DOI: 10.5152/eurasianjmed.2019.18341

Manuscript Type: Original Article

Title: Mifepristone Followed by Misoprostol or Ethacridine Lactate and Oxytocin for Second Trimester Abortion: A Randomized Trial

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You may cite this article as: Dadhwal V, Garimella S, Khoiwal K, Sharma KA, Perumal V, Deka D. Mifepristone Followed by Misoprostol or Ethacridine Lactate and Oxytocin for Second Trimester Abortion: A Randomized Trial. Eurasian J Med 2019; DOI: 10.5152/eurasianjmed.2019.18341.

1. Introduction

Abortion is a major social and health issue, particularly in the developing countries. In India, over 6 lac abortions are performed each year and of these 10-15% are in second trimester [1]. Mifepristone followed by misoprostol is a safe and effective regimen for second trimester abortion. A systematic review of 40 randomized controlled trials addressing various regimens for abortion between 12 and 28 weeks of gestation concluded that the a combination of mifepristone and

misoprostol appeared to have highest efficacy and shortest induction time [2]. The World Health Organization (WHO) [3] and Royal college of Obstetrics & Gynecology (RCOG) [4] strongly recommend the use of the anti-progestin, mifepristone, followed by misoprostol, as the medical method for second-trimester abortion. One of the drawbacks of this regimen is side effects with misoprostol, which can occur in up to 30% of cases [5] and some concern of uterine rupture in women with previous uterine scar [6,7].

Inspite of the available literature, many clinicians in India and South Asia continue to use Ethacridine Lactate (EL) for second trimester abortion.ELis an organic compound based on acridine. In India, extra amniotic instillation of EL followed by high dose oxytocin infusion is popular whereas in China intra-amniotic instillation is commonly used. Extra-amniotic instillation causes stripping of the amniotic membranes from uterine wall, which leads to release of prostaglandin and oxytocin and mechanical stimulation of the uterus. It is a well-accepted method of termination due to its efficacy and good safety profile. The induction time when used with high dose oxytocin infusion is 15-20 hours with success rate of about 90% [8-10]. High doses of oxytocin is required as the uterine myometrium is not sensitised to oxytocin in early pregnancy. In a systematic review of Chinese trials, authors reported that failure of abortion with intra-amniotic EL was 7.4 to 20.7% compared to 2 to 5.9% failure rate in studies using mifepristone and misoprostol [11]. Zhuang et al showed that mifepristone may shorten induction to abortion time when used with intra-amniotic EL [12].

An earlier study showed that priming the uterus with mifepristone before oxytocin improved success rates to 92.3% vs 52.9% when oxytocin is used alone and reduced induction time (11.3$\pm$ 6 to 17.6$\pm$6.5 hours) [13]. As with misoprostol and oxytocin, we postulate that mifepristone priming prior to extra- amniotic instillation of EL followed by oxytocin infusion would reduce induction time.

The aim of the study was to evaluate a regimen that would be comparable to the standard regimen of mifepristone followed by misoprostol in terms of successful abortion and induction time. This study compares two methods of second trimester abortion, mifepristone followed by EL and oxytocin to the commonly used protocol of mifepristone followed by misoprostol.

2. Materials and Methods

This was a prospective randomized trial with 1:1 ratio allocation,conducted in one unit of the department of Obstetrics and Gynecology at a tertiary care centre over a period of 2 years (from July 2014 to May 2016). The study included healthy women who underwent second trimester abortion (13-20 weeks'gestation) for medical or social reasons. Gestational age was defined by last menstrual period and ultrasound estimation of fetal size. Exclusion criteria included women with history of renal or hepatic disease, bronchial asthma, hematological disorder, glaucoma and heart disease, chronic adrenal failure, long term steroid treatment, moderate or severe anemia (Hemoglobin<10gram/dl), previous cesarean or other uterine scars (hysterotomy, myomectomy, unknown scars), symptomatic reproductive tract infections, hypersensitivity to Mifepristone/ Misoprostol/ EL/ Oxytocin and presence of rupture of membranes. Eligible women were recruited after informed consent. Demographic and clinical data was collected, in structured proformas. Women were randomized to one of the two study arms using computer generated randomization table. Using Epi Info software version 7.0 developed by Centre for Disease Control Programme, Atlanta, USA, 6 random numbers were generated between 1 and 120 numbers. Generated random numbers list was put in an envelope and labelled as M. Remaining 60 numbers list was put in another envelope labelled as E. According to inclusion and exclusion criteria recruited patients were assigned identification numbers sequentially from 1 to 120 and appropriate group was decided based on the envelope list. All women received 200mg mifepristone orally. Thirty-six hours after mifepristone administration, women were admitted to hospital, and according to randomization, women in Group M were given 400 microgram misoprostol vaginally every three hours to a maximum of five doses. For women in group E, 0.1% ethacridine lactate was instilled transcervically through the Foley's catheter in the extra amniotic space slowly over 10 minutes under aseptic conditions. The volume instilled was 10ml per week of gestation with a maximum of 150 ml. The Foley's catheter was removed after six hours unless expelled spontaneously. This was followed by oxytocin infusion in 500 ml of ringer lactate starting with 10mIU/min and increased at the rate of 10mIU/min every half hour up to a maximum of 100 mIU/min, depending on response. Oxytocin drip was to be discontinued after 12 hours if patient did not respond. Once fetus is expelled, one hour was given for spontaneous expulsion of placenta. Ultrasound was done

