A STUDY OF SAFTEY AND EFFICACY OF SUBLINGUAL VERSUS VAGINAL MISOPROSTOL IN PRIMIGRAVIDA AT TERM PREGNANCY WITH POOR BISHOP'S SCORE.

ABSTRACT:

INTRODUCTION:

The induction of labour in women with a live fetus at term remains a major challenge in modern obstetrics.Despite a large body of literature on the subject,the optimal agent for this purpose has yet to be established.Induction of labour implies stimulation of uterine contractions before the spontaneous onset of labour, with or without rupture of membranes.It is well recognized that the success of induction of labour which ultimately aims at achieving vaginal delivery, depends to a greater extent on the favourability of cervix, or its readiness to go into labour.

Misoprostol is inexpensive and effective and can be stored at room temperature. American College of Obstetrics and Gynecology [ACOG] supported its usage in 2009 for women who didn't have previous ceserean delivery or a major uterine surgery.The National Institute for Health And Clinical Excellence[NICE] released a clinical guideline in 2008 in its support.Misoprostol costs less than dinoprostone gel and it does not need refridgeration.

MATERIALS AND METHODS:

This study was conducted in the department of Obstetrics and gynecology in Government Multispeciality Hospital, Chandigarh Sector 16 from may 2019 to august 2020.Patients admitted in the labour room for induction of labour were included in the study.Total 116 patients were enrolled and were given sublingual and vaginal misoprostol after dividing into two groups.

RESULTS:

Both groups were statistically similar in terms of age and period of gestation[p value 0.517].Maximum number of patients with post dated pregnancy were induced in both the groups with maximum patients with Bishop's 3 and 4.37.8% of patients with sublingual [group A]misoprostol and 39.7% patients with per vaginal misoprostol[group B] required only one dose of misoprostol for vaginal delivery.48% patients in group A had vaginal delivery where as 70% patients in group B had vaginal delivery.The difference in duration of induction was not statistically significant.Adverse effect like meconium stained liquor,fetal distress, uterine hyperstimulation was more common in group B.

CONCLUSION:

This study shows that sublingual misoprostol may be better in terms of rate of successful vaginal delivery, number of doses,augmentationrequirement,duration of induction,incidence of meconium stained liquor and hyperstimulation syndrome.

KEYWORDS:

Misoprostol,Induction,oxytocin,postdatism,prostaglandin,BISHOP'SSCORE,uterine hyperstimulation

INTRODUCTION:

Induction of labour has been a major challenge in obstetrics.It implies stimulation of uterine contractions before the spontenous onset of labour,with or without ruptured membranes.It has two important components,cervical ripening and stimulation of uterine contraction to achieve dilatation of cervix and delivery of fetus.Methods of induction of labour includes natural ,mechanical [e.g digital stretching of cervix and sweeping of membranes, foleys catheter, artificial rupture of membranes and nipple stimulation] surgical and pharmacological methods.Pharmacological methods include oxytocin,misoprostol,mifepristone,dinoprostone,etc.

The use of prostaglandins preparations with or without oxytocin infusion was widely recognized and accepted as a standard method for cervical ripening and labourinduction.Misoprostol is a prostaglandin E1 analogue marketed since

1988,as a gastric cytoprotective agent.Several routes of administration of misoprostol have been studied which includes oral,vaginal,rectal,buccal,and sublingual route of administration.Vaginal route is commonly practiced for labour induction but it incurs greater risk of undesirable adverse effects such as uterine hyper stimulation syndrome as well as having the inconvenience of vaginal administration.Many clinical studies were conducted on oral route but it was found that vaginal administration was more effective than oral as systemic bioavailability after vaginal misoprostol was 3 times greater than oral misoprostol.Sublingual method of administration may be an alternative method as it combines the higher efficacy of vaginal route by avoiding gastrointestinal and hepatic metabolism and lowers hyperstimulation rates by avoiding direct effect on the cervix.It also has additional advantages which includes its easier administration,greaterfreedom of position of patients and avoidance of repeated vaginal examinations.

After several studies, WHO and FIGO had recommended vaginal misoprostol dosage of 25µg every 4 hourly for maximum of 6 doses.The pharmacokinetic study of different routes of misoprostol has shown that sublingual route has greater bioavilability than vaginal route.The objective of this study is to determine the efficacy and safety of 25µg of sublingual misoprostol compared with 25µg of vaginal misoprostol for induction of labour.The goal of successful induction of labour is to achieve a vaginal delivery and to bring adequate uterine activity sufficient for cervical changes at fetal descent.

Misoprostol is cost effective and can be stored at room temperature.The National Institute for health and Clinical Excellance[NICE] released a clinical guiedline in 2008 and restricted the use of misoprostol only to clinical trials and termination of pregnancy with dead fetus.However ,the ACOG supported its use in 2009 in women who did not have aprevious cesarean delivery or a major uterine surgery.Misoprostol use may decrease the need for oxytocin,achieve higher rates of vaginal delivery within 24 hours of induction and reduce induction to delivery intervals.

MATERIALS AND METHODS:

This study was conducted in the department of Obstetrics and Gynaecology in Government Multi Specialty Hospital,Chandigarh sector 16 from May 2019 to August 2020.Patients admitted in the labour room for induction of labour were included in the study.It was a prospective observational study.Total patients included were 116.

Inclusion Criteria:

1.Live singleton pregnancy at a gestational age of 37 completed weeks and <41 weeks.

