COMPARISON OF SUBLINGUAL MISOPROSTOL AND PER VAGINAL MISOPROSTOL FOR PAIN RELIEF DURING AND AFTER HSG PROCEDURE: A RANDOMIZED CONTROLLED TRIAL

Gynaecology

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ABSTRACT

Background: Misoprostol has been extensively used in obstetrics and has proved to be a very effective cervical softening agent before termination of pregnancy. The beneficial effects on cervical ripening may make misoprostol a desirable agent for helping cervical dilatation on non pregnant women.

Aim: To compare the efficacy and safety of pre-procedure sublingual misoprostol versus pervaginal misoprostol for relief of pain during and after the HSG procedure.

Materials and methods: Study was initiated after approval from the IEC. There after subject recruitment had done from July 2017 to June 2018 in the department of Obstetrics & Gynaecology (indoor setting) of IPGME&R & SSKM Hospital

Result: We found that association of cervical resistance score vs. group was statistically significant ($p < 0.0001$). Association of need for analgesics vs. group was not statistically significant ($p = 0.11004$). Association of any adverse effect vs. group was not statistically significant ($p = 1.0000$). Difference of mean age vs. group was not statistically significant ($p = 0.0717$).

Conclusion: There was no significant difference of pain after the HSG procedure in both the group. The patients who were received sublingual misoprostol had significantly low cervical resistance during the procedure.

KEYWORDS

Misoprostol, cervical ripening, cervical dilatation, pervaginal misoprostol.

INTRODUCTION

Infertility is clinically defined as the failure to achieve a pregnancy after one year of regular unprotected sexual intercourse.¹ Incidence of infertility is 12% to 28% of which 20-30% is attributed to male infertility and 20-35% due to female infertility, 25-40% due to combined problem in both. Causes of female sub fertility are ovulation problems (e.g. PCOS), tubal factors, pelvic inflammatory disease caused by infection like tuberculosis, age related factors, uterine anomaly, genetic causes and other undetermined causes. Of these tubal factors are responsible for infertility in 25-35% of cases.²

Hysterosalpingogram (HSG) is an X-ray test used to see the uterine cavity and fallopian tubes and the area around them. It is done for women with infertility and sub fertility.³

During the test, a dye (contrast material) is pushed through a HSG cannula. That cannula is put through the vagina and into the cervix. Pictures are taken using a steady beam of X-ray (fluoroscopy) as the dye passes through the uterus and fallopian tubes. The pictures can show problems such as abnormal structure of the uterus or fallopian tubes. They can also show a blockage that would prevent an ovum moving through a fallopian tube to the uterus. A blockage also could prevent sperm from moving into a fallopian tube and joining (fertilizing) an ovum. The test also may find problems on the inside of the uterus that prevent a fertilized ovum from attaching (implanting) to the uterine wall.⁴

Although HSG is less invasive than laparoscopic dye test patients sometimes refuse it because of pain perceived by the patient during and after the procedure.

During the HSG procedure there may be difficulty in cannulation and injecting the dye and patients complain of intense pain. Relief of pain can be provided by prescribing NSAID singly or in combination with lidocaine or EMLA cream in the posterior fornix of the cervix. Of the NSAID used naproxen sodium, acetaminophen and fenoprofen are most commonly used.⁵

It is postulated that Misoprostol may also be used to overcome the problem during HSG procedure to a certain extent but there is no

definite recommendation for misoprostol both for ideal route of administration and optimum doses and thus in this study an attempt will be made to study this.⁶

Misoprostol is primarily metabolised in liver and less than 1% of its active metabolite is excreted in urine. Most common adverse effects of misoprostol after oral administration are nausea vomiting diarrhoea, abdominal cramps and fever which are dose dependent.⁷