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after expulsion of placenta to look for retained products. A curettage was done for retained products. Figure 1 depicts the flow of participants through the study.

Hemoglobin (Hb) was sent on the day of induction (pre procedure) and again after the successful abortion (24 hrs post procedure). The Hb difference (pre procedure - post procedure) was taken as an estimate of blood loss. Anti-D 300 microgram was administered in patients with Rh-negative blood group.

Primary outcome measure was success rate, defined as percentage of abortions within 24 hours after use of first dose of misoprostol or instillation of EL. Secondary outcome was induction time, defined as the time from first use of misoprostol or EL to expulsion of fetus and placenta. Other outcome measures included a composite of side effects (nausea, vomiting, flatulence, dyspepsia, diarrhea, constipation, headache, heavy bleeding, hypersensitivity, pyrexia), patient satisfaction (measured on a visual scale of 0-10;0-not satisfied and 10-strongly satisfied), pain perception (measured by visual analog scale 0-10; 0-no pain, 10- maximum pain) and fall in Hb (difference in pre procedure and post procedure Hb). Patients satisfaction, and pain perception were measured after completion of abortion.

Sample size calculation - The study design was non-inferiority trial and for calculating sample size the results of a similar study (Matan Elami-Suzin et al., 2013) [14] was considered [14] . They had shown that the abortion rate using mifepristone followed by misoprostol or oxytocin for second trimester abortion was 100% and 95.8% respectively. Presuming that similar success rates will be obtained for the present study, a difference of 2% between the groups is clinically negligible, with 5% level of significance (one-tailed) and power of 80%, a sample size of 60 in each group will be sufficient to prove equivalence. (sample size calculation was done using R-software version 3.24)

Statistical analysis - Comparison of success rate between the two groups was done by chi-square/fishers exact test as appropriate. The induction abortion interval between the two groups was compared using students t-independent test. All qualitative variables related to side effects were compared between two groups using chi-square test. Other quantitative variables related to side effects were compared using t-independent test. For all the statistical tests, a value of $p <$

0.05 was considered for statistical significance. Cox-regression model was used to evaluate factors affecting success rate. All descriptive and tests of significance were carried out using SPSS software programmer.

The study protocol was approved by Institution Ethics Committee and study is registered with Central Trial Registration, India.

3. Results

This study was conducted to compare two medical methods of second trimester abortion: mifepristone followed by misoprostol (group M) versus mifepristone followed by EL and oxytocin (group E). A total of 120 women fulfilling the eligibility criteria were enrolled in the study and randomised to two groups. No women aborted after mifepristone and none were lost to follow up after mifepristone.

3.1 Baseline characteristics:

The two groups did not differ in age, parity, gestation age and indication of abortion (Table 1). In group M, the mean requirement of misoprostol dose was 3±0.9 tablets (minimum= 1 and maximum= 5), a single dose of misoprostol consists of 400 microgram. In group E, the average duration of oxytocin infusion was 4.97±2.57 hours (minimum=1 & maximum=12.25) and average maximum oxytocin concentration required was 81.55±24.26 mIU/min (minimum=20 & maximum=100).

