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Comparative study of efficacy and safety of misoprostol and oxytocin for induction in premature rupture of membrane at term

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Abstract
The ability to induce labour has been of interest of many societies, from the primitive to the ancient to the modern era. Mostly labour sets in spontaneously but for various obstetrical and medical indications it needs to be induced when the benefits to either the mother or the foetus outweigh those of continuing the pregnancy. There are many indications for induction of labour in which PROM (Premature Rupture of Membrane) is one of them.
The onset of labor in human is a complex biological phenomena controlled by multiple regulatory mechanism. In recent times, prostaglandins analogue are the most widely used agents for induction of labor. This study is done to compare the efficacy and safety of misoprostol and oxytocin for induction of labour in PROM at term.
Method: A total of 200 pregnant women were taken as sample in my study. 100 each in misoprostol (Group A) and oxytocin (Group B) respectively. The randomisation was done by single random sampling. Group A received oral misoprostol and Group B received oxytocin as per the dose decided. The results of the study were compared and decided on the basis of age, gestational age, gravida, Bishop's score, induction delivery interval, mode of delivery, maternal and fetal side effects.
Result: The present study shows that although Induction – Delivery Interval is more in miso post, but is comparable to i.v. oxytocin. Maternal side effects and neonatal outcome were similar with both drugs.
Conclusion: Misoprostol and oxytocin both are equally efficacious and safe drugs and either of the drugs can be used for induction in PROM.

Keywords: Misoprostol, oxytocin, induction of labour, PROM

Introduction
Induction of labour means initiation of uterine contraction by any methods (medical surgical and combined) for the purpose of vaginal delivery. Several options are available for labor induction. Labor induction, when performed in a woman with unripe cervix, often results in prolonged and difficult labor. Failed inductions requiring caesarean delivery are common in this setting [1]. Oxytocin and prostaglandins are the pharmacologic agents most frequently used for induction of labor [2].
Misoprostol, a synthetic PGE_1 analogue, can be administered intravaginally, orally or sublingually and is used for both cervical ripening and induction. Oxytocin, a nanopeptide, is one of the most commonly used drugs for induction of labour.
PROM is defined as rupture of fetal membrane with a latent period before onset of spontaneous uterine activity. It occurs in approximately 10% of all pregnancies and 70% occurs at term [3, 4]. There are significant ante-partum, intra-partum and postpartum maternal risks and increased perinatal mortality and perinatal infections associated with PROM [5]. With expectant management approximately 80% of women with PROM [5] after 37 weeks go into labour within 24 hours and 95% within 72 hours [3]. In contrary longer expectancy brings significant neonatal and maternal morbidities due to infection, so it is better to do induction of labour in order to decrease the latent period [6]. The present study was conducted to study the efficacy and safety of misoprostol and oxytocin for induction in PROM at term. "Revised guidelines on when and how to induce labor in pregnant women were issued 21st July, 2009 by The American College of Obstetricians and Gynecologists (ACOG). Although oxytocin infusion is widely accepted as a safe and effective labor induction method, its success is highly dependent on the condition of the cervix at the beginning of the induction.

Hence, cervical ripening agents are often applied in women with unfavourable cervices before an oxytocin infusion is initiated [7]. Prostaglandins, including a variety of classes, doses, and routes of administration, have been widely studied as alternative to oxytocin [8, 9]. Induction of labor with prostaglandins offers the advantage of promoting both cervical ripening and myometrial contractility. There is some concern that the use of misoprostol may provoke excessive uterine activity leading to hyper stimulation [10, 11].

Uterine contraction is important for cervical dilatation and oxytocin causes contraction during 2nd and 3rd stage of labor. It has a half-life of five to 10 minutes [12], time to steady plasma concentration of 40 minutes [13, 14], and a steady state uterine response of 30 minutes or longer [15].

A meta-analysis [16] comparing prostaglandin and oxytocin for induction of labor suggests that prostaglandins reduce the likelihood of operative delivery and failed induction, but increase the incidence of gastrointestinal side effects and pyrexia.

Aims and Objectives

To study and compare the efficacy or oral misoprostol and oxytocin in terms of cervical ripening and induction of labour in PROM at term.

To study and compare the safety of both drugs in terms of maternal and foetal complications.

Material and Methods

Study population

Pregnant patients at term greater than or equal to 37 weeks with rupture of membrane admitted in Kurji Holy Family Hospital, Patna, a tertiary care centre.

Study design

A prospective, randomized comparative study.