The effects of misoprostol on the reproductive tract are increased and gastrointestinal side effects are decreased if the tablets are administered vaginally. After vaginal application the peak plasma concentration of misoprostol acid is reached in 70 to 80 minutes and then declines slowly by 6 hours. Though vaginal application of misoprostol results in slower increase and lower peak plasma concentration as compared to oral administration, the overall exposure to the drug is increased. The peak plasma concentration following sublingual administration of misoprostol is higher than the peak achieved following PV route and the time taken to achieve peak plasma concentration is about 30 minutes. Thus the onset of action of misoprostol is quicker by the sublingual route compared to the pervaginal route but the total duration of action is shorter and is reported to be about 80 to 120 minutes.⁸ Therefore the pharmacokinetic profile of sublingual misoprostol justifies it being investigated as an alternate route of administration for HSG procedural pain relief.⁹

Aim of the study was to compare the efficacy and safety of pre-procedure sublingual misoprostol versus pervaginal misoprostol for relief of pain during and after the HSG procedure.

MATERIALS AND METHODS

Study setting:

Department of Obstetrics & Gynaecology (indoor setting) of IPGME&R & SSKM Hospital

Period of study:

Study was initiated after approval from the IEC. There after subject recruitment had done from July 2017 to June 2018.

Definition of population:

Patients admitted for HSG in the Gynecology department of SSKM Hospital.

INCLUSION CRITERIA:

Women with infertility who have been advised to undergo HSG with the following criteria:

1. Age: 18 years to 40 years.
2. Semen analysis of husband is normal
3. History of repeated miscarriage
4. Women willing to give written informed consent to participate in the study

EXCLUSION CRITERIA:

1. Women with history of hypersensitivity to misoprostol
2. Women with history of hypersensitivity to HSG dye
3. Significant hepatic impairment with liver enzymes >1.5 times the upper limit of normal.
4. Significant renal impairment. Serum creatinine level >1.5mg/dl

Study design:

Randomized, parallel group, open label, controlled trial.

Test group was receive a single dose of 200 mcg misoprostol sublingually one hour prior to the HSG procedure

Control group was receive a single dose of 400 mcg misoprostol per vagina, 4 hours prior to the procedure

Statistical analysis of plan:

Descriptive statistical analysis was done for the baseline demographic and disease profile. Inferential statistical tests were used for comparing the efficacy and safety profiles. An ITT (Intention to treat) analysis was done for all subjects who have received the study drug. A per protocol analysis shall also be done for subjects who have received the study drug and have all VAS scores at the three time points. SPSS version 17 and Medcal statistical software was used for data analysis. A p value of <0.05 shall be considered as statistically significant.

RESULT AND ANALYSIS

Our study showed that in control group, 33(66.0%) patients had lower, 15(30.0%) patients had middle and 2(4.0%) patients had upper. In test group, 37(74.0%) patients had lower and 13(26.0%) patients had middle. Association of SES vs. group was not statistically significant ($p=0.3055$). According to menstrual history in control group, 37(74.0%) patients had regular and 13(26.0%) patients had irregular. According to menstrual history in test group, 39(78.0%) patients had regular and 11(22.0%) patients had irregular. Association of menstrual history vs. group was not statistically significant ($p=0.6395$).

It was found that according to BMI in control group, 8(16.0%) patients had <18, 38(76.0%) patients had 18-24.9 and 4(8.0%) patients had 25-29.9. According to BMI in test group, 7(14.0%) patients had <18, 38(76.0%) patients had 18-24.9 and 5(10.0%) patients had 25-29.9. Association of BMI vs. group was not statistically significant ($p=0.9149$). In all group all patients had PSH no h/o cervical op. According to TOD in control group, all patients had 4 hrs before. According to TOD in test group, all patients had 1 hr before. Association of TOD vs. group was statistically significant ($p<0.0001$).

We found that according to ROD in control group, all patients had ROD PV. According to ROD in test group, all patients had ROD SL. Association of ROD vs. group was statistically significant ($p<0.0001$). According to during procedure vas in control group, 8(16.0%) patients had VAS <4, 35(70.0%) patients had VAS 4 to 7 and 7(14.0%) patients had VAS >7. According to during procedure vas in test group, 20(40.0%) patients had VAS <4, 28(56.0%) patients had VAS 4 to 7 and 2(4.0%) patients had VAS >7. Association of during procedure vas vs. group was statistically significant ($p=0.0129$).