3.2 Outcome measures (table 2):

Both study arms recorded high success rates, 60/60 patients (100%) in group M and 59/60 patients (98%) in group E aborted within 24 hours, this was not statistically significant. No patient aborted after mifepristone. None of the patients in group M needed an alternative treatment because of side effects. The time to to expulsion of conceptus was significantly shorter for group M compared to group E (8.2±2.3 vs 10.9±2.6 hours; p value = <.001). Cox-regression model was used taking into account "time until expulsion" controlling for type of treatment, age and parity of woman and gestation age at pregnancy termination. The factors significantly

associated with shorter time until expulsion was parity (adjusted HR 3.2; p value 0.001, CI 1.59-6.4) and use of misoprostol (adjusted HR 3.23; p value <0.001, CI-2.05-5.08) (Fig 2).

The two groups were compared for amount of blood loss as determined by the fall in Hb (pre-procedure Hb - post-procedure Hb). The mean pre and post-procedure Hb was comparable in both the groups (10.66 ± 0.86 to 9.97 ± 0.94; P=0.001 and in group B, 10.51±0.95 to 10±0.91; P=0.001). Hb fall was significantly more in Group than group E (0.70 ±0.33 gm/dl & 0.52±0.23 gm/dl respectively; P value = 0.001). Post abortion, dilatation & curettage was required in 78% (47/60) cases in group M and 70% (42/60) in group E. No patient required blood transfusion. There were no major or minor complications encountered in either group during the abortion. The composite side effects defined as headache, fever, and gastrointestinal side effects (nausea, vomiting, diarrhea) were noted. Side effects were significantly higher in group M than group E (97% & 75% respectively; p=0.001). In group M, mean VAS score, for pain experienced, was significantly more than group E (5.97 ±1.23 vs 5.14 ±1.27; p=0.001). Although the difference was statistically significant, the actual difference in score was small, this may be not considered important clinically. Todd KH et al (15) suggested that a minimum change which is clinically significant should be of 13 mm out of 100 mm of VAS. If it is less than 13 mm, it may not have any clinical importance.

Patient satisfaction for the method of abortion was also rated on a scale of 10. In group M, the mean score was 5.90 ±0.85 and in group E, it was 6.0 ±1.08, this was not statistically significant (p=0.57).

4. Discussion

Historically, morbidity associated with second trimester medical abortions was due to prolonged induction times. The regimen of anti progesterone - mifepristone followed by prostaglandin-misoprostol has shortened the induction to abortion time and improved rates of complete abortion. This protocol is approved by the WHO [3] and various professional bodies like ACOG [16] and RCOG [4]. Extra-amniotic instillation of EL followed by oxytocin infusion is a still used protocol in India. The drawback is long induction time, requiring longer hospital stay and physical and emotional trauma to women. As priming with mifepristone before misoprostol

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reduces induction time compared to use of misoprostol alone [17], we could show some benefit with EL also. Though without a direct comparative trial there may be some reservations.

There are concerns about the use of oxytocics in women with scarred uterus. The risk of uterine rupture with misoprostol has been reported in women undergoing second trimester abortion, with or without scar in the uterus [6,7,18,19]. There is report of rupture in unscarred uterus following use of EL and oxytocin also [20]. There has also been reports of rupture in scarred as well as unscarred uterus following use of high dose oxytocin alone and with other oxytocic agents for second trimester abortion [8,21]. Whatever method is used, careful monitoring is required in all patients.

We compared two methods of second trimester medical abortion in patients with similar demographic characteristics. We reported high success rates for both methods. For regimen constituted by mifepristone followed misoprostol the induction time was 8.2±2.3 hours, this was significantly less than the induction time of 10.9±2.6 hours for group E. Moreover, the induction time in group E was much less than that published in literature for extra amniotic instillation of EL with or without another oxytocic agent. Deliwala K et al [22] reported average induction time of 27.6 hours with the use of extra amniotic EL with oxytocin. Tayade SA et al [23] used extra amniotic EL along with misoprostol for first and second trimester abortion and found induction time of 16.43 hours. Nanda S et al [24] studied the use of EL with Prostaglandin alpha in mid trimester abortion and reported induction time of 32.28 hours. The shorter induction time in EL group of our study can be explained by the effect of pretreatment with mifepristone. To the best of our knowledge, this is the first study in which mifepristone is used prior to extra amniotic ethacridine lactate instillation. The success rate and acceptability of the two protocols was not significantly different.

