

EFFECT OF LOWERING THE DOSE OF MISOPROSTOL FOR SECOND TRIMESTER TERMINATION OF PREGNANCY ALONG WITH MIFEPRISTONE

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ABSTRACT

BACKGROUND

In India, second trimester termination is reportedly performed in about 11 - 14% of women. However, abortion is grossly under-reported in the official data. A large number of termination of pregnancies is done by unaccredited centres due to various reasons and thus it is extremely important to ensure the safety of the regimen when used in a low-resource setting. So, we conducted a study to determine if lowering the dose of misoprostol significantly compromises the efficacy of second trimester abortion regimens.

Aims and Objectives- To study if decreasing the dose of misoprostol used for second trimester termination of pregnancy significantly alters the efficacy of the regimen and also if it is more acceptable in terms of complications and side effects.

MATERIALS AND METHODS

100 women seeking termination of pregnancy between 12 - 20 weeks of gestation were randomised into two equal groups using computerised random number tables. Women were given Tab. Mifepristone 200 mg orally followed by 36 hours and later by Tab. Misoprostol 400 mcg or 200 mcg vaginally 3 hourly for a maximum of 5 doses in Group R1 and R2 respectively. Comparison was done using stringent and non-stringent criteria depending on whether a check curettage was required or not. Statistical analysis was done using Chi-square/ Fisher's exact test for qualitative variables and student's 't' test for quantitative variables.

Settings and Design- A prospective randomised comparative study at a District Hospital.

RESULTS

The two groups were comparable in terms of age, parity and gravidity. Success rate at the end of 72 hours was 82% and 88% in Group R1 and R2 respectively using stringent criteria and 98% and 96% using non-stringent criteria. Mean induction abortion interval was 42.89 (\pm 9.66) in R1 and 43.09 (\pm 8.62) in R2 using stringent criteria. We found that regimens are comparable in terms of safety, success, induction-abortion interval and side effects.

CONCLUSION

Reduction in misoprostol dose does not alter the efficacy of the mifepristone and misoprostol regimen significantly.

KEYWORDS

Termination of Pregnancy, Second Trimester Abortion, Misoprostol, Mifepristone.

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BACKGROUND

Pregnancy termination is relatively more effective, simpler and safer in first trimester which comprises about 85% of all abortion cases in India.¹ Second trimester abortion however is an important medico-social problem, as they are responsible for most of the abortion related complications and ideal effective treatment is still a matter of concern.¹ In India ignorance and inability to take early decision regarding abortion, inaccessibility of services and provider as well as paucity of organised abortion facilities compels a large number of women to seek termination of pregnancy in second trimester. A large number of termination of pregnancies is done by unaccredited centres due to various

reasons and thus it is extremely important to ensure the safety of the regimen when used in a low-resource setting. So we conducted a study to determine if lowering the dose of misoprostol significantly compromises the efficacy of second trimester abortion regimens. This study is a small step in the same direction comparing two different doses of misoprostol when combined with fixed dose of mifepristone to improve efficacy without compromising safety.

MATERIALS AND METHODS

The prospective randomised comparative study was conducted in a district hospital at New Delhi, India. The hospital scientific and ethical committee approval was sought before the study.

Based on the past 5-year of hospital census, number of women reporting for second trimester abortion was 836 (considered as population). Assuming confidence level of 95% and confidence interval of 10%. Calculated sample size was 86. So we took 100 patients and divided into two Groups R1 and R2 using computerised random number tables. All women seeking termination of pregnancy between 12 - 20 weeks period of gestation were screened for the inclusion and

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exclusion criteria and those fulfilling the criteria were included into the study. Inclusion criteria were women with singleton pregnancy and willingness to participate in the study. Reasons for termination were either intrauterine death or congenital anomaly incompatible with life or on basis of humanitarian, social or medical grounds as per the Medical Termination of Pregnancy Act of the country.² Exclusion criteria were previously more than one caesarean section, severe hypertension (blood pressure \geq 160/100 mmHg), known intolerance or allergy to mifepristone or misoprostol, contraindications to the administration of mifepristone (chronic systemic corticosteroid therapy, adrenal insufficiency or misoprostol- glaucoma, sickle cell anaemia, poorly controlled seizures, known prostaglandin allergy, severe asthma, arrhythmias, cardiac failure), coagulopathy, multiple pregnancies and haemoglobin $<$ 8 g%.