Sample size

All pregnant women at term with PROM admitted in Kurji Holy Family Hospital, Patna over the stipulated time frame giving consent for this study and meeting inclusion and exclusion criteria were excluded. About 4100 deliveries occurred in 1 year in our hospital KHFH in which about 492 number of cases presented with PROM. Considering a margin of error of 5% and confidence level of 95% the estimated sample size is 216 calculated by using RAOSOFT software. 16 patients were excluded from the study after applying exclusion criteria. A total of 200 pregnant women were taken as sample in my study. 100 each in misoprostol (Group A) and oxytocin (Group B) respectively. The randomisation was done by single random sampling.

Time frame to address the study

November 2016 to October 2017 (One year).

Inclusion criteria

All primigravida and multigravida patents ≥ 37 weeks of gestation with

- Singleton pregnancy.
- Cephalic presentation.
- Rupture of membrane within 12 hours.
- Reactive CTG.
- Bishod score < 6.
- Not in labour.

Exclusion criteria: Pregnant women

- With symptoms & sign suggestive of chorioamnionitis.
- With prior uterine surgery (LSCS, myomectomy).
- With Contraindications to vaginal delivery like placenta previa, CPD.
- Who are allergic to PG and Oxytocin.
- With medical disease.
- Meconium stained liquor.
- Grand multipara.

Methodology

Patients admission charts, labour ward record, operating notes and nursery sheets were reviewed. Information regarding induction of labour was available from labour ward records. Operative finding were noted from operating notes and neonatal data were collected from nursery sheets. Written and informed consent was taken and a standard case record sheet was maintained for each patient. Detailed history of presenting complain particularly duration of rupture of membrane and obstetric history were obtained.

General physical examination was carried out to rule out clinical signs of chorioamnionitis.

Abdominal examination for presentation, engagement of fetal head and fetal size were recorded, sterile per speculum examination was performed to confirm the rupture of membrane. Vaginal examination done to assess Bishop score. All relevant lab investigations were done and reports collected.

Fetal evaluation was done with a CTG and USG with biophysical profile.

Eligible subjects were randomized to misoprostol and oxytocin group by simple randomisation.

Group A patients were given 25 microgram oral misoprostol every 4 hours for a maximum of 4 doses. Repeat dose was withheld on labour onset.

Group B patients were induced by iv. oxytocin. 2.5 units of oxytocin was added increased gradually by 20, 40 and up to 60 drops. Maximum 5 units of 60 drops/minute was used. Dose was modified according to uterine contraction and fetal heart rate.

Before starting therapy CTG was done in both groups.

Labour induction was accepted to be successful, if vaginal delivery occurred in 24 hours of induction.

The two study groups were compared by means of following variables in order to determine the safety and efficacy of misoprostol and oxytocin in PROM at term –

Maternal outcome was measured in terms of improvement in Bishop's score, induction to delivery interval, number of doses of misoprost required, mode of delivery, failed induction, maternal side effects like nausea, vomiting, pyrexia and complication like uterine hyperstimulation, PPH, uterine rupture, meconium stained liquor, abnormal CTG.

Neonatal outcome will be measured in terms of APGAR score in 1 and 5 minutes, incidence and groups of MSL, birth weight, neonatal admission and indication, neonatal mortality.

Results

Table 1: Age distribution of patients

Age (Years)	Group A	Group B	Total
15-19	12	16	28
20-24	48	34	82
25-29	33	38	71
30-34	7	12	19
Total	100	100	100

$X^2 = 4.63$ df = 3, p=0.02, NS

Most of the patients were within the age group between 20 – 29 years, 81 in group A and 72 in group B. the distribution of patient in two groups according to age was not statistically significant.

Table 2: Group distribution according to gravida

Count	Group A	Group B	Total
Prime	91	94	185
Multi	9	6	15

$X^2 = 0.65$, df = 1, p=0.42, NS

Maximum patients were primigravida in both groups. In group A, 91 patients and in group B, 94 patients are primigravida.
In group A 9 patients and in group B 6 patients were multigravida. The distribution of patients in term of gravida between the two groups was not statistically significant.

Table 3: Bishop score

Group	Mean	Std. Deviation
Misoprost	5.11	0.92
Oxytocin	5.23	1.11

t = 0.83, p>0.05, NS

Bishop score in group A patient is 5.11, while in group B it is 5.23. The difference between the two groups in term of initial Bishop Score was statistically insignificant.