In the present study, blood loss was assessed by fall in Hb after the procedure, this was significantly higher in group M. No patient required blood transfusion. We did USG pelvis for every patient after expulsion of placenta, this might be the reasonfor high curettage rate in our study. Gastrointestinal side effects and fever were significantly higher in group M, this was were similar to results shown in a systemic review of literature of Chinese trials [11]. Pain perception and overall satisfaction was similar in both the groups. Ethacridine lactate instillation

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is cheap, effective, safe method and the preferred method for mid trimester abortion in few countries such as China [24]. It has also been considered as a safer alternative in several other studies [24-26].

Few studies have been published where the advantage of mifepristone has been taken in protocols other than those using misoprostol, to improve induction abortion time. Elami-Suzin et al [14] conducted a randomized trial comparing mifepristone followed by misoprostol or oxytocin for second trimester abortion. Success rate defined as expulsion within 36 hours was 100% for mifepristone-misoprostol and 95.8% for mifepristone-oxytocin group, statistically not different. However, induction time was significantly more for mifepristone-oxytocin group, 11.3± 7.4 hours v/s 7±4.9 hours mifepristone-misoprostol group. Addition of mifepristone to oxytocin did reduce induction time, this is evident when we compare to a study by Ramin et al [27] that reported induction time of 21.7 ±11 hours for oxytocin used alone, and success rate was 62%.

Mifepristone has been used in combination with intra-amniotic EL in few studies to shorten induction time. Mei Q et al [28], in a randomized controlled trial, comparing intra-amniotic 100 ml EL to intra-amniotic EL followed by 150mg mifepristone orally reported significantly shorter induction time with use of mifepristone; 36.45±8.05 vs 49.03±9.30hours (p=0.00). No difference was found in success rates and cervical laceration in the two groups. Benefit of use of mifepristone with intra-amniotic EL was also reported by Zhuang Y et al [12]. They found 25.94% women delivered within 24 hours in the mifepristone group while only 10.18% delivered in non-mifepristone group (P=<.001); the complication rate was similar in both groups. Chen et al [29] studied the use of mifepristone combined with intra-amniotic EL for second trimester pregnancy termination in 443 women with placenta previa and/or prior cesarean delivery. All patients had delivered vaginally, the mean induction time was 34±9.4 to 38.56±12.4 hours. There was no incidence of uterine rupture in any patient. We could not find a study that used mifepristone with extra-amniotic EL for second trimester abortion.

Randomised prospective nature was one of the strength of this study. Though the sample size was pre-calculated, a larger sample or a multi-centric study to get a larger sample would have produced more robust results. This was perhaps one of the possible shortcoming of our study.

After analysis of our data, we conclude that both the regimen are safe and equally acceptable by the patients for second-trimester abortion. We suggest the use of mifepristone, 36-48 hours prior to the extra amniotic ethacridine lactate instillation for second trimester abortion. This gives a success rate comparable to mifepristone and misoprostol, though induction to abortion interval is more with ethacridine lactate. The induction to abortion time in present study for ethacridine lactate is much less than that reported in various studies. In addition, this may be an effective alternative method for women in whom there is concern for the use of misoprostol.

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Legends

Fig 1: Flow of participants through study

Fig 2: Kaplan-Meier time curve for induction abortion time

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Table: 1 Demographic description of women undergoing termination of pregnancy

Variable		Group M (n=60)	Group E (n=60)	P value
Age (years)		29.10±3.5	27.45±3.8	0.15
Gestational age (weeks)		16.94±1.85	16.57±1.79	0.27
Parity	Primigravida	11 (18%)	11 (18%)	0.42
	Multigravida	49 (82%)	49 (82%)	
Baseline Hb (gram %)		10.66 ± 0.86	10.51 ± 0.95	0.39
Indication	Unwanted pregnancy	32 (54%)	39 (65%)	0.2
	Congenital malformations/ Anomalies	26 (43%)	21(35%)	
	Missed abortion	2 (3%)	0	

Table 2: Outcomes of termination of pregnancy

Variable	Group M (n=60)	Group E (n=60)	P value
Success rate (24 hours)	100%	98%	0.31
Induction Abortion Interval (hours)	8.2±2.3	10.9±2.6	0.001
Hb difference (gram %)	0.70±0.33	0.52±0.23	0.001
Side effects	97%	75%	0.001
Pain score (VAS)	5.97 ±1.23	5.14 ±1.27	0.001
Satisfaction score	5.90 ±0.85	6.0 ±1.08	0.57

VAS- visual analogue scale