After informed consent, women were randomised by computer generated randomisation tables into two groups (R1 and R2). Women in Group R1 were given Tab. Mifepristone 200 mg orally followed by 36 hours and later Tab. misoprostol 200 mcg vaginally 3 hourly maximum 5 doses. Women in Group R2 were given Tab. Mifepristone 200 mg orally followed by 36 hours and later Tab. misoprostol 400 mcg vaginally 3 hourly maximum 5 doses. Time of expulsion of foetus and placenta were recorded.

Completeness of abortion at 72 hours was taken as successful regimen. Failure was defined as need of recourse to use of any other pharmacological/ surgical intervention for completion of termination. Outcomes were also calculated using less stringent criteria for determining the successful cases by considering the cases of incomplete abortion, which required immediate evacuation of retained products of conception at the time of expulsion of foetus and placenta due to excessive bleeding or tissue hanging out of the cervix to be a success. Statistical analysis was done using Chi-square/Fisher's exact test for qualitative variables and student's 't' test for quantitative variables.

RESULTS

The age of the women enrolled in the study ranged from 18 - 39 years with mean age in the Group R1 being 25.12 ± 4.11 years and in Group R2 was 25.18 ± 3.75 years. The mean parity in Groups R1 and R2 was 1.16 ± 1.36 and 0.9 ± 0.97 respectively. The mean number of previous abortions in Group R1 and R2 were 0.3 ± 0.65 and 0.42 ± 0.86 respectively. The mean parity was 1.02 ± 1.25 in Group R1 and 0.82 ± 0.92 in Group R2. The mean gestational age of patients in two groups was 17.08 ± 2.60 years and 16.95 ± 2.46 years respectively with 'p' value of 0.40. The differences in these parameters amongst the two groups were statistically insignificant. Thus, the two groups were comparable in terms of age, parity, gravidity and number of previous abortions, number of living children and period of gestation and reason for termination of pregnancy (Table 1).

The most common indication for termination was congenital malformations followed by intrauterine death of foetus in both groups. Other indications were limiting family size, multi-drug resistant tuberculosis. Using stringent criteria that is no intervention needed at any time, the number of women with successful outcome at the end of 48 hours were 32 that is 78.04% in Group R1 and 33 (75%) in

Group R2. Successful outcome at the end of 72 hours was observed in 41 (82%) and 44 (88%) women in Groups R1 and R2 respectively. The difference was statistically non-significant at both 48 and 72 hours (Table 2). The cumulative success rates in two groups is depicted in Figure 1.

When non-stringent criteria was used to assess the success rates of two regimens, the success rates were 78% (39) in Group R1 and 74% (37) women in Group R2 at 48 hours. The success was found to be 98% (49) women and 96% (48) women at 72 hours in Group R1 and R2 respectively. The difference was found to be statistically non-significant at both 48 and 72 hours (Table 3).

Check curettage was done if some retained products of conception or placental bits were thought to be left after examining the expelled products or if patients were found to be bleeding more than average. In Group R1 8 women out of 49 and in Group R2 4 out of 48 women required check curettage. The 'p' value calculated was 0.75, which was not statistically significant.

There were 9 failures (aborting after 72 hours) in Group R1 as compared to 6 failures in Group R2, but this difference also did not reach statistically significant levels. There was 1(2%) woman in Group R1 and 2 (4%) women in Group R2 who did not respond to the regimens used and some other method or repeat regimen had to be used to induce abortion.

The mean induction abortion interval starting from the mifepristone dosage was 42.89 hrs. (\pm 9.66) in Group R1 and 43.09 hrs. (\pm 8.62) in Group R2 using stringent criteria. The p-value was calculated as 0.46, which is non-significant. Using the less stringent criteria the interval was 42.20 hrs. (\pm 0.84) in Group R1 and 41.58 hrs. (\pm 10.90) in Group R2. The 'p' value here was 0.39, which again showed insignificant difference (Table 4).

