

# Randomised Comparative Study of Prostaglandin E2 (Pge2) Gel in Combination with Isosorbide Mononitrate (ISMN) and Pge2 Gel alone in Cervical Ripening and Induction of Labor

Laul P<sup>1</sup>, Doley B<sup>2</sup>, Miglani U<sup>1\*</sup>, Madaan R<sup>1</sup> and Miglani I<sup>3</sup>

<sup>1</sup>Senior Specialist, OBG, Deen Dayal Upadhyay, Hospital New Delhi, India

<sup>2</sup>PG Student, Deen Dayal Upadhyay, Hospital New Delhi, India

<sup>3</sup>Medical student, Maulana Azad Medical College, Hospital New Delhi, India

## \*Corresponding author:

Urvashi Miglani,  
Senior Specialist, OBG, Deen Dayal Upadhyay,  
Hospital New Delhi, E 13/9 First floor Vasant  
Vihar 110057, India

Received: 02 Jan 2024

Accepted: 19 Jan 2024

Published: 27 Jan 2024

J Short Name: AJSCCR

## Copyright:

©2024 Miglani U, This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and build upon your work non-commercially.

## Citation:

Miglani U. Randomised Comparative Study of Prostaglandin E2 (Pge2) Gel in Combination with Isosorbide Mononitrate (ISMN) and Pge2 Gel alone in Cervical Ripening and Induction of Labor. Ame J Surg Clin Case Rep. 2024; 7(8): 1-5

## 1. Abstract

**1.1. Objectives:** Aim of this study was to compare PGE2 gel in combination with ISMN and PGE2 gel alone in cervical ripening and induction of labor. Primary objective was to study the interval of time from induction of labor to delivery of baby in both the groups. Secondary objectives were to study the mode of delivery, and maternal adverse effects (tachysystole, headache) in both the groups and to study neonatal outcome, APGAR score, intensive neonatal care unit (NICU) admission and its course in both the groups.

**1.2. Methods:** Randomized comparative study of 100 women was conducted in the labor room in the Department of obstetrics and Gynaecology, DDUH, New Delhi. Statistical analysis was performed using a 2-sample t-test and Chi-Square test. A p value of <0.05 was considered statistically significant.

**1.3. Results:** In our study, Modified Bishop Score was comparable in both the groups during admission. But the modified Bishop score of Group 1 was significantly higher than Group 2 at 6 hours. There was no significant difference noted at 12 hours and 24 hours. Mean time interval between induction to delivery in Group 1 and Group 2 was  $866 \pm 275$  minutes and  $1067 \pm 301$  minutes. Induction to delivery time interval was significantly lower in group 1 than group 2 (p value 0.001, 2-sample t test). Number of doses administered in Group 1 was  $1.720 \pm 0.607$  and Group 2 was  $2.102$

$\pm 0.586$ . Significantly less number of doses was required in Group 1 (P value 0.002, 2 sample t test). In group 1, 92% delivered vaginally and 8% by cesarean section. On the other side in group 2, 88% delivered vaginally and 12% by cesarean section. There was no significant difference (p value 0.739) in mode of delivery in two groups. APGAR score was significantly higher in newborns of group 1 in comparison to group 2. 8% of newborns of group 1 and 28% of newborns of group 2 required NICU admission. Number of newborns with NICU admission was significantly lower in group 1 than in group 2 (P value 0.045, Chi square test). In our study, there was no significant difference in side effects (tachysystole, headache) of two groups.

**1.4. Conclusion:** This randomized observational study suggests that intravaginal isosorbide mononitrate in combination with PGE2 gel (Group 1) is more effective than PGE2 gel alone (Group 2) in cervical ripening prior to induction of labor.

## 2. Introduction

Induction of labor can be defined as an intervention designed artificially to initiate uterine contractions leading to progressive dilatation and effacement of the cervix and birth of the baby [1]. This includes both women with intact membranes and women with spontaneous rupture of membranes who are not in labor. Induction is indicated when the benefits to either mother or fetus outweigh those of pregnancy continuation. There may be situations when

induction of labor is necessary, as it could be hazardous to wait for spontaneous onset of labor e.g. gestational hypertension, pre-eclampsia, post term pregnancy, intrauterine growth retardation, oligohydramnios and various maternal condition such as chronic hypertension and diabetes [2-5].

