Original Research Article

Efficacy of Mifepristone and Misoprostol combination in termination of early pregnancy

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Abstract

Background: Unplanned and unwanted pregnancies are common occurrences in all societies, regardless of the level of medical, economic, educational or religious development present within them. Despite wider availability of contraceptive methods, the incidence of induced abortion is increasing.

Aim: To study the efficacy of Mifepristone 200 mg orally followed 48 hours later by Misoprostol 600 µg per vaginally in women undergoing medical termination of early pregnancy (up to 73 days of gestational age).

Materials and methods: The present study included 50 pregnant women requesting termination of pregnancy in first trimester attending the department of Obstetrics and Gynecology. Women with gestational age up to 73 days from the first day of the last menstrual period with previous regular cycles were studied. Patients without medical or surgical contraindications to Mifepristone and Misoprostol were included. Women without prior caesarean section were studied.

Results: Majority of the patients were of age group between 21-25 years. 92% of these women were married, 15% were nulliparous and 35% were multiparous. The period of gestation varied from 38-73 days. Majority of women were between 36-50 days of gestational age, constituting 50%. 94% of the patients had complete abortion and 4% had incomplete abortion. Success rate was not affected by the parity or gestational age, 72% of the patients expelled the products of conception within 10 hours, 84% in 15 hours and almost all the patients within 24 hours of prostaglandin administration. Most of the adverse effects reported were of the gastrointestinal system of which nausea was reported by 40%, abdominal pain by 70%, vomiting by 16% and diarrhoea by 4% of the cases. 6% of the patients reported excess bleeding at the time of abortion but none of them required hospitalization or blood

transfusion. The mean duration of bleeding was 7.24 days. A significant fall in hemoglobin was not observed in any patient (less than 1 gm/dl). This combination has the advantage of high complete abortion rate with low frequency of side effects.

Conclusion: The combination of RU 486 200mg orally and misoprostol 600 µg intravaginally appears to offer safe, efficient, acceptable, out-patient procedure and an alternative to surgical abortion in early termination of pregnancy (up to 73 days of gestation).

Key words

Mifepristone, Misoprostol, Caesarean section.

Introduction

Unplanned and unwanted pregnancies are common occurrences in all societies, regardless of the level of medical, economic, educational or religious development present within them. Despite wider availability of contraceptive methods, the incidence of induced abortion is increasing. The surgical nature of abortion procedures is problematic, requiring expense and technology that challenge many patients and their health care systems, particularly in undeveloped nations. Although surgical abortion has been found to be safe and effective, the surgery entails some risks, and is frequently felt by patients to be invasive and "unnatural". The development of safe, effective, inexpensive, nonsurgical methods to induce abortion is thus highly desirable. The use of mifepristone and misoprostol combination in termination of early pregnancy appears to meet the above criteria [1, 2]. Hence this medical method of abortion has been taken up to study the efficacy of this combination. Abortion is defined as the termination of pregnancy by any means before the fetus is sufficiently developed to survive. In United States this definition is confined to the termination of pregnancy before 20 weeks of gestation or delivery of a fetus that weighs less than 500 gm. Abortions can be spontaneous abortions and induced abortions. Induced abortions: Induced abortions signify voluntary and wilful termination of pregnancy whether permitted by law or not (Legal or Illegal) before the viability of fetus. Induced abortions are further classified into therapeutic abortions and elective (Voluntary) abortions. Therapeutic abortion is the termination of pregnancy before the time of fetal viability for the purpose of safe guarding the health of the mother.

Voluntary abortion is the termination of pregnancy before fetal viability at the request of the women but not for reasons of impaired maternal health or fetal disease. Most of the abortions done today are elective abortions. Induced abortions may be legal (Medical termination of pregnancy) or illegal. It is estimated that 40-60 million abortions are performed in the world each year, of which about 33 million are legal procedures; these numbers imply a worldwide abortion rate of 37-55 per 1000 women, aged 15-44 years and an abortion ratio of 24-32 abortions per 100 known pregnancies. Induced abortions are the third common means of fertility control next to sterilization and oral contraceptives. The abortion rate and ratios are very much under estimated in some countries. For instance, in India the legal abortion rate is 3.3 and abortion ratio is 2.1 but illegal induced abortions are estimated to have numbered 4-6 million, giving an abortion rate of 36-55 and abortion ratio of 13-20 per 100 estimated pregnancies per year.