The difference in mean induction abortion interval from the start of misoprostol administration using less stringent criteria was non-significant as shown by the 'p' value of 0.39. The mean time till abortion in Group R1 was 8.46 hours and in Group R2 was 8.82 hours.

Using stringent criteria, the mean time for abortion after starting mifepristone in primigravida was 48.58 hrs. and 42.02 hrs. in Groups R1 and R2 respectively. The corresponding figures in multigravida were 39.94 hours and 43.75 hours in Groups R1 and R2 respectively. Analysis showed a statistically non-significant 'p' values (Table 5).

Using less stringent criteria, the mean abortion interval in primigravida was 47.40 hrs. and 40.05 hrs. in Groups R1 and R2 respectively. The corresponding figures in multigravida were 39.46 hrs. and 42.50 hrs. in Groups R1 and R2 respectively. This was statistically non-significant (Table 6).

The side effects reported were nausea, vomiting and fever. In Group R1 two (4%) women had nausea and vomiting, whereas no woman complained of these in Group R2. Fever was reported in four (8%) women in Group R1 and three (6%) women in Group R2. Postpartum psychosis developed in one patient in Group R1 and none in Group R2. There were 5 patients with previous caesareans and no additional complications were noted, though number of scarred uterus cases was too small to reach any conclusion. The 'p' value calculated for the complications was not statistically significant (Table 7).

	Group R1 Mean ± SD	Group R2 Mean ± SD	P value
Age	25.12 ±4.11	25.18 ±3.75	0.47
Parity	01.16 ±1.36	00.90 ±0.97	0.14
No. of Previous Abortions	00.30 ±0.65	00.42 ±0.86	0.22
No of Living Children	01.02 ±1.25	00.82 ±0.92	0.18
Period of Gestation	17.08 ± 2.60	16.95 ±2.46	0.40

Table 1. Demographic Distribution

	Successful Outcome	
	At 48 Hours N (%)	At 72 Hours N (%)
R1	32 (78%)	41 (82%)
R2	33 (75%)	44 (88%)
	p= 0.90	p= 0.75

Table 2. Successful Outcome at 48 and 72 hours using Stringent Criteria

	Successful Outcome using Less Stringent Criteria	
	At 48 Hours N (%)	At 72 Hours N (%)
R1	39 (78%)	49 (98%)
R2	37 (74%)	48 (96%)
	p= 0.82	p= 0.90

Table 3. Successful Outcome at 48 and 72 hours using Less Stringent Criteria

	Mean Induction Abortion Interval in Hours Mean ± SD	
	Using Stringent Criteria	Using Less Stringent Criteria
R1	42.89 ± 9.66	42.20 ± 0.84
R2	43.09 ± 8.62	41.58 ± 10.90
	p= 0.46	p= 0.39

Table 4. Mean Induction Abortion Interval

	Mean Induction Abortion Interval in Hours	
	Primigravida	Multigravida
R1	48.58 ± 7.54	39.94 ± 9.42
R2	42.02 ± 8.52	43.75 ± 8.77
	p= 0.49	p= 0.67

Table 5. Mean Induction Abortion Interval as per Gravidity using Stringent Criteria

	Mean Induction Abortion Interval In Hours	
	Primigravida	Multigravida
R1	47.40 ± 7.47	39.96± 9.95
R2	40.05 ± 11.44	42.50 ± 10.44
	p= 0.43	p= 0.73

Table 6. Mean Induction Abortion Interval as per Gravidity using Less Stringent Criteria

Side Effects/ Complications	Group R1		Group R2		P value
	No.	%	No.	%	
Nausea	2	4	0	0	0.15
Vomiting	2	4	0	0	0.15
Diarrhoea	0	0	0	0	1.00
Fever	4	8	3	6	0.70
Excessive Bleeding	0	0	0	0	1.00
Others	1	2	0	0	0.32
Total	9		3		

