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Full Length Research Paper

Comparison of efficacy and safety of mifepristone-misoprostol combination with ethacridine lactate in mid-trimester termination of pregnancy

Smiti Nanda and Anshu Paul*

Department of Obstetrics and Gynaecology, 32/11J, Medical Campus, PGIMS, Rohtak, 124001, Haryana India.

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This study was done to compare the effectiveness and safety of mifepristone/misoprostol versus extra-amniotic injection of ethacridine lactate for the termination of second trimester pregnancy. Sixty women requesting voluntary termination of pregnancies, between 13 and 20 weeks of gestation, were randomly assigned into two groups. Group 1 (MM) received a single oral dose of 200 mg mifepristone and 48 h later 400 mcg vaginal misoprostol every 4 h, with up to five additional doses. Group 2 (EL) received an extra-amniotic injection of 150 ml of ethacridine lactate with 250 mcg of PGF2α. The primary outcome was successful abortion rate. Secondary outcomes included the difference in the induction-to-abortion interval and the frequency of adverse events. Both MM and EL regimens were effective, with successful abortion rates of 96.67 and 93.33%, respectively (P value > 0.05, NS). The complete abortion rates were 90 and 86.66%, respectively. The induction-to-abortion interval was longer in the MM group than in the EL group that is, (58.31 ± 3.62 h) versus (32.28 ± 9.94 h), respectively, P < 0.001, VHS). Both treatments were safe, although there was a significant difference in duration of hospital stay between the two groups. Both MM and EL regimens were effective with high success rates and were safe for the termination of second trimester pregnancy.

Key words: Mifepristone, misoprostol, pregnancies, abortion, treatments.

INTRODUCTION

Second trimester termination of pregnancy carried out from 13 to 20 weeks can be physically and psychologically traumatic for the patient. Surgical termination of pregnancy is of high risk for the woman's health and medical ways are required. Important reasons for termination of pregnancy include fetal demise, pregnancy induced hypertension, fetal anomalies; where termination of pregnancy has to be performed to safeguard maternal health.

An ideal method for termination of pregnancy should be safe, easy and effective and associated with less complications, morbidity and mortality. The need for termination of pregnancy in second trimester has resulted in inventing various methods and the research continues since ancient days till date for example, intracervical laminaria tents, surgical evacuation, intraamniotic instillation of hypertonic saline, ethacridine lactate and prostaglandins (World Health Organization, 1997).

MATERIALS AND METHODS

In a retrospective analysis of prospectively collected data, 60 healthy women over the age of legal consent, coming for second trimester termination of pregnancy, between 13 to 20 weeks, were recruited over 2 years. They were counseled regarding various methods, their side effects, dosage schedules and need for

*Corresponding author. E-mail: Anshupaul81@gmail.com. Tel: 09050425513.

subsequent follow up. Termination was done only after the opinion of two registered medical practitioners were soughted. Patients with anemia, scarred uterus, allergy, low lying placenta and coagulation disorders were excluded from the study. Women were randomized in two groups by using random number tables, each group comprising 30 women.

In Group 1, each woman received a single oral dose of mifepristone 200 mg on day 1 followed by 400 mcg of vaginal misoprostol, 48 h later. This was followed by vaginal misoprostol 400 mcg every 3 h for a maximum of five doses. In Group 2, 150 ml of ethacridine lactate was instilled in extra amniotic space by foleys catheter; along with this, one ampoule of PGF2 alpha was added. The catheter was removed after 24 h, unless expelled spontaneously. Side effects including nausea, vomiting, diarrhea, headache, dizziness, rash, fever, shivering and pain were recorded. The induction abortion interval was calculated from the time of administration of mifepristone/ethacridine lactate to the time when fetus and placenta aborted. Also, induction abortion interval after misoprostol administration was calculated and final outcome was assessed at 48 h and classified as complete, incomplete, or failure. If placenta was found to be incomplete, suction evacuation or check curettage were performed. If fetus was not expelled, oxytocin infusion of 10 units in 500 ml of ringer lactate was used. Comparisons of two groups were done in terms of (a) induction abortion interval from the time of start of mifepristone/ethacridine lactate, (b) intensity of side effects, (c) evacuation required for incomplete abortion.

Comparison of group 1(mifepristone-misoprostol combination) and Group 2 (ethacridine lactate, 0.1%) was assessed by applying chi square test. The difference was said to be significant when probability was less than 0.05.

RESULTS

The present study was carried out on 60 pregnant women with the aim to compare the efficacy and safety of mifepristone-misoprostol combination with ethacridine lactate (0.1%) and 250 µg of injection PGF2x combination in second trimester termination of pregnancy between 13 to 20 weeks. Patients were randomly divided into two groups, each comprising 30 patients. The most patients (63.33%) were Group 1 between 21 to 25 years and 56.67% patients in Group 2 between 26 to 30 years. The mean age of Groups 1 and 2 were 24.43 ± 2.44 years and 25.4 ± 2.40 years, respectively ($p > 0.05$, NS).

