Original Article

Comparison of Efficacy of Oral and Vaginal Tablet Misoprostol for Medical Management of Missed Miscarriage

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ABSTRACT

Objective: To compare the efficacy of tablet Misoprostol orally and vaginally for medical management of missed miscarriage.

Study Design: Double blind randomized clinical trial study.

Place and Duration of Study: This study was conducted at the Gynecology and Obstetrics department (Tertiary care hospital Bolan Medical College / Hospital, Quetta for 6 months since 2nd June 2019 to 2nd Dec 2019.

Materials and Methods: Total of 180 patients with clinically diagnosed of missed miscarriage and confirmed by ultrasound were included in this study. Patients were divided into two groups. The group A received tablet Misoprostol orally while group B received tablet Misoprostol vaginally.

Results: Out of 180 patients with clinically diagnosed of missed miscarriage were used. Age wise distribution shows that women of most cases were effective with Misoprostol between 21-30 years followed by 31-40 years and <=20 years in both groups.General characteristics such as mean age, gravity, parity and gestational age were not important between groups.Rate of successfully complete miscarriage was significantly high in vaginal Misoprostol patients (Group B) as compare to oral Misoprostol patients (Group A)[78.9% vs. 54.4%; p=0.001]. Stratification analysis was also performed to control effect of age and parity. Rate of successfully complete miscarriage was significantly high in vaginal Misoprostol patients (Group B) as compare to oral Misoprostol patients (Group A) for the age 21 to 30 years of age cases while below and equal to 20 as well as above 30, it was not observed significant.For primiparous and multiparous groups, successfully complete miscarriage was significant between groups while nulliparous it was not significant

Conclusion: It is concluded that Misoprostol is an effective and safe agent so it may be used for second trimester termination of pregnancy.

Key Words: Miscarriage, Misoprostol, Oral, Vaginal, Tablet.

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INTRODUCTION

Clinical miscarriage accounts for approximately 12% of pregnancies [1]. Dilatation and curettage, which is usually done in an operating room, has been the preferred procedure for missed miscarriage for the last 50 years, thus greatly raising the costs [2].

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Worldwide abortions over the mid-trimester constitute only 10%-15% of all induced abortions, but they are responsible due to its higher success rate due to its particular myometrial sensitivity, Misoprostol has substituted all other methods for pregnancy termination, as well as being inexpensive, stable at room temperature, can be kept for a long time, and easily accessible[3].

However, compared to similar studies from China and India that used 600ug of sublingual and vaginal Misoprostol and reported an overall success rate of 87.5 percent and 86 percent, respectively, it is much less than that reported [4].

A second trimester pregnancy termination study of oral verses of vaginal Misoprostol shows that the success rate at 24 hours in the vaginal group 70 percent corresponds to oral group 50 percent in addition, no significant difference in the success rate at 48 hours oral 65 percent and 70 percent [5]. There are few retrospective studies that show that there is no increased risk of uterine rupture[6].

Given the reported better efficacy and comparatively easy absorption of misoprostol for medical management of missed miscarriage, this study aims to analyze the effect of this treatment specially in the perspective of a population belonging to a relatively less developed areas of this country. This study will help our understanding regarding some important aspects in terms of efficacy and less complication of misoprostol treatment for missed miscarriage in such a population and will open the avenues for further research in this area.

MATERIALS AND METHODS

All patients who presented with sign and symptoms of missed miscarriage diagnosed by consultant having experience of 10 years and senior registrar having experience of 5 years and also confirmed by ultrasound was admitted in Gynecology and Obstetrics department (Tertiary care hospital BMCH) through OPD and giving the informed consent and fulfilling the inclusion and exclusion criteria was included in this study.

Complete data of patients regarding age, gravidity, parity, last menstrual period, gestational age, ultrasound finding (conformation of missed miscarriage) was taken. These findings were observed by a single person of level of consultant or senior registrar so as to avoid any intra observational bias in the misdiagnosis of missed miscarriage. Patients were divided into two groups. The group A received tablet Misoprostol orally while group B received tablet Misoprostol vaginally. The researcher was blind by giving tablet Misoprostol to each group.

The dose of Misoprostol 400micrograms (2 tablets) was given at the start. The effect of the tablet was seen four hourly and if the product of conception are expelled within 16 hours by 4 doses given by either route, then drug was labeled as efficacious with that particular route of administration. Clinical outcome in the form of complete expulsion of product of conception successful or unsuccessful and complications was compared in two groups and was filled on proforma by researcher herself.

Statistical analysis: The data collected was analyzed using computer packages SPSS version 17.0. The quantitative data like age, gravidity, parity, gestational age was analyzed by calculating mean and standard deviation (SD). The study result like complete miscarriage (successful/ unsuccessful) was compared among group A and group B to look the efficacy of oral and vaginal tablet Misoprostol for medical management of missed miscarriage, frequency and percentages was analyzed in both groups by chi square test. The level of significance was less than and equal to 0.05. Stratification was done to controlled effect modifies like age and parity. Post stratification chi-square test was done.