Table 7. Side Effects and Complications

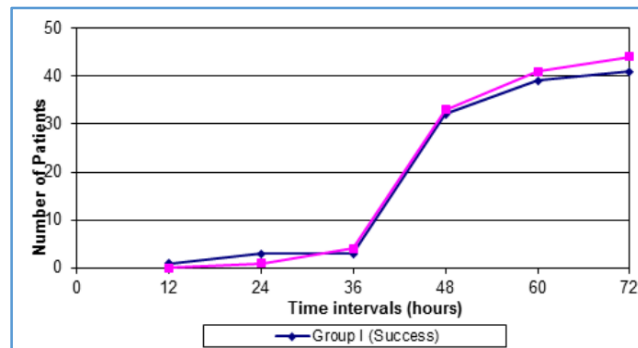


Figure 1. Cumulative Successful Outcome at Time Intervals

DISCUSSION

The combination of mifepristone and misoprostol has been found to be an effective method of termination of pregnancy in second trimester. The optimisation of the mifepristone and misoprostol regimens is still on to decrease the economic burden on hospitals and to improve efficacy, acceptability and compliance with minimal effects to women’s health.

A 2011 Cochrane³ review compared different methods of second trimester medical termination of pregnancy for their efficacy and side effects and concluded that low doses of misoprostol appear to be associated with fewer side effects, while moderate doses appear to be more efficient in completing abortion. It also found that the induction to abortion interval with 3-hourly vaginal administration of prostaglandins is shorter than 6-hourly administration without an increase in side effects.

In our study, we found no statistically significant difference in efficacy by lowering the dose of misoprostol from 400 µg to 200 µg, keeping the interval of administration fixed at 3 hrs. Success rates were 88% and 82% with 400 µg and 200 µg respectively at 72 hrs. using stringent criteria. Success rates reached 96% and 98% with 400 µg and 200 µg respectively at 72 hrs. using less stringent criteria.

We also did not find any significant difference in the side effects between the two dose regimens. Side effects were nausea (4% vs. 0%), fever (8% vs. 4%) and vomiting (4% vs. 0%) and were in fact lower in Group R2 in absolute numbers despite higher dose.

The latest recommendation by ACOG⁴, RCOG⁵ and WHO⁶ recommends Loading Dose (LD) of 800 µg misoprostol followed by 400 µg 3 hourly. Varying success rates have been reported upto 100%.

In present study, without using any LD we compared misoprostol dose of 400 µg and 200 µg 3 hourly max 5 doses and found success rates upto 98% and 96%.

Pongsatha⁷ et al compared a vaginal misoprostol LD regimen (600 mcg, then 400 mcg 6 hourly) with a non-loading dose regimen (400 mcg 6 hourly) in 157 women and found both equally effective with adverse drug effects associated more with loading dose regimens.

Similarly, a study without any LD by Koh et al⁸ found 400µg and 200µg misoprostol 4 hourly regimens very effective with a success rates of 92.5% and 70.3% (p= 0.017) with significantly less side effects with 200 µg regimen (fever in 70% and 24.3%, p < 0.001). Brouns et al⁹ using misoprostol 200 µg and 400 µg four hourly found success rates of 66% and 73% with induction abortion interval of

11.6 and 9.3 hours respectively ($p= 0.04$) with no significant difference in side effects and Ho¹⁰ found 400 µg and 200 µg 3 hourly regimens very effective with success rates of 92% and 90% with induction abortion interval of 11.8 and 14.8 hours.

Loading dose studies conducted by Yazdani et al (2012)¹¹ found 85% success rates, Bartley et al (2002),¹² Hamoda et al(2005)¹³ and Hou et al (2010)¹⁴ found success rates of 94-100%, but with higher side effects i.e. hot flushes, vomiting, diarrhoea, pain, fever, chills. Mean induction abortion interval varied from 4.9 hours in a study by Chai et al,¹⁵ 6.2 hrs. in Hou's¹⁴ study, 6.1 hrs. in Bartley's study,¹² 6.9 hours in a study by Websters.¹⁶ Dickinson et al¹⁷ found induction abortion interval of 9.5h with oral misoprostol, 7.8h with sublingual and 7.4h with vaginal but with failure rates of 37% with oral, 20.5% with vaginal, 21% with sublingual.