Materials and methods

The present study included 50 pregnant women requesting termination of pregnancy in first trimester (up to 73 days of gestation) attending the department of Obstetrics and Gynecology at Govt. Maternity Hospital/ Kakatiya Medical college Warangal, Telangana during March 2012 to March 2013.

Inclusion criteria

- Women with gestational age up to 73 days from the first day of the last menstrual period with previous regular cycles.
- Patients without medical or surgical contraindications to mifepristone and misoprostol.
- Women without prior caesarean section.

Exclusion criteria

- Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass.
- Intrauterine device in place.
- Patients with cardiac, pulmonary diseases, epilepsy, asthma, renal failure.
- Concurrent long term corticosteroid therapy.
- Hemorrhagic disorders or concurrent anticoagulant therapy.
- Inherited porphyrias.
- Patients on antifungal drugs and antiepileptic drugs.

50 patients who fulfilled the inclusion criteria requesting medical termination of pregnancy were taken up for the study. A complete case record was prepared and detailed history of all the patients was taken. A thorough clinical examination including general, per abdominal and per vaginal examination was done. All the patients were subjected to investigations like complete urine examination, hemoglobin estimation (Hb%), blood grouping and Rh typing and random blood sugar were done prior to the administration of the regimen. Ultrasonogram was done to confirm the gestational age. All the patients were informed the success rate of medical treatment and explained that if it fails they may need surgical intervention. A written consent was taken. Each patient was given Tab. Mifepristone 200 mg orally on the same day as the clinic visit or within the following two days. The women were allowed home half an hour after the mifepristone administration with an instruction to return to the Gynecology ward after 48 hours. Patients were also informed that in some cases abortion might occur at home following mifepristone. After 48 hours Tab Misoprostol 600ug was kept in the posterior fornix of vagina under strict aseptic precautions. Vitals were monitored half an hourly before and after the insertion of tablet. Patients were discharged 4 hours later on the same day, and were advised to report if there was excessive bleeding, fever, foul smelling discharge, vomiting or any other complications were experienced. All the patients were kept on Tab Doxycycline 100 mg bid for 5 days. Patients were instructed to report on the 14^{th} day if no complications occurred in between. Ultra sound was repeated on 14^{th} day to confirm the completeness of abortion. Success was defined as the complete expulsion of the products of conception without the need for surgical intervention. Women who have not responded to medical treatment within 24 hours of misoprostol administration, were offered surgical methods to terminate the pregnancy.

Results

Results were analysed according to age, marital status, parity, gestational age, induction abortion interval, completeness of abortion, need for surgical intervention, failure of procedure and complications.

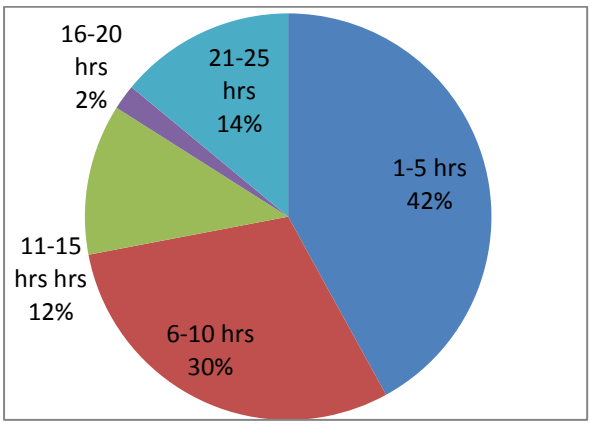
In the present study youngest patient was 18 years old while the oldest was 35 years old, around 42% belonged to 21-25 years. In the present study, 30% were prirnigravida, 34% were 2^{nd} gravida, 18% were 3^{rd} gravida and 18% were 4^{th} gravida and above. Most of the patients were 2^{nd} gravida. Most of the patients (50%) in the present study were between 36-50 days of gestational age. 92% of the patients were married and termination was done as a birth spacing measure (**Table – 1**).

The average induction abortion interval in this study was 8.66 hours. 72% of patients aborted within 10 hours and all the patients aborted within 24 hours (**Figure – 1**).

Table - 1: Demographic Distribution.

Age (Years)	No. of Patients	%
15-20	8	16
21-25	21	42
26-30	17	34
31-35	4	8
Gravidity		
Primigravida	15	30
2nd gravida	17	34
3rd gravida	9	18
4th gravida and above	9	18
Gestational age in days		
20-35	1	2
36-50	25	50
51-65	19	38
66-80	5	10
Marital status		
Unmarried	4	8
Married	46	92

Figure – 1: Induction abortion interval.