Table 4: Induction delivery interval

Group	N	Mean	Std. Deviation
Group A	45	757	215.26
Group B	44	684.6	127.54

t = 1.92, p>0.05, NS

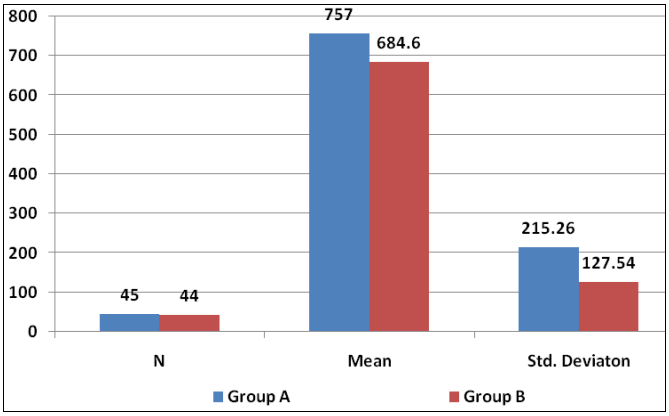

Fig 1: Induction delivery interval

Mean induction delivery interval (IDI) group A is 757 minutes, whereas mean IDI is group B is 684.6 minutes. But the difference was not statistically significant.

Table 5: Normal delivery

VID	Group A	Group B	Total
<13 Hrs.	22	30	52
13 - 18 Hrs.	23	14	37

$X^2 = 3.41$, df = 1, p=0.06, NS

Vaginally delivery occurred in < 13 hrs. in 22 (22%) patients in group A and 30 patients (30%) in group B. vaginally delivery occurred in between 13 – 18 hrs. in 23 patients in group A and 14 patients in group B p=0.06. the difference was not statistically significant.

Table 6: Mode of delivery

Mode	Group A	Group B	Total
NVD	37	38	75
FORCEPS	8	6	14
LSCS	55	56	111

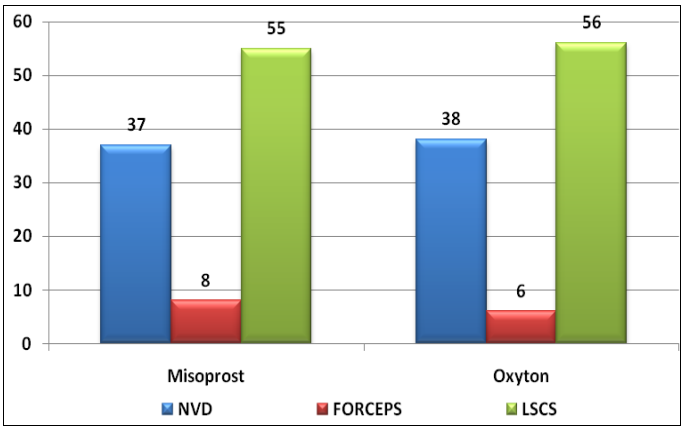

Fig 2: Mode of delivery

In Group A, 45 patients had vaginal delivery in which 8 patients had forceps delivery. Whereas in Group B, 44 patients had vaginal delivery in which 6 patients had forceps delivery. In Group A, 55 patients had LSCS and in group B, 56 patients had LSCS.

Table 7: Uterine contractile abnormalities

Hyperstimulation	Group A	Group B	Total
N	91	93	184
Y	9	7	16
Tachysystole	0	0	0
Rupture of Uterus	0	0	0

The incidence of hyperstimulation was done in Group A (9%) compared to Group B (7%). The difference was not statistically significant. Tachysystole did not occurred in any patients in both group. There was no incidence of rupture of uterus between the two groups.

Table 8: Complications

Placental abruption	Group A	Group B	Total
N	100	99	199
Y	0	1	1

Only 1 case of placental abruption occurred in Group B.

Table 9: Fetal outcome

	Group A	Group B	Total
Non Meconium	51	60	75
Meconium	49	40	14

$X^2 = 1.64$, df = 1, p=0.2, NS.

Meconium stained liquor occurred in 49 patients in Group A and 40 patients in Group B. The difference was not statistically significant (p=0.02).

Table 10: Comparison of APGAR score

		APGAR 1	APGAR 5
Group A	Mean	8.42	9.11
	Std. Deviation	1.31	1.02
Group B	Mean	8.54	9.16
	Std. Deviation	1.15	0.81

APGAR (1 Minute) t = 0.68 p> 0.05, NS
APGAR (5 Minute) t = 0.38 p> 0.05, NS
In Group A, mean APGAR score at 1 minute is 8.42 and is Group B, it is 8.54.
In Group A mean APGAR score at 5 minute is 9.11 and it is 9.16 in Group B.