RESULTS

A total of 180 patients with clinically diagnosed of missed miscarriage and confirmed by ultrasound were included in this study. Patients were randomly allocated into two groups; group A were treated with tablet Misoprostol orally while group B were treated with tablet Misoprostol vaginally.Age wise distribution shows that women of most cases were effective with Misoprostol between 21-30 years followed by 31-40 years and <=20 years in both groups as shown in Figure-1.

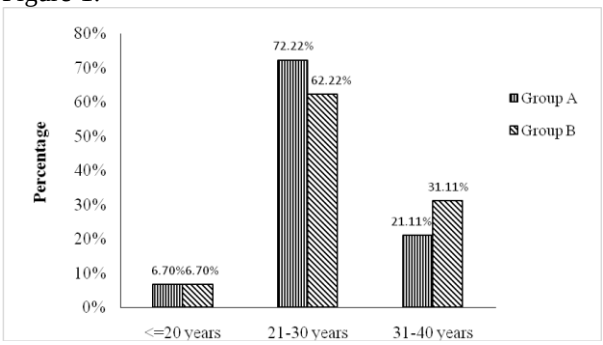

Figure No.1: Age wise distribution of the patients with respect to Groups (n=180)

General characteristics such as mean age, gravity, parity and gestational age were not important between groups as shown in Table-1.

Table No.1: Comparison of general characteristics of the between groups

Variables	**Group A** (Oral) **n=90**	**Group B** (Vaginal) **n=90**	**P-Value**
Age (Years)	27.40±4.54	28.08±5.33	0.36
Gravida	2.41±0.51	2.47±0.58	0.41
Parity	1.20±0.71	1.29±0.72	0.40
Gestational Age (Weeks)	20.46±2.78	19.87±2.96	0.17

*Data are presented as mean and standard deviation Independent sample t test.

Table No. 2: Compare the efficacy of oral with vaginal tablet Misoprostol for medical management of missed Miscarriage

Complete Miscarriage	**Group A** (Oral) **n=90**	**Group B** (Vaginal) **n=90**	**Total**
Successful (Efficacy-Yes)	49(54.4%)	71(78.9%)	120(66.7%)
Unsuccessful (Efficacy-NO)	41(45.6%)	19(21.1%)	60(33.3%)

Comparison of the efficacy of oral with vaginal tablet Misoprostol for medical management of missed miscarriage is presented in Table-2. Rate of

successfully complete miscarriage was significantly high in vaginal Misoprostol patients (Group B) as compare to oral Misoprostol patients (Group A) as shown in Table-2.

Efficacy was measured in terms of complete expulsion (successful) of dead fetus after 4 doses given over 16 hour's period without complications. Stratification analysis was also performed to control effect of age and parity. Rate of successfully complete miscarriage was significantly high in vaginal Misoprostol patients (Group B) as compare to oral Misoprostol patients (Group A) for the age 21 to 30 years of age cases while below and equal to 20 as well as above 30, it was not observed significant as shown in Table-3.

Table No. 3:Compare the efficacy of oral with vaginal tablet Misoprostol for medical management of missed miscarriage with respect to age groups

Age Groups (Years)	Complete Miscarriage	Group A (Oral) n=90	Group B (Vaginal) n=90	P-Value
≤ 20 Years	Successful Unsuccessful Total	3(50%) 3(50%) 6	5(83.3%) 1(16.7%) 6	0.22
21 to 30 Years	Successful Unsuccessful Total	34(52.3%) 31(47.7%) 65	48(85.7%) 8(14.3%) 56	0.0005
31 to 40 Years	Successful Unsuccessful Total	12(63.2%) 7(36.8%) 19	18(64.3%) 10(35.7%) 28	0.93

For primiparous and multiparous groups, successfully complete miscarriage was significant between groups while multiparous it was not significant as shown in Table-4.

Table No.4:Compare the efficacy of oral with vaginal tablet Misoprostol for medical management of missed Miscarriage by parity

Parity	Complete miscarriage	Group A (Oral) n=90	Group B (Vaginal) n=90	P-Value
Nulli-parous	Successful Unsuccessful **Total**	9(75%) 3(25%) **12**	4(50%) 4(50%) **8**	0.25
Primi-parous	Successful Unsuccessful Total	24(47.1%) 27(52.9%) 51	41(77.4%) 12(22.6%) 53	0.001
Multi-parous	Successful Unsuccessful Total	16(59.3%) 11(40.7%) 27	26(89.7%) 3(10.3%) 29	0.009