Drugs commonly used in hospital settings such as prostaglandin (PGE2, PGE1) are effective for cervical ripening. However, there is high incidence of myometrial hyper stimulation, uterine tachysystole and fetal distress associated with their use [6-8].

In contrast to it, nitric oxide donors like nitroglycerine, isosorbide mononitrate (ISMN), sodium nitroprusside, glyceryl trinitrate etc. are thought to bring the ripening of the cervix without producing uterine contractions and they also promote uterine blood flow thus probably decreasing the risk of fetal side effects [9-12]. They act by altering cervical collagen tissue. Most common side effects associated with nitric oxide donors are headache [13-15]. There is a high incidence of adverse effects with the required dosage of PGE2 gel and isosorbide mononitrate such as tachysystole and headache respectively when used individually. So probably a combination of the two may produce the desired effects on cervical ripening with a reduced dosage. In this context the present study was aimed to compare PGE2 gel in combination with nitric oxide donor (ISMN) and PGE2 gel alone in cervical ripening and induction of labor in term pregnancy.

### 3. Methodology

This study was undertaken in the Department of Obstetrics and Gynaecology in Deen Dayal Upadhyay Hospital, New Delhi. Study duration was one and a half years. Sample size was 100 (50 in each group). Women with singleton live pregnancy at term ( $\geq 37$  weeks) with cephalic presentation not in labor, Intact membranes, Bishop score  $\leq 6$ , Parity  $\leq 2$  were included. Women with scarred uterus, malpresentation, placenta previa, fetal macrosomia, multiple pregnancy, polyhydramnios, contraindication to receive ISMN and PGE2 (allergy, history of severe asthma, hypotension, palpitation) were excluded. On admission a complete history was taken as per the patient pro forma and general and systemic examination was done. Fetal heart rate, pelvic examination and Bishop scoring was recorded at the start of induction. Complete hemogram, blood grouping and RH typing, ultrasonography for fetal wellbeing and NST was also done. Cervical assessment was done to see dilatation, length, position, consistency and station. The eligible participants were randomized into two groups, group 1 and group 2 by envelope technique. Group 1 was given PGE2 gel (0.5 mg dinoprostone) intracervical in combination with ISMN 40 mg tablet vaginally at posterior fornix and Group 2 was given PGE2 gel alone intracervical. Maximum of 3 doses were given at 6 hour intervals after checking bishops score at every 6 hour till score of  $\geq 6$  i.e., after 6 hours of first dose cervical assessment was repeated and if Bishop score was  $\leq 6$  then a second dose was administered. Third dose was administered if Bishop score

remained  $\leq 6$  after 12 hours. Then the Bishop score was assessed again at 18 hours and 24 hours after the first dose of administration of cervical ripening agent. After that labor was augmented with either amniotomy or oxytocin if Modified Bishop score was  $\geq 6$  and then progress of labor was plotted on partograph. Subjects who failed to achieve an active phase of labor despite oxytocin stimulation for 6 hours were labeled as failed induction. Active labor was defined as at least 3 regular uterine contractions in 10 minutes, each lasting for at least 40 seconds with cervical dilatations of 3 cm or more.

The primary objective was to study the interval of time from induction of labor to delivery of baby in both the groups. Secondary outcome variables were subsequent number of doses required, incidence of maternal adverse effects (tachysystole, headache), mode of delivery and fetal outcomes like APGAR score, Birth weight, Admission in neonatology unit (NICU) and its course.

### 4. Results and Observations

A total of 100 women were recruited by envelope technique, 50 to each in group 1 and group 2 and simple randomization was done. The maternal characteristics were similar in between the 2 groups. Mean age of group 1 was  $25.90 \pm 3.79$  years and group 2 was  $25.32 \pm 3.74$  years. There was no significant difference of age between the two groups. (p value 0.443, 2 sample t test).

Modified Bishop Score was comparable in both the groups during admission. But the modified Bishops score of Group 1 was significantly higher than Group 2 at 6 hours (p=0.001). There was no significant difference noted at 12 hours and 24 hours (Table 1). Mean time interval between induction to delivery in Group 1 and Group 2 was  $866 \pm 275$  minutes and  $1067 \pm 301$  minutes. Induction to delivery time interval was significantly lower in group 1 than group 2 (p value 0.001, 2-sample t test).