It was found that according to after procedure vas in control group, 7(14.0%) patients had VAS <4, 41(82.0%) patients had VAS 4 to 7 and 2(4.0%) patients had VAS >7. According to after procedure vas in test group, 8(16.0%) patients had VAS <4, 40(80.0%) patients had VAS 4 to 7 and 2(4.0%) patients had VAS >7. Association of after procedure vas vs. group was not statistically significant ($p=0.9613$). According to 4 hour post procedure vas in control group, 48(96.0%) patients had VAS <4 and 2(4.0%) patients had VAS 4 to 7. According to 4 hour post

procedure vas in test group, 47(94.0%) patients had VAS <4 and 3(6.0%) patients had VAS 4 to 7. Association of 4 hour post procedure vas vs. group was not statistically significant ($p=0.6463$).

We observed that according to cervical resistance score in control group, 5(10.0%) patients had 1 and 42(84.0%) patients had 2 and 3(6.0%) patients had 3. According to cervical resistance score in test group, 46(92.0%) patients had 1 and 3(6.0%) patients had 2 and 1(2.0%) patients had 3. Association of cervical resistance score vs. group was statistically significant ($p<0.0001$). In control group, 47(94.0%) patients had need for analgesics. In test group, 42(84.0%) patients had need for analgesics. Association of need for analgesics vs. group was not statistically significant ($p=0.11004$).

We also found that according to duration of analgesics in control group, 4(8.0%) patients had 1 day, 43(86.0%) patients had >1 day. According to duration of analgesics in test group, 25(50.0%) patients had 1 day, 17(34.0%) patients had >1 day. Association of duration of analgesics vs. group was statistically significant ($p<0.0001$). In control group, 4(8.0%) patients had adverse effect. In test group, 4(8.0%) patients had adverse effect. Association of any adverse effect vs. group was not statistically significant ($p=1.0000$). In control group, the mean age (mean $\pm$ s.d.) of patients was 25.3600 ± 3.3305 years. In test group, the mean age (mean $\pm$ s.d.) of patients was 26.4600 ± 2.6742 years. Difference of mean age vs. group was not statistically significant ($p=0.0717$).

DISCUSSION

Test group was received a single dose of 200 mcg misoprostol sublingually one hour prior to the HSG procedure. Control group was received a single dose of 400 mcg misoprostol per vagina, 4 hours prior to the procedure. We found that in control group, the mean age (mean $\pm$ s.d.) of patients was 25.3600 ± 3.3305 years. In test group, the mean age (mean $\pm$ s.d.) of patients was 26.4600 ± 2.6742 years. Difference of mean age vs. group was not statistically significant ($p=0.0717$).

According to BMI in control group, 8(16.0%) patients had <18, 38(76.0%) patients had 18-24.9 and 4(8.0%) patients had 25-29.9. According to BMI in test group, 7(14.0%) patients had <18, 38(76.0%) patients had 18-24.9 and 5(10.0%) patients had 25-29.9. Association of BMI vs. group was not statistically significant ($p=0.9149$). In all group all patients had PSH no h/o cervical op.

Hassa H et al¹⁰ found that the primary outcome of the study was to evaluate the severity of pain during and 30 minutes after the procedure using a visual analog scale (VAS) ranging from 1 (very favorable) to 10 (very unfavorable). The secondary outcomes were to assess the rate of completion and the vasovagal effects including nausea, vomiting, sweating, weakness, syncope, hypotension, and bradycardia. There was no statistically significant difference in the median (25%-75%) VAS pain scores between women administered vaginal misoprostol (median, 6.7 cm; range, 4.7-9 cm) and the control group (median, 6.7 cm; range, 4.6-8.8 cm) during the HSG. However, women in the NSAID group (median, 5.5 cm; range, 3-7.6 cm) reported less pain than did those in the misoprostol group ($p=.009$) and the control group ($p=.03$). At 30 minutes after HSG, there was no significant difference in the median VAS pain scores between patients administered NSAIDs (median, 2.3 cm; range, 1.4-4.2) or misoprostol (median, 2.3 cm; range, 1.2-4.4) and the control group (median, 2.2 cm; range, 1.3-4.4). There is no benefit in terms of pain reduction with the use of misoprostol during HSG or at 30 minutes after the procedure. However, NSAIDs are associated with pain relief during the HSG procedure.

