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EVALUATION OF THE EFFICACY OF MIFEPRISTONE/MISOPROSTOL AND METHOTREXATE/MISOPROSTOL FOR MEDICAL ABORTION

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ABSTRACT

BACKGROUND: Unsafe abortion is a major cause of mortality among women in India accounting for 12% of all maternal deaths. In developing countries, annually, up to 200,000 women die of complications after illegal abortion. Medical abortion is potentially a simple and a safe method for use in developing countries. We conducted a prospective controlled trial to compare the efficacy of low-lose mifepristone and methotrexate for medical abortion. OBJECTIVE: To find out the efficacy of low-dose mifepristone and methotrexate for inducing abortion. METHOD: In this prospective clinical study, 100 women opted for a medical method of abortion. Out of these, 50 patients were given 50 mg/m2 of methotrexate intramuscularly followed by 800 micro gm of intravaginal misoprostol, and 50 patients were given 200 mg of mifepristone orally followed by 800 micro gm of intravaginal misoprostol. MAIN OUTCOME MEASURES: Complete abortion was the principal outcome measure. Secondary outcome measures were side effects and acceptability data. RESULTS: The rate of expulsion by first week after initiation of treatment was 58% in methotrexate and 98% in mifepristone group (P < 0.001). CONCLUSION: Low-dose mifepristone and intravaginal misoprostol is safe, effective, and well tolerated as compared to methotrexate and misoprostol.

KEY WORDS: abortion; methotrexate; mifepristone; misoprostol

An estimated 30 million abortions are performed worldwide each year.^[1] The safety of the procedure is therefore of importance to the global public health. Over the years, we have been using surgical evacuation to terminate early pregnancy with the risk of

Correspondence K Dahiya 74-R, Model Town Rohtak – 124001 Haryana India E-mail: krishnadahiya@rediffmail.com certain complications like incomplete abortion, perforation, hemorrhage, sepsis, cervical incompetence, etc. Medical termination of pregnancy with a combination of mifepristone and prostaglandin is a relatively safe and effective alternative to surgical abortion.^[2] Mifepristone was approved by the US FDA in September 2000 for use in combination with misoprostol for medical abortion £49 days of gestation. FDA-approved regimen of mifepristone/misoprostol is mifepristone 600 mg followed 2 days later by 400 mg of oral misoprostol.^[3]

The regimen that use mifepristone in lower

doses, specifically 200 mg, are equally safe and effective, and use of vaginal misoprostol in dose of 800 mg result in fewer side effects, decrease the time of expulsion, and have better efficacy when compared to the use of oral misoprostol.^{[4]-[6]}

Alternative regimens with intramuscular methotrexate combined with misoprostol have demonstrated complete abortion rates in the same range as mifepristone regimen ≤49 days of gestation. Multiple investigators have confirmed the safety, efficacy, and acceptability of various methotrexate and misoprostol regimens.^{[7]–[9]}

The present study was undertaken to evaluate the clinical efficacy and safety of mifepristone and misoprostol, and methotrexate and misoprostol for medical abortion of \leq 56 days gestation.

MATERIALS AND METHODS

A total of 649 women got registered over a period of 2 years for early, induced abortion. Of the 649 women, 100 opted/were willing for a medical method of abortion. Only those women with gestation less than 56 days, age >18 years, who had requested for Medical termination of pregnancy with the indications as per the guidelines of 1971 Medical termination of pregnancy act, and were willing to comply with the schedule of visits were included in the study.

The patients with suspected ectopic pregnancy, history of seizure disorder, abnormal uterine bleeding, Hb < 9 g%, Blood pressure > 140/90 mmHg, previous scarred uterus, and history of active liver or renal disease were excluded from the study. Written consents were obtained from all study participants. Detailed history, general physical examination, obstetrical examination, and routine investigations were performed in all cases. If a woman was Rh negative, she received 50 mg Rh immunoglobulin intramuscular. Estimated gestational age was based on the last menstrual period (LMP) (first day of LMP, pelvic examination, and confirmed by vaginal ultrasound). The other women, entering the study were offered mifepristone/ misoprostol regimen.

Fifty women were offered methotrexate/ misoprostol regimen (Group I). On day 1, injection methotrexate 50 mg/m² was given intramuscularly. These women were asked to return on day 5 for the vaginal administration of 800 mg of misoprostol (four tablets of 200 mg each) tablets. These tablets were placed high in the vagina after moistening them with 2–3 drops of water.

Fifty women were offered mifepristone/ misoprostol regimen (Group II). On day 1, these patients were given 200 mg of mifepristone by oral route. On day 3, 800 mg of misoprostol was administered intravaginally, after moistening.

Patients were counseled about vaginal bleeding and other side effects associated with misoprostol. The patients were instructed to return earlier if bleeding was excessive. The patients were asked to come on day 7 and ultrasonography was done. Presence of gestational sac or products of conception was considered as failure and suction and

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evacuation was performed. All patients were questioned on day 7 for a detailed account of side effects related to both drugs [Table 1].

The following outcomes were noted. An abortion was considered successful if complete abortion occurred without surgical procedure within 24 h after the dose of misoprostol. Treatment failure was considered if women did not pass the gestational products within 24 h after the misoprostol. The protocol was approved by the institutional ethics committee.

Statistical analysis

Statistical evaluation was done using Students' *t*-test and chi-square test where appropriate. The two groups were compared with chi-square test and the results are given as number and percentages with 95% confidence interval for the difference between two groups and degree of freedom one. *P* values that were less than 0.05 were considered to indicate statistical significance.