Number of doses administered in Group 1 was  $1.720 \pm 0.607$  and Group 2 was  $2.102 \pm 0.586$ . Significantly a smaller number of doses was required in Group 1 (P value 0.002, 2 sample t test).

In group 1, 92% delivered vaginally and 8% by cesarean section. On the other side in group 2, 88% delivered vaginally and 12% by cesarean section. There was no significant difference (p value 0.739, Chi-square test) in mode of delivery in two groups.

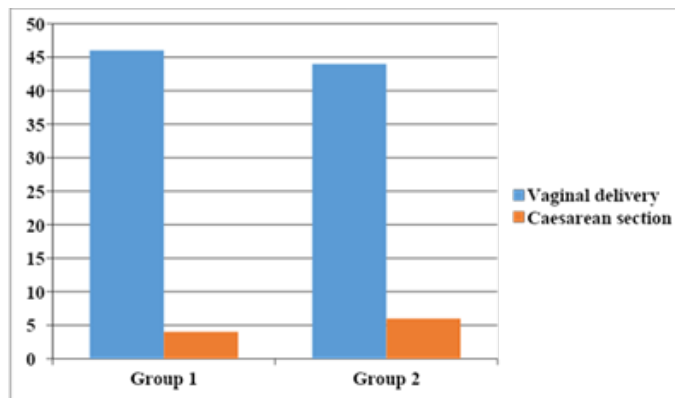
In the current study, APGAR score was significantly higher in newborns of group 1 in comparison to group 2 after 1 and 5 minutes of delivery (P value 0.029 and 0.001 respectively).

8% of newborns of group 1 and 28% of newborns of group 2 required NICU admission. Number of newborns with NICU admission was significantly lower in group 1 than in group 2 (P value 0.045, Chi square test).

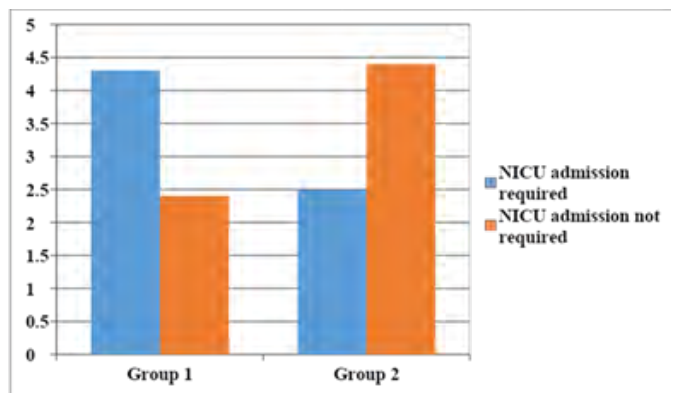
There was no significant difference in side effects of two groups (headache, p value 0.444 and tachysystole, p value 0.433) (Table 2-4 and figure 1-2)

**Table 1:** Comparison of modified Bishop Scores in two groups.

Time	Bishop score		P value
	Group 1	Group 2	
During admission	2.78 ± 0.815	2.64 ± 0.776	0.381
6 hours	5.14 ± 1.55	4.24 ± 1.13	0.001
12 hours	6.41 ± 1.13	6.14 ± 1.51	0.379
24 hours	6.50 ± 1.00	6.08 ± 1.31	0.528



**Figure 1:** Column chart comparing mode of delivery in two groups.



**Figure 2:** Column chart comparing NICU admission in newborns of two groups.

**Table 2:** Descriptive statistics of time interval between induction to delivery in two groups.

Group	Mean (minutes)	SD
Group 1	866	275
Group 2	1067	301

p value 0.001, 2-sample t test

**Table 3:** Descriptive statistics of number of doses administered in two groups.

Group	SD	Mean
Group 1	1.72	0.607
Group 2	2.102	0.586

P value 0.002, 2 sample t test

**Table 4:** Comparison of APGAR score of newborns in groups.

APGAR score	Group 1	Group 2	P value
1 min	8.788 ± 0.824	8.480 ± 0.789	0.029
5 min	9.300 ± 0.678	8.880 ± 0.558	0.001

### 5. Discussion

Recent studies has shown that isosorbide mono nitrate which was primarily being used for angina pectoris, can facilitate the production of NO to induce cervical ripening [3-4]. Studies have established that prolabor cervical status highly correlates with the inducibility of labor. So probably a combination of the two may produce the desired effects on cervical ripening with a reduced dosage. In this context the present study was aimed to compare PGE2 gel in combination with nitric oxide donor (ISMN) and PGE2 gel alone in cervical ripening and induction of labor in term pregnancy.