*Data are presented as n(%). Chi-Square test applied for each age categories

DISCUSSION

In our part of the world, Termination of Pregnancy (TOP) is performed only if there is a significant risk of a fetus with severe congenital abnormalities, intrauterine fetal death or in the presence of medical conditions that pose a real threat to the health or life of the mother. Other prostaglandins, such as prostaglandin E2 and prostaglandin F2 alpha (PGF2 alpha), were mostly used for second trimester terminations prior to the availability of Misoprostol (a synthetic analogue of prostaglandin E1). These agents are effective but costly, require refrigeration and need higher doses, which in a high percentage of patients are associated with side effects such as nausea, vomiting, diarrhea and fever.[7]Since 1993, abortifacient properties of Misoprostol have been documented in medical literature for second trimester termination.[8] Misoprostol is an economical agent, can be kept at room temperature, sustainable for years, and has few systemic effects[9].Misoprostol is an economic and efficient abortifacient drug for second trimester pregnancy termination in these days of financial constraints with shorter induction to abortion interval with few side effects.[10] Due to scary economic resources and high temperatures, this agent is particularly important for a country like ours. In these days of financial constraints, Misoprostol is an economical and effective abortifacient drug for second trimester pregnancy termination with shorter induction to abortion interval with few side effects.[10] This agent is especially relevant for a country like ours because of scare economic resources and high temperature.[11]

Age wise distribution shows that women's of most cases were effective with Misoprostol between 21-30 years followed by 31-40 years and <=20 years in both groups.General characteristics such as mean age, gravity, parity and gestational age were not important between groups. In Shah et al[12] study there was no significant difference with respect to age, parity, gestational age and uterine size between the two groups.

In this study rate of successfully complete miscarriage was significantly high in vaginal Misoprostol (Group B) as compare to oral Misoprostol (Group A) [78.9% vs. 54.4%; p=0.001]. In a study regarding oral verses vaginal Misoprostol in second trimester pregnancy termination shows that the success rate at 24 hours at vaginal group 70% corresponds with oral group 50% in addition, no significant difference in the success rate at 48 hours oral 65% and 70%.[5.] Few observational studies have shown that there is no increased risk of uterine rupture in women who experience Misoprostol second trimester pregnancy termination.[6]Second trimester pregnancy termination that is complicated by fetal demise is usually more predictable with a shorter induction-expulsion interval than that conducted when the fetus is alive, an observation revealed this could be due to the increased sensitivity of the uterus to prostaglandins and the release of tissue factors following fetal demise.[13]Bebbington et al[14], Dickinson[15] and Ho et al[16] revealed a shorter induction-expulsion interval for vaginal route of the drug as compared to oral route for Misoprostol it. Ho et al [16] used

mifepristone as a pre-induction agent and none of pregnancy in their study were terminated because of fetal demise or fetal anomalies, whereas in the present study pregnancies were terminated mainly because of fetal demise and structural anomalies.Surgical evacuation was required in about 37% of cases in oral group versus 33% in vaginal group in Mahjabeen et al[17] study, while Iqbal quoted the need of surgical evacuation in 21.4% in oral protocol versus 13.8% in vaginal protocol.[18] The difference in the results could be due to higher dosage schedule as compared to this study, which also resulted in decreased failure rate in their study.A study which compared the efficacy of sublingual and vaginal Misoprostol in second trimester termination of pregnancy has reported a higher success rate (85%) for vaginal Misoprostol compared to sublingual Misoprostol (64%) at 24 hours but there was no significant difference in the abortion rate at 48 hours.[19]A study from UK which compared sublingual and vaginal Misoprostol for medical abortion also reported unpleasant taste in 63.9% of women in the sublingual group as compared to 37.5% of women in the vaginal group ($p = 0.02$).[20] In addition, two other studies comparing sublingual and vaginal Misoprostol have reported a significantly increased frequency of unpleasant taste in women taking sublingual misoprostol.[21] It is suggested that this side effect may be overcome by making the misoprostol tablet sugar coated. Other side effects like nausea and shivering were also seen slightly more frequently in the sublingual group. This increased frequency of side effects may be explained by the higher bioavailability of sublingual misoprostol.[22]

Gilbert and Reid[23] also reported no significant difference in side effects between both groups of oral and vaginal misoprostol.[23]However, Bebbington et al[15] reported increased febrile morbidity in patients who received misoprostol by vaginal route. This may be due to high dose of the drug (400 µg) in their study. Dickinson et al[16] also noticed more side effects with higher dosage of vaginal misoprostol, while Kamalet al[24] reported no significant difference between side effects of misoprostol while comparing vaginal with orovaginal route.The main limitation was single center study, smaller sample size and involvement of different gastroenterologists. So additional studies with larger sample sizes are necessary.

CONCLUSION

Misoprostol is an effective and safe agent so it may be used for second trimester termination of pregnancy. Vaginal route of administration appear to more effective as compared to oral route so vaginal route can be a convenient option as it will be preferable for patients as well as health care providers.

Author's Contribution:

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Conflict of Interest: The study has no conflict of interest to declare by any author.

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