Discussion

Present study is the comparative study of the efficacy and safety of misoprostol and oxytocin in PROM at term.
This prospective, randomized, comparative study has been conducted over a period of one year in Kurji Holy Family Hospital, Patna, a private teaching institute and referral centre with tertiary care facilities of Bihar.
About 4100 deliveries occurred in one year in our hospital out of which 492 number of cases presented with PROM. Incidence of PROM in our study was found to be around 10 percent which is comparable to other studies in our country and South Asia Region.
After applying Raosoft formula sample size came at 216, and after applying exclusion criteria 16 patients were excluded from study and a total of 200 patients were taken as sample in my study, 100 each in misoprostol and oxytocin group respectively.
Maskey S *et al.* [17] did a comparative study where out of 100 women 50 were induced with 50 mcg of oral misoprostol 4 hours apart (max 6 doses) and other 50 received intravenous oxytocin infusion. Rezvan A *et al.* [18] assessed between 2008 and 2010. 260 women were randomly assigned to one of the two groups according to the method of treatment, misoprostol or oxytocin. Deshpande *et al.* [19] between February, 2012 to July, 2012 compared 65 subjects with rupture of membranes without labour beyond 36 weeks were assigned to receive. Vaginally administered misoprostol 50 mcg, every 4 hrs. and another 65 subjects with rupture of membranes at term received intravenous oxytocin infusion. Fatima U *et al.* [20] did a study between April, 2006 to April, 2007 on 100 pregnant women at term with PROM were taken as sample. Selected patients were given oral misoprostol. Kimberly *et al.* [21] 180 pregnant women at term were randomly assigned misoprost 50 microgram orally every 4 hrs. as needed or i.v. oxytocin.
Induction leading to vaginal delivery in misoprost group is 45 (45%) and in oxytocin group is 44 (44%). Mean IDI in misoprost & oxytocin is 757.00 min (12 hrs.) and 684.66 minutes (11.4 hrs.) respectively. Though IDI is more in misoprost but it is non-significant. Induction leading to vaginal delivery in misoprost group is 45 (45%) and in oxytocin group is 44 (44%). Mean IDI in misoprost & oxytocin is 757.00 min (12 hrs.) and 684.66 minutes (11.4 hrs.) respectively. Though IDI is more in misoprost but it is non-significant. Fatima U *et al.* [20] mean IDI 12.8+_4.24hrs. in misoprost which is comparable to the present study. Wing D A *et al.* [19] showed that average interval from start of induction of vaginal delivery was about 1 hour longer in misoprost (811.5+-511.4 min) than in oxytocin group (747.0+-44.8 min.) p=0.65 comparable to our study.
In oxytocin group, induction failed in 2 cases (2%) & were delivered by LSCS whereas none of the induction failed in misoprost group in the present study. It is comparable to study done by Suk Ngai *et al.* [23], Maskey *et al.* [17]. Rashmi *et al.* [24] found one case of failed induction in misoprost and none in oxytocin. Shabana AA *et al.* [25] showed one case of failed induction both in misoprost (2%) and oxytocin (2%).
Hyper stimulation of uterus occurred in 9 (9%) patients with the use of misoprost group and 7 (7%) patients in oxytocin group, p value was > 0.60, showing the difference was non- significant. In studies carried out by Wing D A *et al.* [6, 9] Shabana AA *et al.* [25] and Kimberley D *et al.* [22] also showed difference between the two drugs as non-significant. In this study no cases of uterine hyper stimulation was encountered.
In the present study, 45 patients in misoprost group and 44 patients in oxytocin group delivered vaginally. 8 and 6 patients have instrumental deliveries in misoprost and oxytocin group respectively. 55 and 56 patients undergone LSCS in misoprost and oxytocin respectively. There was no significant between the two groups in the mode of delivery. This is in agreement with the studies done by Rashmi *et al.* [24], Kimberly D *et al.* [22], Ngai *et al.* [23] Deshpande *et al.* [20] Shabana AA *et al.* [25]
Meconium stained liquor was found in 49 cases (49%) in the misoprost group and 40 cases (40%) in oxytocin group, p value = 0.2, which is non-significant.
In study done by Rezvan A H *et al.* [18], meconium staining of liquor occurred in 0% cases in misoprost and 0.7% in oxytocin group with a p value of 1.0 which is non- significant. Mean APGAR score at 1 minute in misoprostol group is 8.42 and 8.54 in oxytocin group, having a p value of > 0.05, rendering it non-significant. Mean APGAR score at 5 minutes in misoprostol group is 9.11 and 9.16 in oxytocin group, p value > 0.05, which was non- significant.

Conclusion

Although Induction – Delivery Interval is more in misoprost, but

is comparable to i.v. oxytocin. Maternal side effects and neonatal outcome were similar with both drugs.

Therefore we conclude that oral misoprostol is as safe & effective as i.v. oxytocin in inducing labour in women with PROM at term.

Misoprostol is easily stored at room temperature and rapidly absorbed both orally and vaginally. Its costs make it more attractive in our poor socio-economic strata. Oral misoprostol has the advantage of avoiding repeated vaginal insertions eliminating risk of infection. It has low risk of hyperstimulation in comparison to vaginal route.

Therefore oral misoprostol is safe alternative in inducing labour in premature rupture of membrane at term. Although more studies may be required to support this.

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