Successful abortion was achieved in 96.67% patients in Group 1 and 93.33% patients in Group 2 ($p > 0.05$). Success of induction was not related to age and parity. Abortion was complete in 90% patients in Group 1 and 86.67% patients in Group 2. There was one case of failure in Group 1, and 2 cases of failure in Group 2 ($p > 0.05$). Mean induction abortion interval was 10.51 ± 4.46 h in Group 1 and 32.28 ± 9.94 h in Group 2 ($p < 0.001$, VHS). However in Group 1, mean mifepristone to abortion interval was 58.31 ± 3.62 h. The maternal side effects to either medication included nausea, vomiting, diarrhea, fever, abdominal cramps. The incidence of side effects was more in Group 2, as compared to Group 1. There were no cases of rupture uterus or hyper-stimulation in both the groups. Mean number of days of hospital stay in Groups 1 and 2 were 4.13 ± 0.77 and 3.06 ± 0.78 days, respectively ($p < 0.001$, VHS).

There was no significant correlation between bishop score and induction to abortion interval. In Group 1, 8/9 (88.88%) primigravidae delivered within 24 h, while 100% multigravida (21/21) delivered within 24 h. However in Group 2, only 12.5% primigravidae and 18.18% (4/22) multigravidae delivered within 24 h. However, this data did not reach up to a significant p value ($p > 0.05$, NS).

DISCUSSION

According to WHO (1997), the preferred medical method for induction of abortion after 14 weeks of pregnancy is a combination of antiprogestogen, followed 24 to 48 hours later by a prostaglandin. Hence, newer methods of second trimester abortion like mifepristone and misoprostol have almost replaced the traditional methods and very few studies have compared them to currently recommended methods. Ethacridine lactate (EL) method is one of them. Contrary to other countries, ethacridine lactate is still the first line method for second trimester abortion in China. This is because EL is an inexpensive, effective and safe method that offers an alternative to mifepristone-misoprostol regimen in countries or areas, where mifepristone is unaffordable or unavailable.

In the present study, two groups were comparable in terms of age, parity and initial Bishop score. The primary outcome measure was the achievement of successful abortion and induction abortion interval. The success of induction was defined as complete abortion occurring within 48 h of administration of ethacridine lactate or within 24 h of administration of first dose of misoprostol. In the present study, 96.67% patients (29/30) had successful abortion in Group 1 (MM) and 93.33% patients in Group 2 that is, EL (28/30). Bhatena et al. (1999) reported a success rate of 92% with 0.1% ethacridine lactate which increased to 98% after addition of 250 µg of PGF2α extraamniotically. However, Kalekci et al. (2006) reported a reduced success rate of 70.6% with 0.1% ethacridine lactate which improved to 80.4% on addition of oxytocin infusion. Almost similar successful abortion rates were shown by other authors (Shukla et al., 1984; Zauva et al., 1989; Sofat et al., 1994).

Ashok and Templeton (1999) studied the efficacy and safety of mifepristone misoprostol combination in patients requiring second trimester termination of pregnancy and reported a successful abortion rate of 97% which is similar to the present study. Similar successful abortion rates were reported by other authors (le Roux et al., 2001; Bartley and Baird, 2002).

In the present study, the mean induction abortion interval was 58.31 ± 3.62 and 32.28 ± 9.94 h in Groups 1 and 2, respectively ($p < 0.001$, VHS) (Table 1) and difference was highly significant. However, misoprostol to abortion interval was significantly shorter that is, 10.51 ± 4.46 h (Table 2). Bhatena et al. (1990) reported median IAI of 35 h with EL alone and 19 h with EL and PGF2α combination which is not comparable to the present

Table 1. Induction abortion interval (mifepristone abortion).

Induction abortion time (h)	Group 1 (MM) Mifepristone-abortion interval (%)	Group 2 (EL) (%)
<24	0	5 (16.66)
24-36	2 (6.67)	20 (66.66)
37-48	4 (13.33)	2 (6.66)
49-60	18 (60)	3 (10)
>60	6 (20)	0
Total	30	30
Mean±SD	58.31±3.62	32.28±9.94
p value	< 0.001 very highly significant	

MM: Mifepristone/misoprostol; EL: ethacridine lactate.

Table 2. Induction abortion interval (misoprostol abortion)

Induction abortion time (h)	Group 1 (MM) Misoprostol-abortion interval (%)	Group 2 (EL) (%)
<12	21 (70)	0
12-24	8 (26.67)	5 (16.67)
25-36	1 (3.33)	20 (66.67)
37-48	0	2 (6.67)
49-60	0	3 (10)
Total	30	30
Mean±SD	10.51±4.46	32.28±9.94
p value	P value < 0.001 VHS	

MM: Mifepristone/misoprostol; EL: ethacridine lactate.

study. Kelekci et al. (2006) reported an IAI of 17.3 h with EL alone and 15.8 hrs with EL and oxytocin infusion. IAI of EL is comparable to the study by Chaudhari et al. (2004) who compared extraamniotic instillation of 0.1% ethacridine lactate with misoprostol 400 µg 12 h and reported an induction abortion interval of 31.3 h, which is similar to the present study, with a successful abortion rate of 95% (Chaudhuri et al., 2004). Purandre et al. (1977) showed an induction abortion interval of 29.54 h and a complete abortion rate of 82% with 0.1% ethacridine lactate which is almost similar to the present study. Similarly, Sofat et al. (1994) also reported 92% success rate within 48 h and 98% within 72 h following ethacridine lactate instillation for second trimester MTP. The mean induction abortion interval was 31 h 31 min which is comparable with our results. Almost similar results were reported by Hou et al. (2010). He showed a significant difference between the two groups in term of mean induction to abortion interval.