2.Cephalic presentation

3.Unfavourable Cervix(Bishop'score less than or equal to 6)

4.Reassuring fetal heart rate

5.Absence of uterine contraction

Exclusion criteria:

1.Multiple gestation

2.Malpresentation(presentation other than cephalic)

3.Previous uterine surgery including Cesarean delivery

4.Known contraindications to the use of prostaglandins(e.g. asthma)

5.Multiparity

6.Chorioamnionitis

7.Active vaginal bleeding(antepartum hemorrhage-placenta previa,abruption placenta)

8.Severe preeclampsia and eclampsia

9.Uncontrolled Diabetes mellitus

10. known case of renal,liver and autoimmune disease

Patient admitted for induction of labour and fulfilling the inclusion criteria,were explained about the two different methods of induction and only those who voluntered to participate in the study were selected.Informed consent was taken .Total 116 patients were enrolled and got allotted one of the following group randomly:

Group A:Sublingual misoprostol[SLM]:induction was done with 25µg of SLM administered 4 hourly for maximum of 6 doses.

GroupB: Vaginal misoprostol[VM]:induction was done with 25µg vaginal misoprostol[posterior fornix] every 4 hourly for maximum of 6 doses.

During induction,labour was monitored for contractions,BISHOP'S score and fetal heart rate.The next dose of misoprostol was withheld if any of the following were presents

1.BISHOP'S SCORE ≥8

2.Adequate uterine contractions

3.Cervical dilatation≥3cm

4.Presence of hyperstimulation,tachysystole or hypertonus

Following outcome variables have been measured in both groups.

1.Interval from the start of induction to vaginal delivery/induction delivery interval

2.Number of women delivered vaginally within 24 hours of the 1st dose of misoprostol.

3.Cesarean rates

4.Number of misoprostol doses given

5. Need for oxytocin augmentation

6.Number of per vaginal examination

7.Uterine tachysystole rates

8. Uterine hyperstimulation rates

9.Other maternal adverse effects

10.Incidence of meconium stained liquor

11.NICU Admissions

12.APGAR SCORE at 1 and 5 minute

OBSERVATION AND RESULTS:

A. Patient's age

The mean age in the group A was 24.7 ± 2.9 years old.

The mean age in the group B was 24.3 ± 3.4 years old.

Both groups were statistically similar in term of age (P value 0.517, table 2).

Table 1: Age distribution in both groups

	Group A (SL)	***Group B (PV)***

Age (years)	***≤20***	4 (6.9%)	12 (20.7%)
	21 to 25	33 (56.9%)	27 (46.6%)
	25 to 30	20 (34.5%)	17 (29.3%)
	>30	1 (1.7%)	2 (3.4%)
Total		58 (100%)	58 (100%)

Figure 1. Age distribution in both groups.

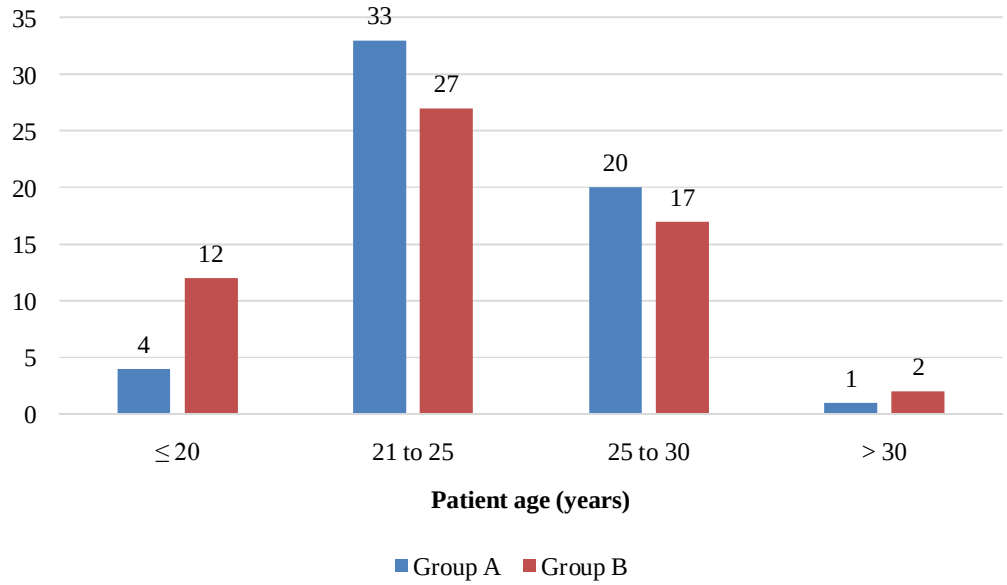


Table 2. Comparison of age distribution between group A & B (unpaired t test).