Different studies have tried to show the effect of NO on cervical pre-induction ripening [19-23]. In our study, induction to delivery time interval was significantly lower in group 1 than group 2 (p value 0.001, 2-sample t test). Similar observations were seen in other studies. Harb HM, et al. [23], there was statistically significant difference between ISMN and misoprostol group versus misoprostol only group regarding induction to delivery time (mean 19.55+/-1.41 to 22.94+/-1.44). Malathi TM, et al [19], there was a significant reduction in induction to delivery interval in the study group (ISMN) 15.2 hours when compared to 23.2 hours in the control group (PGE2 gel) with P value 0.000. In contrast to it Osman et al [8] found time from initiation of treatment to delivery interval was significantly shorter in PGE2 group, 26.9 hours versus 39.7 hours in ISMN group.

Bishop Score of Group 1 was significantly higher than Group 2 at 6 hours. Similar observation was noted by Meena N, et al. [18], where Bishop score was significantly improved 24 hours after initiation of the outpatient ISMN treatment. The change in Bishop's score was 4.83+/-1.88 and 1.07+/-1.27 in the study group (ISMN) and the control (placebo) group respectively. A significant improvement in Bishop score was noted in study group after second dose of ISMN in different studies by Rameez MF, et al. [32] and Bullarbo M, et al. [3].

Significantly a smaller number of doses were required in Group 1 (P value 0.002, 2 sample t test) signifying that addition of ISMN can decrease the net dose of PG E2 gel when used in combination. Similar observation was noted by Sharma N, et al. [21] and Harb HM, et al. [23].

There was no significant difference (p value 0.739) in mode of delivery in two groups . Similarly, study conducted by Agarwal K, et al. [13] have shown lower incidence of caesarean deliveries in IMN group albeit statistically insignificant.

In current study ISMN in combination with PGE2 gel was found to be safe to use for cervical ripening without being associated with

any adverse neonatal outcomes. APGAR score was significantly higher in newborns of group 1 in comparison to group 2. Similar observation was noted by Bullarbo M, et al. [3] and Bollapragada SS, et al. [33]. In contrast Meena N, et al. [18] didn't find any significant difference. Number of newborns with NICU admission was significantly lower in group 1 than in group 2 (P value 0.045, Chi square test). It agreed with the study conducted by Krishnamurthy R, et al. [16]

There was no significant difference in side effects of two groups. Headache was the most common side effect in both groups. Similar observation was noted by Dülger Ö, et al. [20] and Malathi TM, et al. [19]. Chanrachakul B, et al. [9] administered IMN and misoprostol for cervical ripening in 107 women with term pregnancies and compared their adverse effects. They observed remarkably less uterine tachysystole (0 vs. 19.2%,  $P < 0.01$ ) and hyperstimulation (0 vs. 15.4%,  $P < 0.01$ ) in the IMN group.

Induction of labour is a challenge to all obstetricians. Various drugs are used for labour induction, among which PGE2 gel is most widely accepted. ISMN has been studied as a pre-induction cervical ripening agent in recent times. Advantage of using both ISMN and PGE2 gel was that cervix became soft and respond well to induction with other drugs. Side effect was mainly headache which subsided with analgesics. Induction to delivery interval in this group was significantly reduced. It is a cost-effective method of cervical ripening which does not require monitoring during the period of ISMN induction.

## 6. Conclusions

This randomized observational study suggests that intravaginal isosorbide mononitrate in combination with PGE2 gel (Group 1) is more effective and safer than PGE2 gel alone (Group 2) in cervical ripening and induction of labor.

