative blood loss should be taken into consideration to stabilize the hemodynamic of the moms who may have an undetected underlying health issue in the case of low Hb and Hct readings. Moreover, following an acute hemorrhage, post-operative Hb and Hct readings may fluctuate for 24 to 48 hours before stabilizing.[26]

The average length of the third stage of labor was found to be significantly shorter in the 800µg dosage of Sublingual misoprostol than in the other two doses ($p<0.05$) when the duration of the third stage of labor was compared. **Sharma T &Jaju PB**[27]concluded that the context of active management of 3rd grade labour.

In 400µg Sublingual Misoprostol 10.0% of cases needed additional use of other uterotonic drugs where whereas 5.0% of cases needed additional use of other uterotonic drugs in both 600 & 800µg 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% of patients in the misoprostol group need to additional uterotonic drugs.

In 400µg Sublingual Misoprostol 5.0% of cases needed one unit and 5.0% of cases needed more than one unit of blood transfusion. In the case of the 600 & 800µg Sublingual Misoprostol group, 5.0% of cases of each group needed one unit of blood transfusion. **Pakniat H et al**[30]reported that when comparing the sublingual misoprostol group to the tranexamic acid group, the overall bleeding was noticeably less. **Ahmed AA et al**[31]reported that Reducing blood loss during and after CS appears to be less successful when misoprostol

400 mcg is administered intrauterine. **Nahar K et al**[32]declared that the thermostability of sublingual misoprostol at 200 µg may make it a viable substitute for injectable oxytocin in the active treatment of the third stage of labor. **Vodouhe MV et al**[33]reported that when it comes to preventing postpartum hemorrhage, oxytocin and the 600µg misoprostol dosage administered sublingually are equally beneficial and don't have any serious side effects.

Pyrexia, which is characterized as an unexplained, asymptomatic rise in body temperature, is a common misoprostol adverse effect. Even while pyrexia is self-limiting and typically of a low degree—severe forms of hyperthermia are rare—mothers typically experience discomfort and anxiety.[34]The first interaction between a mother and her newborn will be delayed as a result of this encounter. Compared to previous trials using different dosages of misoprostol, this study found a significant proportion of pyrexia in all groups (52-26%).[24,34]Nonetheless, pyrexia was shown in 66.7% of 800 µg intrauterine misoprostol in a prior randomized trial trail in 2018, which was somewhat higher than the current study.[20]The increased rate of pyrexia associated with a high misoprostol dose is comparable to a 2019 systematic study.[24]0.8–23% of the previous research on misoprostol doses also included nausea and vomiting.[24,35]

Our study noted that rise in the incidence of adverse effects (such as shivering, fever, abdominal pain, nausea and vomiting, hypotension, and tachycardia) with a higher dosage of sublingual misoprostol which was similar to the study done by **Acharya G et al,**[36] **Hamm J et al**[37]and**Vimala N et al**[38]. Dose of misoprostol in various studies have 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] which was also similar to our study. As the side effects are dose-related, a dose of 400 mcg was taken in the present study to minimize maternal adverse effects with optimal therapeutic benefit. **Hofmeyr GJ et al**[41] reported that it was discovered that 400 mcg of misoprostol was just as effective as and safer than 600 mcg which was similar to our study, which also showed that there is no significant difference in average blood loss between 40ug and 60ug sublingual misoprostol. **Sood AK & Singh S**[18]also reported that Misoprostol side effects include shivering, pyrexia, nausea, vomiting, and diarrhea, which are dose-related.

LIMITATION

The sample size in each group was small and our study was single centric and was single blinded.

CONCLUSION

In conclusion, our findings advocatesthat lower doses of misoprostol may be as effective as high doses in term of total blood loss and loss of hematocrit level. Although the average blood loss appears to decrease with increasing dosage of sublingual misoprostol, this difference is not statistically significant according to one way ANNOVA test (p=0.480).Study results suggest that 800µg sublingual misoprostol is more effective in preventing the fall in hemoglobin level in comparison to 400µg and 600µgsublingual misoprostol. Our study further concludes that the frequency of incidence of side effects was seen more with increasing dose of 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 other injectable uterotonics 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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