	Age (years)	***t stat***	***P value***	***df***
Group A (SL)	24.7 ± 2.9	0.650	0.517	114
Group B (PV)	24.3 ± 3.4			

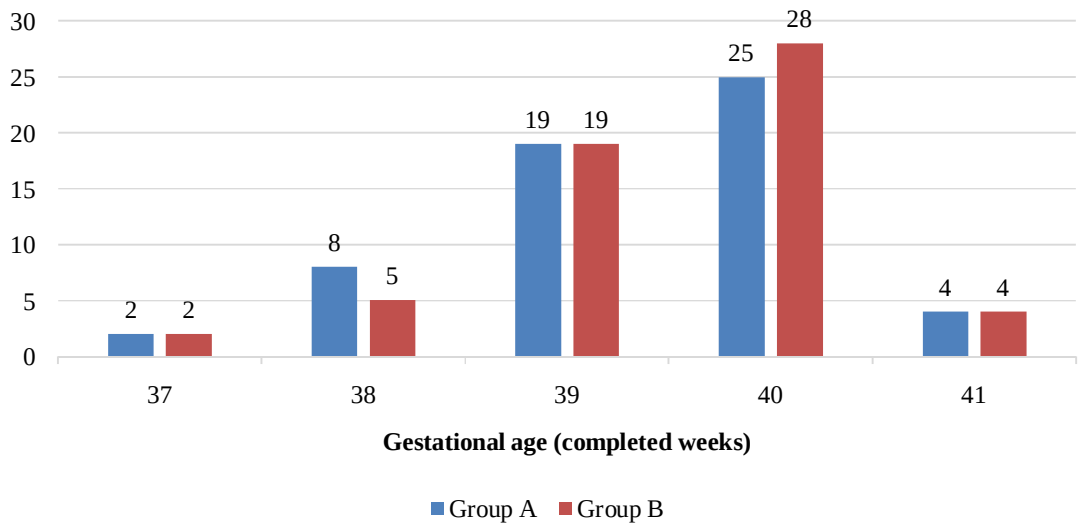
B. Gestational age

- The mean gestational age in group A was 39.4 ± 0.9 weeks. The median was 39.5 weeks.
- The mean gestational age in group B was 39.5 ± 0.9 weeks. The median was 40 weeks.

Both groups were statistically similar in term of gestational age (P value 0.528, table 3).**Table 3. Comparison of gestational age between group A & B (Mann Whitney U test)**

		Group A (SL)	***Group B (PV)***	**Mann-Whitney U**	***P value***
Gestationalage (completedweeks)	***37***	2 (3.4%)	2 (3.4%)	1575.500	0.528
	38	8 (13.8%)	5 (8.6%)		
	39	19 (32.8%)	19 (32.8%)		
	40	25 (43.1%)	28 (48.3%)		
	41	4 (6.9%)	4 (6.9%)		
Total		58 (100%)	58 (100%)		

Figure 2. Gestational age distribution in both groups.



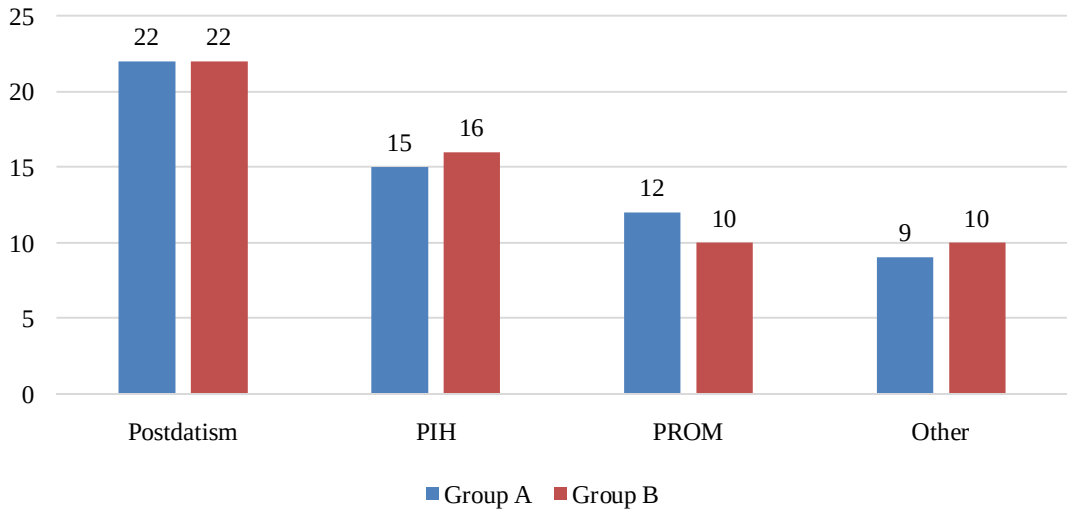
C. Indication for IOL

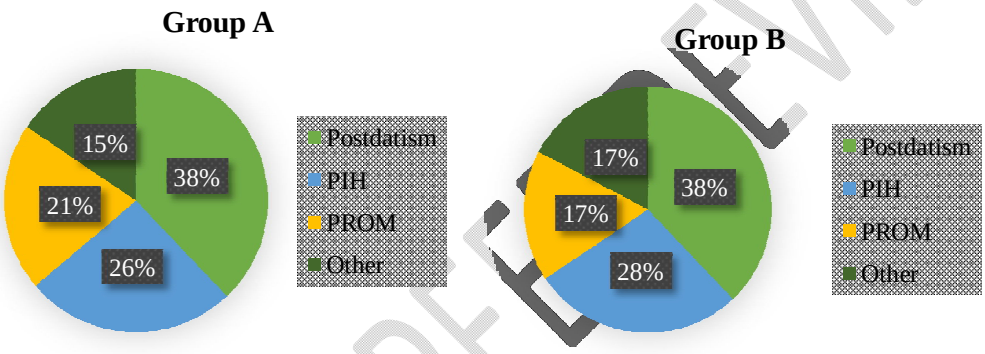
In both group the most common indication for IOL was postdatism (37.9%) followed by PIH (25.9% vs 27.6%) and then PROM (20.7% vs 17.2%). Both groups were statistically similar in term of indication for IOL (P value 0.966, table 4).