## References

1. Ezebialu IU, Eke AC, Eleje GU, Nwachukwu CE. Methods for assessing pre-induction cervical ripening. *Cochrane Database Syst Rev.* 2015; 2015(6): 1-33.
2. Ekerhovd E, Bullarbo M, Andersch B, Norström A. Vaginal administration of the nitric oxide donor isosorbide mononitrate for cervical ripening at term: a randomized controlled study. *Am J Obstet Gynecol.* 2003; 189(6): 1692-7.
3. Bullarbo M, Orrskog ME, Andersch B, Granström L, Norström A, Ekerhovd E. Outpatient vaginal administration of the nitric oxide donor isosorbide mononitrate for cervical ripening and labor induction postterm: a randomized controlled study. *Am J Obstet Gynecol.* 2007; 196(1): 50-5.
4. Bullarbo M, Norström A, Andersch B, Ekerhovd E. Isosorbide mononitrate induces increased cervical expression of cyclooxygenase-2, but not of cyclooxygenase-1, at term. *Eur J Obstet Gynecol Reprod Biol.* 2007; 130(2): 160-4.
5. Bullarbo M, Tjugum J, Ekerhovd E. Sublingual nitroglycerin for management of retained placenta. *Int J Gynecol Obstet.* 2005; 91(3): 228-32.
6. Abdellah MS, Hussien M, AboAlhassan A. Intravaginal administration of isosorbide mononitrate and misoprostol for cervical ripening and induction of labour: a randomized controlled trial. *Arch Gynecol Obstet.* 2011; 284(1): 25-30.
7. Bala A, Bagga R, Kalra J, Dutta S. Early versus delayed amniotomy during labor induction with oxytocin in women with Bishop's score of  $\geq 6$ : a randomized trial. *J Matern Fetal Neonatal Med.* 2018; 31(22): 2994-3001.
8. Osman I, MacKenzie F, Norrie J, Murray HM, Greer IA, Norman JE. The "PRIM" study: a randomized comparison of prostaglandin E2 gel with the nitric oxide donor isosorbide mononitrate for cervical ripening before the induction of labor at term. *American journal of obstetrics and gynecology.* 2006; 194(4): 1012-21.
9. Chanrachakul B, Herabutya Y, Punyavachira P. Randomized trial of isosorbide mononitrate versus misoprostol for cervical ripening at term. *International Journal of Gynecology & Obstetrics.* 2002; 78(2): 139-45.
10. Dave A, Nigam P, Maru L. Isosorbide Mononitrate a Nitric Oxide Donor: A Study of Its Efficacy and Safety as an Agent for Cervical Ripening. *J Obstet Gynaecol India.* 2015; 65(3): 162-6.
11. Collingham JP, Fuh KC, Caughey AB, Pullen KM, Lyell DJ, El-Sayed YY. Oral misoprostol and vaginal isosorbide mononitrate for labor induction: a randomized controlled trial. *Obstet Gynecol.* 2010; 116(1): 121-6.
12. Abdellah MS, Hussien M, Aboalhassan A. Intravaginal administration of isosorbide mononitrate and misoprostol for cervical ripening and induction of labour: a randomized controlled trial. *Arch Gynecol Obstet.* 2011; 284(1): 25-30.
13. Agarwal K, Batra A, Batra A, Dabral A, Aggarwal A. Evaluation of isosorbide mononitrate for cervical ripening prior to induction of labor for postdated pregnancy in an outpatient setting. *Int J Gynaecol Obstet.* 2012; 118(3): 205-9.
14. Yazdizadeh H, Abedi P, Najar S, Angali KA. The impact of isosorbide mononitrate on cervical ripening and labor induction in primiparous women with term pregnancy: A double-blind, randomized, controlled trial. *Iran J Nurs Midwifery Res.* 2013; 18(3): 246-50.
15. Guha K, Fatema A, Biswas PK, Haque E. Isosorbide Mononitrate versus Misoprostol for Cervical Ripening and Induction of Labour at Term. *Mymensingh Med J.* 2015; 24(2): 346-51.
16. Krishnamurthy R, Pallavee P, Ghose S. Evaluation of Isosorbide Mononitrate for Preinduction of Cervical Ripening: A Randomized Placebo-Controlled Trial. *J Family Reprod Health.* 2015; 9(2): 75-81.
17. Poovathi M, Kanagasabhai D. Effect of Vaginal Administration of Nitric Oxide Donor Isosorbide Mononitrate on Cervical Ripening Before Induction in Term Pregnancy: A Randomized Controlled Study. *Int J Sci Stud.* 2016; 3(12): 148-51.