The mean time from initial drug administration to fetal expulsion was 50.57 ± 6.80 h in mifepristone-misoprostol group versus 43.02 ± 8.74 h in EL group ($p < 0.001$). However, the mean time from administration of misoprostol to fetal delivery in mifepristone-misoprostol group was 10.54 ± 5.81 h which is almost similar to the present study that is, 10.51 ± 4.46 h (Table 2).

In the present study, two groups were also compared for the number of days of hospital stay. In Group 1 (mifepristone-misoprostol) 60% patients (18/60) had a hospital stay of 4 days whereas in Group 2 (EL) 60% of patients (18/60) had a hospital stay of 3 days. This may be due to the fact that in Group 1, all the patients were admitted 48 h prior to induction with misoprostol, for mifepristone administration, which had probably led to increase in the number of days of hospital stay in mifepristone-misoprostol group.

The induction abortion interval was significantly shorter in parous women than in nulliparous in Group 1. In Group 1 8/9 (88.88%) delivered within 24 h while 100% (21/21) multigravida delivered within 24 h. However in Group 2, 12.5% primigravida and 18.18% multigravida delivered within 24 h. Hou et al. (2010) also reported that mean induction abortion interval between the two groups was significantly shorter in parous women than in nulliparous women ($p < 0.05$).

In the present study, the ethacridine lactate group experienced more gastrointestinal side effects as compared to mifepristone misoprostol group. 13 patient (43.33%) experienced abdominal cramps, requiring analgesia and 11 patients (36.67%) experienced nausea

Table 3. Side effects of two groups.

Side effect	Group I (MM) (%)	Group 2 (EL) (%)	χ^2, (p value)
Nausea/vomiting	4 (13.33)	11 (36.67)	4.35, (<0.05 S)
Headache	3 (10)	1 (3.33)	1.07, (>0.05 NS)
Fever	6 (20)	1 (3.33)	4.04, (<0.05 S)
Abdominal cramps	1 (3.33)	13 (43.33)	13.41, (<0.001 VHS)
Diarrhoea	2 (6.60)	0	2.06, (>0.05 NS)
Hyperstimulation	0	0	
Rupture	0	0	
Others	0	0	
Total	16	26	

MM: Mifepristone/misoprostol; EL: ethacridine lactate; S: significant; NS: non significant; VHS: very highly significant.

Table 4. Effectiveness of procedure.

Measure of effectiveness	Group 1 (MM) (%)	Group 2 (EL) (%)
Successful	29 (96.67)	28 (93.33)
Failure	1	2
Total	30	30
P value	χ^2 = 0.350, p>0.05 NS	

Table 5. Hospital stay (number of days).

Number of days	Group 1 (MM)	Group 2 (EL)
2	0	6
3	5	18
4	18	4
5	5	2
>5	2	0
Total	30	30
Mean±SD	4.13±0.77	3.06±0.78
p value	<0.001 very highly significant	

and vomiting in EL group (Table 3). There was only 1 case of fever. There were no cases of hyperstimulation or rupture uterus. Increase in the number of gastrointestinal side effects in ethacridine lactate can be attributed to the extraamniotic injection of PGF2α; which has known side effects of nausea, vomiting and abdominal cramps. Hou et al. (2010) reported higher incidence of side effects in mifepristone misoprostol combination as compared to ethacridine lactate group.

In mifepristone misoprostol group, 28.57% patients experienced nausea, vomiting, as compared to 3.81% in EL group, 17.14% patients experienced diarrhea, 36.19% patients had fever, chills and rigors. EL group reported minimal side effects in the form of nausea, vomiting (3.8%) and fever (8.57%) (Table 3). Mifepristone-misoprostol group experienced fewer side effects in the form of nausea/vomiting (13.33%), headache (10%), fever (20%) and diarrhea (6.60%) (Table 3). On the basis of these findings, the present study has shown that both ethacridine lactate and mifepristone-misoprostol combination are safe and effective for the termination of second trimester pregnancy (Table 4).

Though ethacridine lactate has a longer abortion interval compared to mifepristone misoprostol combination, total number of days of hospital stay was lesser with ethacridine lactate than with mifepristone-misoprostol regimen, as the patients were admitted at the time of administration of mifepristone (Table 5). Thus, ethacridine lactate offers an alternative to the mifepristone-misoprostol regimen in countries where mifepristone is either unavailable or unaffordable.

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