Table 4. Comparison of indication for IOL between group A & B (χ^2 test).

		Group A (SL)	*Group B (PV)*	χ^2	*P value*	*df*
Indication for IOL	***Postdatism***	22 (37.9%)	22 (37.9%)	0.267	0.966	3
	PIH	15 (25.9%)	16 (27.6%)			
	PROM	12 (20.7%)	10 (17.2%)			
	Other	9	10 (17.2%)			
Total		58 (100%)	58 (100%)			

Figure 3. Distribution of indication for IOL in both groups.





D. Bishop`s score

The mean Bishop`s score was 3.69 ± 1.0 in group A & 3.65 ± 1.0 in group B. The median was the same in both groups, namely 4. Both groups were statistically similar in term of Bishop`sscore (P value 0.839, table 5).

Table 5. Comparison of Bishop`s score between group A & B (χ^2 test).

		Group A (SL)	*Group B (PV)*	Mann-Whitney U	*P value*
Bishop`s score	***2***	5 (8.6%)	7 (6.9%)	1647.000	0.839
	3	22 (37.9%)	21 (36.2%)		

	4	21 (36.2%)	19 (32.7%)		
	5	6 (6.9%)	7 (6.9%)		
	6	4 (10.3%)	4 (12%)		
Total		58 (100%)	58 (100%)		

II COMPARISON OF EFFICACY

We have successfully confirmed that the 2 groups were statistically similar and homogeny. We can proceed by comparing the efficacy of both regimens according to different criteria.

A. Number of doses of misoprostol requirement

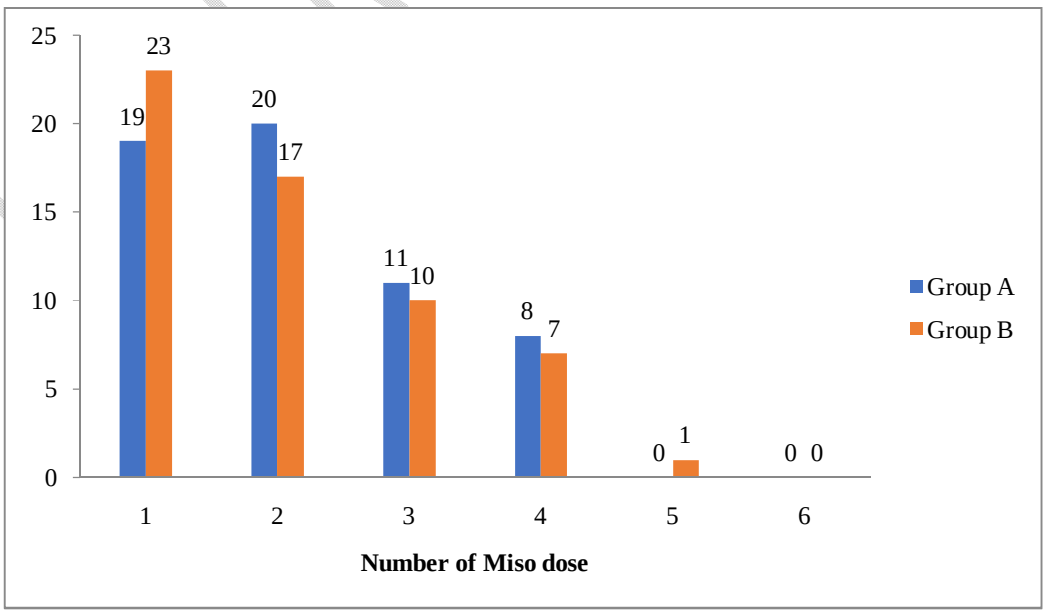
The mean number of doses given was 2.1 ± 1.0 in group A & 2.1 ± 1.1 hours in group B.

The median was the same in both groups, namely 2 doses. The number of doses of Misoprostol required was statistically similar in both group (P value 0.839, table 6).

Table 6. Comparison of number of doses between group A & B (Mann Whitney U test).

		Group A (SL)	*Group B (PV)*	Mann-Whitney U	*P value*
Number of Miso doses	***1***	19 (37.8%)	23 (39.7%)	1647.000	0.839
	2	20 (34.5%)	17 (29.3%)		
	3	11 (18.9%)	10 (17.2%)		
	4	8 (37.8%)	7 (12.1%)		
	5	0 (0%)	1 (1.8%)		
	6	0 (0%)	0 (0%)		
Total		58 (100%)	58 (100%)		

Figure 4. Distribution of number of doses in both groups.



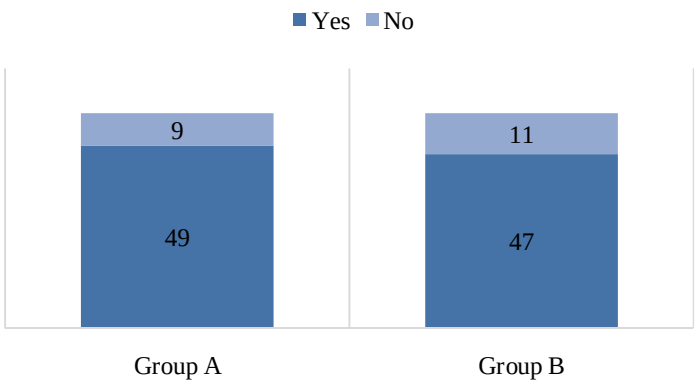
B. Augmentation requirement

Augmentation was required more commonly in the sublingual group (84.5% vs 81%). But the difference was not statistically significant (P value 0.623, table 7).