18. Meena N, Bindal N, Meena S. Evaluation of isosorbide mononitrate for cervical ripening prior to induction of labor at term pregnancy in an outpatient setting. *Int J Reprod Contracept Obstet Gynecol.* 2016; 5(3): 793-7.
19. Malathi TM, Kanchanamalai K. A comparative study of safety and efficacy of vaginal isosorbide mononitrate (40mg) with dinoprostone gel (0.5mg). *Int J Reprod Contracept Obstet Gynecol.* 2018; 7(10): 4197-201.
20. Dülger Ö, Sik BA, Aba YA. A comparative randomized study on effect of vaginally administered glyceryl trinitrate placebo on cervical ripening prior to induction of labor in overdue pregnancies. *Indian J Pharmacol.* 2018; 50(5): 260-5.
21. Sharma N. Comparative Study of Efficacy of Intravaginal Isosorbide Dinitrate with Dinoprostone Gel on Cervical Ripening Prior To Induction of Labor. *IOSR-JDMS.* 2018; 17(3): 44-8.
22. Somalwar S, Tathe GR, Dixi MS. Effectiveness of Isosorbide Mononitrate vs Prostaglandin E2 Gel for Cervical Ripening: A Study. *Journal of SAFOG.* 2019; 11(5): 288-91.
23. Harb HM, Mansour DY, Abouahmed YM. Intravaginal isosorbide mononitrate in addition to misoprostol versus misoprostol only for induction of labor: a randomized controlled trial. *QJM.* 2020; 113(1): 1-5.
24. Arif R, Mazhar T, Jamil M. Induction of Labor in Primigravid Term Pregnancy with Misoprostol or Dinoprostone: A Comparative Study. *Cureus.* 2019; 11(9): 1-8.
25. Thomas J, Fairclough A, Kavanagh J, Kelly AJ. Vaginal prostaglandin (PGE2 and PGF2a) for induction of labour at term. *Cochrane Database Syst Rev.* 2014; 2014(6): 1-263.
26. Yazdizadeh H, Abedi P, Najar S, Angali KA. The impact of isosorbide mononitrate on cervical ripening and labor induction in primiparous women with term pregnancy: A double-blind, randomized, controlled trial. *Iran J Nurs Midwifery Res.* 2013; 18(3): 246-50.
27. Mirteimouri M, Pourali L, Najaf Najafi M, Ghaffarian Omid M. Intravaginal administration of isosorbide mononitrate for cervical ripening in prolonged pregnancy: a randomised clinical trial. *J Obstet Gynaecol.* 2020; 40(6): 792-6.
28. Malathi TM, Kanchanamalai K. A comparative study of safety and efficacy of vaginal isosorbide mononitrate (40mg) with dinoprostone gel (0.5mg). *Int J Reprod Contracept Obstet Gynecol.* 2018; 7(10): 4197-201.
29. Haghighi L, Moukhah S, Goshtasbi A. Comparing the effect of oral and vaginal isosorbide dinitrate in pre-induction cervical ripening in term pregnancy: A controlled clinical trial. *Adv Biomed Res.* 2015; 4(6): 129-35.
30. Souizi B, Mortazavi F, Haeri S, Borzoe F. Comparison of vaginal misoprostol, laminaria, and isosorbide dinitrate on cervical preparation and labor duration of term parturient: a randomized double-blind clinical trial. *Electron Physician.* 2018; 10(5): 6756-63.
31. Singh K, Deo S, Jaiswar SP, Singh R, Sinha S. Intravaginal Isosorbide Mononitrate and Misoprostol Versus Misoprostol Alone For Induction Of Labour.
32. Rameez MF, Goonewardene IM. Nitric oxide donor isosorbide mononitrate for pre-induction cervical ripening at 41 weeks' gestation: A randomized controlled trial. *J Obstet Gynaecol Res.* 2007; 33(4): 452-6..
33. Bollapragada SS, MacKenzie F, Norrie JD, Eddama O. Randomised placebo-controlled trial of outpatient (at home) cervical ripening with isosorbide mononitrate (IMN) prior to induction of labour - clinical trial with analyses of efficacy and acceptability. The IMOP study. *BJOG.* 2009; 116(9): 1185-95.