RESULTS

A total of 100 women included in the study were analyzed. In both the groups most women were between 25 and 35 years of age and 38 (76%) in Group I and 41(82%) in Group II were either para I or II [Table 1]. Only two patients in Group I and one patient in Group II were Rh negative and received 50 mg of antiD.

Most of these women gave no history of previous-induced abortions. Only seven in Group I and nine in Group II gave history of previous-induced abortion. The period of gestation ranged from 32 to 55 days with a mean of 44.1 5.1 days in Group I and 42.68 \pm 5.98 days in Group II (*P* value 0.20). The age, parity, and period of gestation were comparable in the two groups.

On follow up visit during day 7, all the patients were enquired about the sequence of events

Table 1: Patient characteristics

	Methotrexate + misoprostol		Mifepriston + misoprostol		
	Range	Mean ± SD	Range	Mean ± SD	P value
Age (years)	19—36	26.46 ± 3.64	19–38	28.24 ± 4.77	0.14 (NS)
Parity (median)	0—4	2	0–4	2	-
Gestational age (days)	35—55	44.1 ± 5.1	32–55	42.68 ± 5.98	0.20 (NS)

Table 2: Side effects

	Methotrexate	Mifepristone	Misoproste Group I	ol Group II	Chi-square	95% C.I.	P value
Nausea	6	-	9 (18%)	18 (36%)	4.10	1–35	0.042 (S)
Vomiting	-	-	6 (12%)	5 (10%)	0.102	-10–14	1.0 (NS)
Diarrhea	2	-	14 (28%)	10 (20%)	0.87	-9–25	0.48 (NS)
Warmth/chill	-	-	8 (16%)	13 (26%)	1.50	-6–26	0.32 (NS)
Headache	-	-	1 (2%)	2 (4%)	0.343	-5–9	1.0 (NS)
Dizziness	4	-	2 (4%)	6 (12%)	2.173	-3–19	0.26 (NS)
Cramping	-	1	24 (48%)	37 (74%)	7.10	8–44	0.007 (S)
Generalized weakness	9	-	7 (14%)	5 (10%)	0.37	-9–17	0.7 (NS)

* Many patients reported more than one side effect.

and side effects that followed misoprostol administration [Table 2]. Side effects are shown in Table 2. Thirty-one (62%) cases reported no side effects after methotrexate administration (chi-square 5.75; *P* value 0.016). Only one (2%) with mifepristone reported cramping. Significantly, more women had nausea in Group II (*P* value 0.042). Also

Group II (P value 0.07).

Results are shown in Table 3. After the administration of mifepristone + misoprostol, 49 (98%) cases aborted successfully, while one (2%) patient had incomplete abortion. There were no continued pregnancies and misoprostol regimen. With methotrexate and misoprostol regimen, 29 (58%) aborted successfully, while 13 (26%) cases had incomplete abortion with retained products of gestation and eight (16%) had missed abortion. In all those cases, suction and evacuation was done. When patients were asked about their preference for the method of abortion,

significantly, more women had cramping in

the overall acceptability of the medical method of abortion was 98% with mifepristone and misoprostol regimen, and 62% with methotrexate and misoprostol regimen, None of the patients with either regimen had heavy bleeding and no emergency surgical intervention was required. Forty-nine (98%) patients reported bleeding within 24 h of misoprostol administration in mifepristone + misoprostol group, whereas 35 (70%) patients reported bleeding within 24 h in methotrexate + misoprostol group.

DISCUSSION

In the last decade, medical abortion has emerged as a realistic alternative to surgical abortion. Medical abortion has been described as a safe, more private, and natural method by patients who have had an experience with this method.

A recent randomized trial by Wieibe et al. compared the efficacy and side effects of mifepristone 600 mg followed by 400 mg of misoprostol orally 36-48 h later and methotrexate 50 mg/m² intramuscularly followed by 4–6 days later by misoprostol 800 mg vaginally in women £49 days of gestation.

The abortion rate by the first week follow-up examination was 75% in the methotrexate group and 90% in misoprostol group (P < 0.001).^[7] The rate of expulsion by first week after initiation of treatment in our hospital was 58% in methotrexate and 98% in misoprostol group. The methotrexate regimen was the same, but we used lower dose mifepristone

Table 3: Results

	Methotrexate/misoprostol		Mifepristone/misoprostol		
	Number	%	Number	%	
Complete abortion	29	58	49	98	
Incomplete abortion	13	26	1	2	
Missed abortion	8	16	-	-	

* Highly significant (P < 0.001) by using chi-square for trend (chi-square – 21.189, d.f. – 1).

and 800 mg of vaginally misoprostol.

The side effects that were reported after the use of each medication were generally in the same range as those reported by other investigators.^{[10],[11]}

Congenital anomalies in continuing pregnancy are a concern. Although there are no confirmed reports of congenital anomalies after the administration of Mifepristone, yet the risk of malformations appears to be lower with mifepristone than with methotrexate and misoprostol.^[12] Methotrexate is an antimetabolite and has been associated with craniofacial and digital anomalies.^[13] But these congenital malformation occurred when larger cumulative doses of methotrexate were given. Severe side effects to women after a single dose have not been reported. The use of misoprostol in first trimester, which has been associated with a specific type of anomaly mobius sequence with or without limb deficiency, is another issue of concern.[14]

The clinical experience reported here provides substantial evidence that termination of early pregnancy ≤56 days with the combination of low-dose mifepristone and intravaginal misoprostol is safe and effective. It is well tolerated and highly acceptable as compared to the methotrexate and misoprostol regimen.

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