Table 7. Comparison of augmentation requirement between group A & B (χ^2 test).

		Group A (SL)	*Group B (PV)*	χ^2	*P value*	*df*
Augmentation requirement	***Yes***	49 (84.5%)	11 (81%)	0.242	0.623	1
	No	9 (15.5%)	47 (19%)			
Total		58 (100%)	58 (100%)			

Figure 5. Distribution of augmentation requirement in both groups.



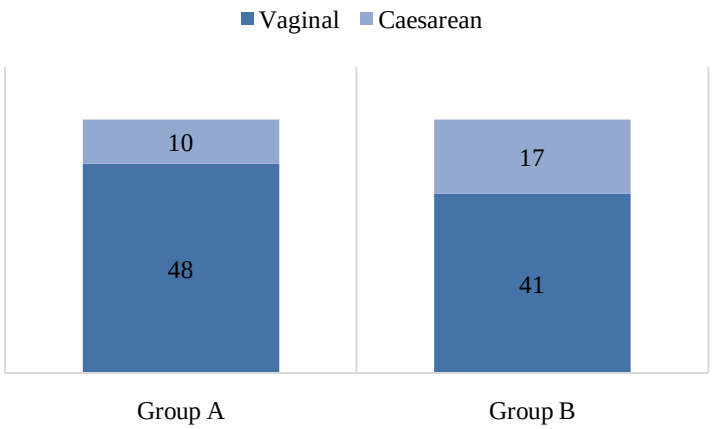
C. Rate of vaginal deliveries

Successful vaginal delivery was more common in the sublingual group (82.8% vs 70.7%). But the difference was not statistically significant (P value 0.124, table 8).

Table 8. Comparison of mode of delivery between group A & B (χ^2 test).

		Group A (SL)	*Group B (PV)*	χ^2	*P value*	*df*
Mode of delivery	***Vaginal***	48 (82.8%)	41 (70.7%)	2.365	0.124	1
	Caesarean	10 (17.2%))	17 (29.3%)			
Total		58 (100%)	58 (100%)			

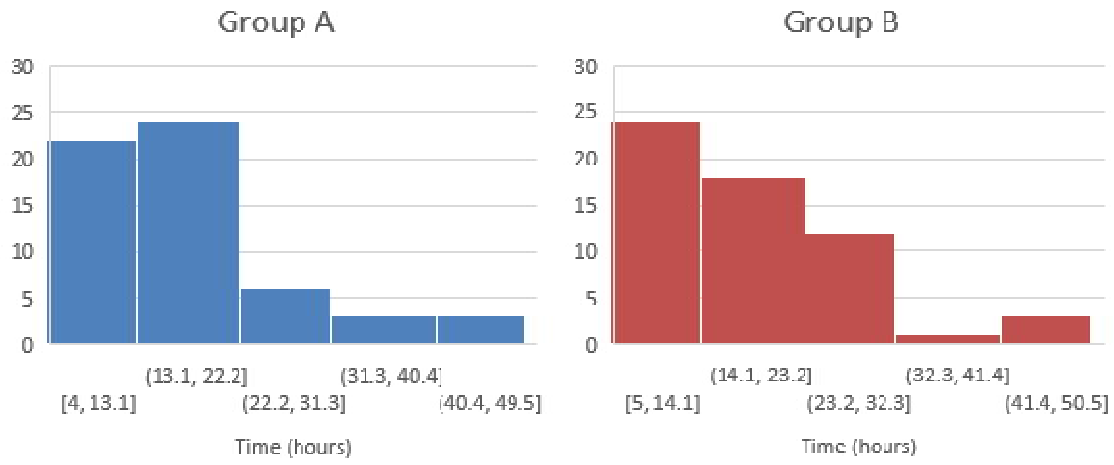
Figure 6. Distribution of mode of delivery in both groups.



D. Duration of induction

The duration of the induction is an important criterion in the assessment of the efficacy of the regimen. It is measured from the moment the first dose of Misoprostol is given till the time of delivery. It is expected that an efficient treatment should have a short duration of induction. An arbitrary cut-off of 24 hours has been chosen to differentiate an efficient induction from a delayed delivery. Figure 7 shows the distribution of the duration of induction in both groups.

Figure 7. Distribution of duration of induction in both groups.



The mean duration of induction was 17.7 ± 10.1 hours in group A. The median was 15.5 hours.

The mean duration of induction was 18.9 ± 10.0 hours in group B. The median was 18 hours.