Considering the literature reviews, regimens with and without LD seems to be not very different in success rates, although it results in slight decrease in induction to abortion intervals. Side effects in LD regimens appear to be higher. A balance needs to be established between side effects, efficacy and induction to abortion intervals. In India where the government is proposing expanding abortion provision by nurses, auxiliary nurse-midwives and practitioners trained in the Indian System of Medicine with recognised qualifications in Ayurveda, Unani, Siddha or homeopathy. It is extremely important to use safer regimens even at the cost of little more time.

CONCLUSION

We thus conclude that lowering the dose of misoprost from 400 mcg to 200 mcg does not significantly alter the efficacy of the regimen and causes lesser side effects. Also the induction abortion interval is not different. The safety and acceptability will be better in a low resource setting where trained, round the clock facility might not be available.

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REFERENCES

- [1] Stillman M, Frost JJ, Singh S, et al. Abortion in India: a literature review. New York: Guttmacher Institute, 2014. <https://www.guttmacher.org/report/abortion-india-literature-review>.
- [2] Government of India. Ministry of Health & Family Welfare. The medical termination of pregnancy (Amendment) Act, 2002.
- [3] Wildschut H, Both MI, Medema S, et al. Medical methods for mid-trimester termination of pregnancy. *Cochrane Database Syst Rev* 2011;(1):CD005216.
- [4] American College of Obstetricians and Gynecologists (ACOG). ACOG Practice Bulletin no. 135: Second-trimester abortion. *Obstet Gynecol* 2013;121(6):1394-406.
- [5] RCOG. Best practice in comprehensive abortion care. Best Practice Paper No. 2. 2015.
- [6] WHO. Safe abortion: technical and policy guidance for health systems. 2nd edn. Geneva: World Health Organization, 2012.
- [7] Pongsatha S, Tongsong T. Randomized controlled trial comparing efficacy between a vaginal misoprostol loading and non-loading dose regimen for second-trimester pregnancy termination. *J Obstet Gynaecol Res* 2014;40(1):155-60.
- [8] Koh SCD, Ang EPJ, Lim SL, et al. A randomised controlled trial comparing two intravaginal misoprostol regimens and gemeprost for mid-trimester termination of pregnancy. *BJOG* 2015:122.
- [9] Brouns JF, van Wely M, Burger MP, et al. Comparison of two dose regimens of misoprostol for second-trimester pregnancy termination. *Contraception* 2010;82(3):266-75.
- [10] Ho PC, Ngai SW, Liu KL, et al. Vaginal misoprostol compared with oral misoprostol in termination of second-trimester pregnancy. *Obstet Gynecol* 1997;90(5):735-8.
- [11] Yazdani SH, Zeinalzadeh M, Bouzari Z, et al. Effects of vaginal versus oral misoprostol to terminate second-trimester pregnancy. *Clin Exp Obstet Gynecol* 2012;39(4):529-31.
- [12] Bartley J, Baird DT. A randomized study of misoprostol and gemeprost in combination with mifepristone for induction of abortion in second trimester of pregnancy. *Br J Obstet Gynaecol* 2002;109(11):1290-4.
- [13] Hamoda H, Ashok PW, Flett GMM, et al. A randomised trial of mifepristone in combination with misoprostol administered sublingually or vaginally for medical abortion at 13-20 weeks gestation. *Hum Reprod* 2005;20(8):2348-54.
- [14] Hou SP, Fang AH, Chen QF, et al. Termination of second-trimester pregnancy by mifepristone combined with misoprostol versus intra-amniotic injection of ethacridine lactate (Rivanol®): a systematic review of Chinese trials. *Contraception* 2011;84(3):214-23.
- [15] Chai J, Tang OS, Hong QQ, et al. A randomized trial to compare two dosing intervals of misoprostol following mifepristone administration in second trimester medical abortion. *Hum Reprod* 2009;24(2):320-4.
- [16] Webster D, Penney GC, Templeton A. A comparison of 600 and 200 mg mifepristone prior to second trimester abortion with the prostaglandin misoprostol. *Br J Obstet Gynaecol* 1996;103(7):706-9.
- [17] Dickinson JE, Jennings BG, Doherty DA. Mifepristone and oral, vaginal or sublingual misoprostol for second-trimester abortion: a randomized controlled trial. *Obstet Gynecol* 2014;123(6):1162-8.