Completeness of abortion and complications were as per **Table – 2**. In the present study, two cases had retained products of conception on repeat ultra-sonogram, which needed surgical intervention. With check curettage few retained products came out. One case was second gravida with 49 days of gestational age and the other was third gravida with 60 days of gestation. One patient was lost for follow up. In the present study 90% of women reported adverse reactions following the administration of misoprostol on day three of the treated procedure. 70% of women complained abdominal pain within 4 hours of prostaglandin administration and severity of pain was more in nulliparous women compared with parous women. These patients were treated with NSAIDs (Mefenamic acid). Nausea, vomiting and diarrhoea followed PG administration in about 40%, 16%, and 4% of patients respectively. Majority of women reported more than one side effect. After the third day of the treatment procedure adverse reactions declined progressively and by day 14, reports were rare except for bleeding and spotting.

Table - 2: Completeness of abortion and complications.

Abortion	No. of cases	%
Complete	47	96
Incomplete	2	4
Complications		
Nausea	20	40
Vomiting	8	16
Pain abdomen	35	70
Diarrhoea	2	4
Excess bleeding	3	6

Discussion

Unsafe abortion is a major cause of mortality among women in India accounting for approximately 15% of maternal deaths. The Ministry of Health and Family Welfare, Government of India declared the year 2001 as the "Year of Safe Abortions" [3]. There has been a constant endeavour to make abortion safer and accessible to women. Although the idea of using medication to induce late menses or cause abortion dates back centuries, medically proven regimes are available only in the last 50 years. In 1950 folic acid antagonist, "Aminopterin" was used orally to induce medically indicated abortions in women at less than three months gestation. As it is associated with severe adverse effects it is no more in use. It was in the 1970s that researchers found that natural prostaglandins such as PGE2 and PGF, were effective in inducing abortions when administered intravaginally or intracervically. In 1982,

Erienne-Emile Baulieu discovered and developed an antiprogestin, Mifepristone (RU 486). "Mifepristone only" therapy for termination3 of early pregnancy was evaluated initially in clinical studies with a success rate of 50-86%. Later several studies have evaluated the efficacy of mifepristone and prostaglandin combination in terminating early pregnancy in women with gestational age of 49-63 days. The complete abortion rates with this combination therapy varied from 92.1% in U.S trials to 95.5% in French trials.

Currently in India, mifepristone has been approved for use in medical termination of intrauterine pregnancy up to 49 days of gestation. The efficacy and acceptability of this combination has been established by different studies even up to 63 days of gestation. Various studies have used RU 486 in the dose range of 200-600 mg orally as a single dose. Comparative trials have shown that a reduction in the oral dose of RU 486 from 600 to 200 mg does not affect the efficacy in termination of early pregnancy. WHO Task force has done a largest clinical trial in women of less than 35 days of gestational age using 200 mg mifepristone and 400 µg misoprostol orally. The success rate in this trial was 89.3%. Another study done by McKinley, et al. [4], up to less than 63 days of gestation using 200 mg of RU 486 and 600 µg of misoprostol orally reported 89.8% success rate. In the present study, 200 mg of RU 486 orally and 600 µg of misoprostol intravaginally was used in women of less than 73 days of gestation. Complete abortion occurred in 94% of cases. Elaine. V. Gouk, et al. [5], in his study using 200 mg of oral RU 486 and 800 µg of misoprostol intravaginally between 63-83 days of gestation reported 94.5% success rate and surgical intervention was needed in 4%. Following the administration of mifepristone alone, 1.6% of cases had complete abortion. These results are comparable to that of the present study. The success rate of the present study is also comparable to those done by WHO and Ashok, et al. [6], using the same regime in women between 52-63days of gestation (**Table – 3**).

Table - 3: Different studies with different dosage regimen and their outcome.