The sublingual route seemed to be more efficient than the per vaginal route but the d**Table 9. Comparison of duration of induction (Mann Whitney U test).**

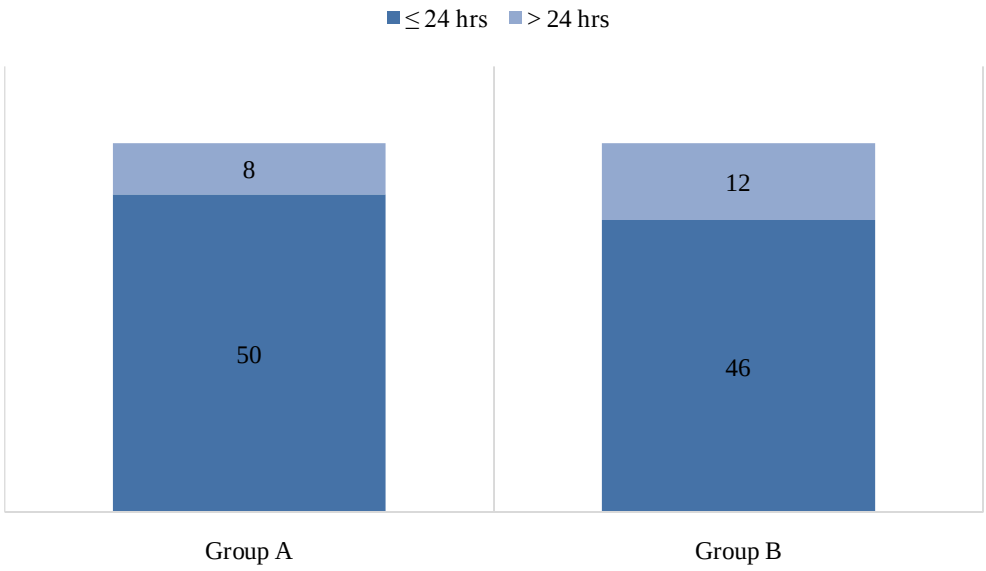
	Duration of induction (hours)	**Mann-Whitney U**	***P value***
Group A (SL)	17.7 ± 10.1	1514.0	0.353
Group B (PV)	18.9 ± 10.0		

If we compare both groups using a 24 hours cut-off, we can divide our cases into early delivery and late delivery. We find again sublingual route to be more efficient (82.8% vs 70.7%) but the difference was again not statistically significant (P value 0.323, table 10).

Table 10. Comparison of early & late delivery using a 24 hours cut-off (χ^2 test).

		Group A (SL)	Group B (PV)	χ^2	P value	df
Duration of induction	≤ 24 hrs	50 (82.8%)	46 (70.7%)	0.967	0.326	1
	>24 hrs	8 (17.2%)	12 (29.3%)			
Total		58 (100%)	58 (100%)			

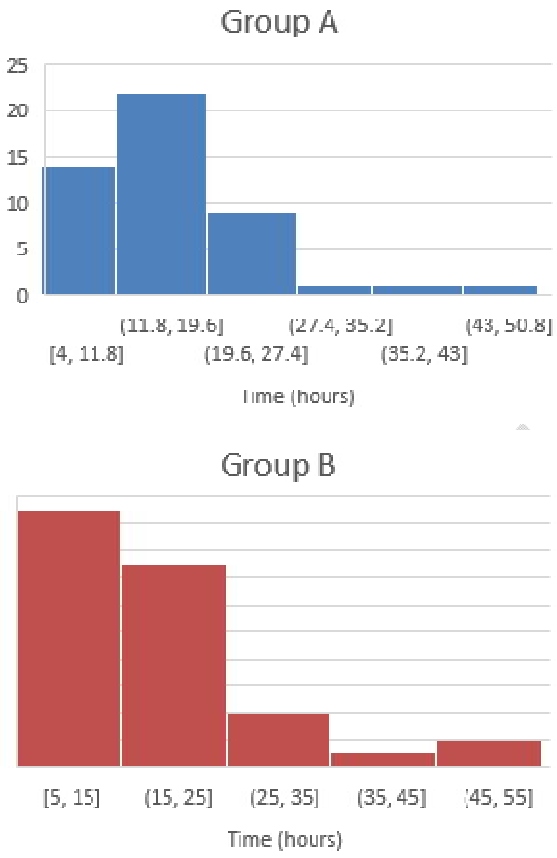
Figure 8. Distribution of early & late delivery in both groups.



E. Duration of induction in vaginal delivery sub groups

We now decide to refine our statistics by discarding all the patients who ended up in cesarean section (considered as failure) and we keep only patients who achieved a successful vaginal delivery. Group A as now 48 patients and group B has 41 patients. The new distribution of duration of treatment in shown in figure 9.

Figure 9. Distribution of duration of induction in vaginal delivery sub groups



The mean duration of induction was 15.5 ± 8.1 hours in group A. The median was 14.

The mean duration of induction was 18.5 ± 10.3 hours in group B. The median was 17.

The sublingual route seemed again more efficient than the per vaginal route but this time, the difference was statistically significant (P value 0.014, table 11).

Table 11. Comparison of duration of induction in vaginal delivery sub groups (Mann Whitney U test).

ifference was not statistically significant (P value 0.353, table 9).

Table 11. Comparison of duration of induction in vaginal delivery sub groups (Mann Whitney U test).

	Duration of induction (hours)	**Mann-Whitney U**	***P value***
Group A (SL)	15.5 ± 8.1	2160.0	0.014
Group B (PV)	18.5 ± 10.3		

If we compare both new groups using a 24 hours cut-off (early delivery vs late delivery). We find again sublingual route to be more efficient (93.8% vs 80.5%) but the difference is not statistically significant (P value 0.058, table 12).

Table 12. Comparison of early & late delivery in vaginal delivery sub groups (χ^2 test).

		Group A (SL)	***Group B (PV)***	χ^2	***P value***	***df***
Duration of treatment	***≤ 24 hrs***	45 (93.8%)	33 (80.5%)	3.590	0.058	1
	>24 hrs	3 (6.2%)	8 (19.5%)			
Total		48 (100%)	41 (100%)			

Figure 10. Distribution of early & late delivery in vaginal delivery sub groups.