According to TOD in control group, all patients had 4 hrs before. According to TOD in test group, all patients had 1 hr before. Association of TOD vs. group was statistically significant ($p<0.0001$).

According to ROD in control group, all patients had ROD PV. According to ROD in test group, all patients had ROD SL. Association of ROD vs. group was statistically significant ($p<0.0001$).

We found that according to during procedure vas in control group, 8(16.0%) patients had VAS <4, 35(70.0%) patients had VAS 4 to 7 and 7(14.0%) patients had VAS >7. According to during procedure vas in test group, 20(40.0%) patients had VAS <4, 28(56.0%) patients had VAS 4 to 7 and 2(4.0%) patients had VAS >7. Association of during procedure vas vs. group was statistically significant ($p=0.0129$).

According to after procedure vas in control group, 7(14.0%) patients had VAS <4, 41(82.0%) patients had VAS 4 to 7 and 2(4.0%) patients had VAS >7. According to after procedure vas in test group, 8(16.0%) patients had VAS <4, 40(80.0%) patients had VAS 4 to 7 and 2(4.0%) patients had VAS >7. Association of after procedure vas vs. group was not statistically significant ($p=0.9613$).

According to 4 hour post procedure vas in control group, 48(96.0%) patients had VAS <4 and 2(4.0%) patients had VAS 4 to 7. According to 4 hour post procedure vas in test group, 47(94.0%) patients had VAS <4 and 3(6.0%) patients had VAS 4 to 7. Association of 4 hour post procedure vas vs. group was not statistically significant ($p=0.6463$).

We found that in according to cervical resistance score in control group, 5(10.0%) patients had 1 and 42(84.0%) patients had 2 and 3(6.0%) patients had 3. According to cervical resistance score in test group, 46(92.0%) patients had 1 and 3(6.0%) patients had 2 and 1(2.0%) patients had 3. Association of cervical resistance score vs. group was statistically significant ($p<0.0001$).

Milani F et al¹¹ found that the course of misoprostol was repeated if the women did not abort within 24 hours. The median induction-to-abortion interval was shorter in sublingual group (12/72 hours in sublingual and 14/67 hours in vaginal). There was no significant difference in the success rate at 24 and 48 hours and in side effects. The preference for the sublingual route of administration was higher. Both vaginal and sublingual misoprostol are effective for medical abortion in second trimester termination. But it appears from shorter induction interval in sublingual and higher acceptability that sublingual route is a better choice.

We found that in control group, 47(94.0%) patients had need for analgesics. In test group, 42(84.0%) patients had need for analgesics. Association of need for analgesics vs. group was not statistically significant ($p=0.11004$).

According to duration of analgesics in control group, 4(8.0%) patients had 1 day, 43(86.0%) patients had > 1 day. According to duration of analgesics in test group, 25(50.0%) patients had 1 day, 17(34.0%) patients had > 1 day. Association of duration of analgesics vs. group was statistically significant ($p<0.0001$).

We found that in control group, 4(8.0%) patients had adverse effect. In test group, 4(8.0%) patients had adverse effect. Association of any adverse effect vs. group was not statistically significant ($p=1.0000$).

CONCLUSION

It is found that pain during HSG procedure significantly reduced in patients who were received sublingual misoprostol.

There was no significant difference of pain after the HSG procedure in both the group. The patients who were received sublingual misoprostol had significantly low cervical resistance during the procedure.

Need for analgesics also significantly reduced in test group. The patient in test group who required analgesic, needed it for short duration in respect to control group.

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