Study done by	**Duration of pregnancy (no. of patients)**	**RU 486 and PG dose**	**Success rate**	**Ongoing Pregnancy**
WHO task force Multicenter	< 56 days (1182)	200-600 mg + 1 µg gemeprost vaginally	94%	0.5%
Ashok, et al. [6]	< 49 days (928) 50-63 days	200 mg + 500 µg misoprostol vaginally	98.5%, 96.7%	0.2% 0.8%
Elaine, et al. [5]	63-83 days (253)	200 mg + 500 µg misoprostol vaginally	94.5%	2.3%
Present study	< 73 days (50)	200 mg + 600 µg misoprostol vaginally	94%	Nil
Peyron, et al. [7]	<49 days (890)	600 mg + 400 µg oral misoprostol	----	96%
Mckinley, et al. [4]	<63 days (220)	200-600 mg + 600 µg oral misoprostol	----	94%
Spitz, et al. [8]	<49 days (827)	600 mg + 400µg oral misoprostol	----	92%

The ongoing pregnancy rate in the present study was nil compared to 0.4% in WHO trials, 0.8% in Ashok, et al. [6], study. The most common adverse effects after the treatment were that of gastrointestinal in almost all the studies including the present study. Heavy bleeding was reported by 2.8% of cases in Elaine, et al. [5], study compared to 6% in the present study. No

correlation was noted between the period of gestation and excess bleeding. Nulliparous and multiparous women did not differ in this respect. There was no significant alteration in hemoglobin concentration (<1 gm/dl). None required blood transfusion or hospitalization in the present study. Lourie Silvestre, et al. have studied 2115 women seeking voluntary termination of pregnancy up to 49 days of gestation by giving 600 mg of mifepristone followed 36-48 hours later by one of the prostaglandin analogues either gemeprost (1 mg vaginal suppository) or sulprostone (0.25-0.5 mg intramuscularly) [7, 8]. The efficacy rate was 96% and ongoing pregnancy was 1%. Sulprostone was found to be effective than gemeprost in his study. In another study Ulman A Silvestre [9] found that the success rates for various prostaglandins have been found to be very similar. Similar study was done by Nicholas C. W. Hill [10] in 100 patients with a gestation of less than or equal to 63 days, revealed 95% success rate. In 88% abortion occurred within 4 hours of prostaglandin administration. 25% had nausea, 15% had vomiting after RU 486, 13% vomited after PG treatment and 10% had diarrhoea.

El-Refaey [11] in his study found that 95% of the women who received 800 µg misoprostol vaginally after RU 486 had abortion within 4 hours when compared to those who received it orally (78%). Misoprostol by vaginal route appears to decrease the side effects, reduces the induction abortion interval and failure rates when compared to oral administration. WHO task force conducted a study on 1182 patients with an early pregnancy 7-28 days menstrual delay requesting abortion. They were divided into 3 groups. Each group received either 200 mg; 400 mg or 600 mg of RU 486 orally followed 48 hours later by vaginal pessary of 1 mg of PGE analogue. Complete abortion occurred in 93.8% of those given 200 mg of RU 486, 94.1% in those given 400 mg and 94.3% of those in 600 mg group. Hence for the termination of early pregnancy a single dose of 200 mg is as effective as 600 mg of RU 486. Elaire V Gouk, et al. [5], studied patients with 63 to 83 days of gestation by giving 200 mg of mifepristone 500 mg of misoprostol and found 94.5% success rate.

Ashok, et al. [6], had done the same study with the same regimen and found 97.5% success rate. Tang GWK, et al. [12] studied that the side effects of RU 486 alone include nausea and vomiting in 76%, bleeding 48%, fatigue in 31%, abdominal pain in 31%, dizziness in 29%, anorexia in 11%, headache in 6% and breast tenderness in 4%. Gastrointestinal symptoms are more frequent with oral prostaglandins. Ingestion of misoprostol in early gestation has been associated with unusual skull malformation if pregnancy continues to term. The most common anomalies were equinovarus with cranial nerve deficiencies commonly of nerve V, VI, VII, arthrogryposis, terminal transverse limb defects with or without Mobius sequence (congenital facial paralysis). Healthy apparently normal infants have been delivered after exposure to mifespristone in early pregnancy. The full teratogenic potential has not yet delineated. The acceptability data has been quantified after abortion with the standard regimen in five countries (China, Cuba, India, United States and Vietnam). The acceptability has been outstandingly high. The experience of the treatment was recorded as satisfactory by 88 to 97% of women and the method would be preferred for a next abortion by 84 to 96% of women.

Conclusion

The combination of RU 486 200 mg orally and misoprostol 600 µg intravaginally appears to offer safe, efficient, acceptable, out-patient procedure and an alternative to surgical abortion in early termination of pregnancy (up to 73 days of gestation).

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