III COMPARISON OF ADVERSE EFFECT

We are now going to compare the incidence of adverse effect in the 2 regimens.

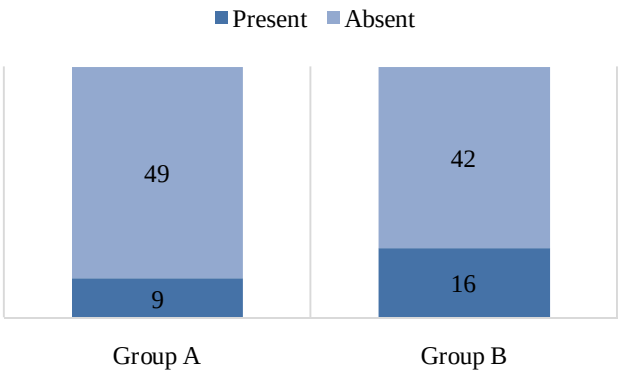
A. Presence of MSL/FD

Fetal distress or suspected fetal distress (MSL) has been seen more commonly in the per vaginal group (29.3% vs 17.2%). But the difference was not statistically significant (P value 0.114, table 13).

Table 13. Comparison of MSL/FD between group A & B (χ^2 test).

		Group A (SL)	*Group B (PV)*	χ^2	*P value*	*df*
MSL/FD	***Present***	9 (17.2%)	16 (29.3%)	2.498	0.114	1
	Absent	49 (82.8%)	42 (70.7%)			
Total		58 (100%)	58 (100%)			

Figure 11. Distribution of MSL/FD in both groups.



B. Hyperstimulation syndrome

Hyperstimulation syndrome has been seen more commonly in the per vaginal group (12.1% vs 5.2%). But the difference was not statistically significant (P value 0.185, table 14).

Table 14. Comparison of hyperstimulation syndrome between group A & B (χ^2 test).

		Group A (SL)	*Group B (PV)*	χ^2	*P value*	*df*
Hyperstimulation syndrome	***Present***	3 (5.2%)	7 (12.1%)	1.751	0.185	1
	Absent	55 (94.8%)	51 (87.9%)			
Total		58 (100%)	58 (100%)			

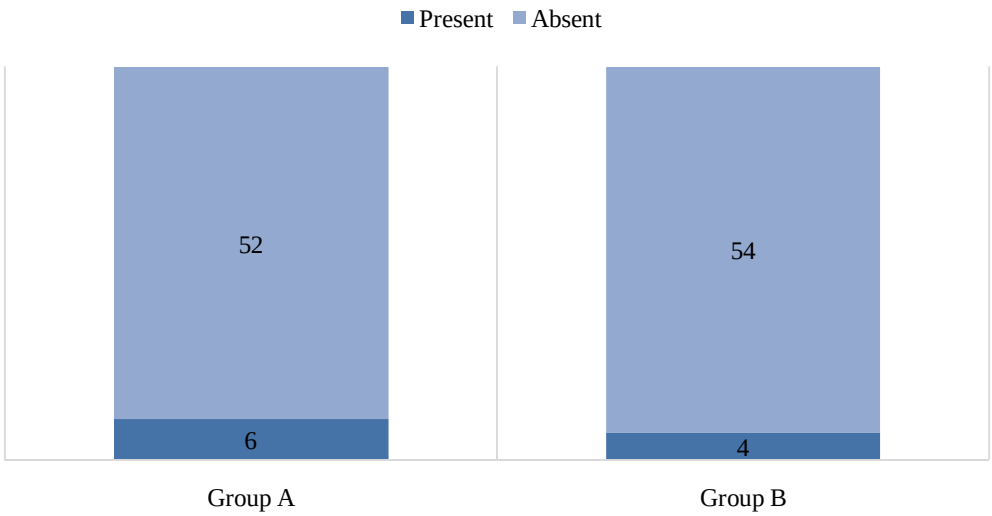
C. Maternal side effect

Maternal side effect has been seen more commonly in the sublingual group (10.3% vs 6.9%). But the difference was not statistically significant (P value 0.508, table 15).

Table 15. Comparison of maternal side effect between group A & B (χ^2 test).

		Group A (SL)	*Group B (PV)*	χ^2	*P value*	*df*
Maternalsideeffect	***Present***	6 (10.3%)	4 (6.9%)	0.438	0.508	1
	Absent	52 (89.7%)	54 (93.1%)			
Total		58 (100%)	58 (100%)			

Figure 12. Distribution of maternal side effect in both groups.



DISCUSSION:

In our study 116 patients were included and as per pubmed search machine sublingual misoprostol study was done on 160, 120, 140, 150 patients.There was no difference in age, gestational age, BISHOP's score and indication of induction of both groups.The results had showed that 25µg of sublingual misoprostol admistration resulted in shorter induction to delivery interval but the difference was not statistically significant[p-0.35].The number of misoprostol dose required was also stastiscally similar [p-0.83].

In Tang et al. study,the sublingual route has been shown to produce significantly higher serum peak concentration of misoprostol than either oral or vaginal administration.In addition the area under the curve for plasma levels over 4 to 6 hours was significantly greater following sublingual administration than for either oral or vaginal administration.A recently published study evaluated the effects of misoprostol on uterine contractility following different routes of administration.The sublingual application of misoprostol has, with regard to effects on the myometrium,had rapid effect on uterine contractility as oral administration and the bioavilability was similar to that following vaginal administration.Bartusevicius et al had also observed shorter induction to delivery interval after using 50µg of sublingual misoprostol in contrast to 25µg in our study.

Tang et al on studying pharmacokinetics of misoprostol in different route of administration had found that at the end of 6th dose, the serum levels of misoprostol in vaginal groups were higher than sublingual and oral

routes.Sublingual doses interval should be less than this interval to get significant plasma level.

Comparison of efficacy:

Efficacy of the two regimens has been compared in terms of number of doses required,augmentationrequirement,rate of successful vaginal delivery,duration of induction.There was no significant difference between the two regimens.There was also no significant difference when instead of using the exact duration of induction, an arbitrary cutoff of 24 hours was use to divide early from delayed delivery. We also conclude that there was not any difference in the cost of management in both groups.

NEONATAL OUTCOME:

The APGAR score of almost all our babies were equal or above 7,which is considered to be normal. Only one baby was born with an APGAR below 7.Due to small sample size proper assessement of neonatal outcome couldnot be done.Although perinatal outcome was assessed in terms of fetal distress and meconium stained liquor.

There were no significant differences between the two groups with respect to the number of women experiencing hyperstimulation syndrome,or with regard to the mode of delivery or neonatal outcome.Maternal adverse effect was assessed in terms of vomiting,fever,diarrohea.Sublingual dosing for labour induction is attractive because of ease of administration, less frequent need for vaginal examination,greater freedom of position and the possibility of it use despite vaginal bleeding or ruptured membranes.Even though there was no significant difference in terms of outcome,we assume higher patient exceptance of sublingual route, when compared to vaginal route.

SUMMARY AND CONCLUSION:

- The mean age in the groupA was 24.7±2.9 years old,where as in the groupB it was 24.3±3.4 years old.The mean gestational age in group A was 39.4 ± 0.9 weeks. The median was 39.5 weeks.
- In both group the most common indication for IOL was postdatism (37.9%) followed by PIH (25.9% vs 27.6%) and then PROM (20.7% vs 17.2%).The mean Bishop`s score was 3.69 ± 1.0 in group A. The median was 4.
- The mean Bishop`s score was 3.65 ± 1.0 in group B. The median was 4.

- The mean number of Miso doses given was 2.1 ± 1.0 in group A. The median was 2.The mean number of Miso doses given was 2.1 ± 1.1 hours in group B. The median was 2.
- The difference in Miso dose was not statistically significant score (P value 0.839)
- The rate of augmentation requirement was 84.5% in group A.
- The rate of augmentation requirement was 81% in group B.
- The difference augmentation requirement was not statistically significant (P value 0.623).
- The rate of successful vaginal delivery was 82.8% in group A.
- The rate of successful vaginal delivery was 70.7% in group B.
- The difference in successful vaginal delivery was not statistically significant (P value 0.124).
- The mean duration of induction was 17.7 ± 10.1 hours in group A. The median was 15.5 hours.
- The mean duration of induction was 18.9 ± 10.0 hours in group B. The median was 18 hours.
- The difference in duration of induction was not statistically significant (P value 0.353).
- The rate of early delivery (within 24 hours) was 82.8% in group A.
- The rate of early delivery (within 24 hours) was 70.7% in group B.
- The difference in early delivery was not statistically significant (P value 0.323).
- The mean duration of induction was 15.5 ± 8.1 hours in the subgroup A who delivered vaginally. The median was 14.
- The mean duration of induction was 18.5 ± 10.3 hours in the subgroup B who delivered vaginally. The median was 17.

- The difference in duration of induction in patient who delivered vaginally was statistically significant (P value 0.014).
- The rate of early delivery was 93.8% inthe subgroup A who delivered vaginally.
- The rate of early delivery was 80.5% in the subgroup B who delivered vaginally.
- The difference in early delivery in the subgroup who delivered vaginally was not statistically significant (P value 0.058).
- The rate of MSL/FD was 17.2% in group A.
- The rate of MSL/FDwas 29.3% in group B.
- The difference in MSL/FD was not statistically significant (P value 0.114).
- The rate of hyperstimulationwas 5.2% in group A.
- The rate of hyperstimulation was 12.1% in group B.
- The difference in HSwas not statistically significant (P value 0.185).
- The rate of maternal side effects were10.3% in group A.
- The rate of maternal side effects were6.9% in group B.
- The difference in maternal side effects were not statistically significant (*P* value 0.508).

Conclusion:

This study shows that sublingual Misoprostol may be better in term of rate of successful vaginal delivery, number of doses, augmentation requirement, duration of induction, incidence of meconium stained liquor/fetal distress and hyperstimulation syndrome but all these superior criteria were not statistically significant compared to per vaginal route. The incidence of maternal side effect may be slightly more in sublingual Misoprostol but it is again not statistically significant.

It neither alter vaginal deliveryrate and caesarean section rate nor produce significant complications likehypertonus, tachysystole and hyperstimulation syndrome than vaginalmisoprostol route of administration.

By restricting the study to patients who have delivered vaginally, sublingual Misoprostol is significantly more efficient than per vaginal Misoprostol in term of duration of induction but not if we simply use a 24 hours cut-off as success criteria.

We conclude that the efficacy, cost and side effect of both routes of administration are similar, so both routes can be used depending on doctor and patient preference.

We believe further studies on safetywith larger numbers of women need to be conducted before we advocatesublingual misoprostol as routine labour induction agent.

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