Original Article

Comparison of Efficacy of Vaginal VS Oral Prostaglandin E1 Analogue (Misoprostol) in Management of First Trimester Missed Abortion

Nighat Kafil[1] and Farzana Rizwan Arain[2]

ABSTRACT

Objective: To compare the efficacy of misoprostol vaginally/orallyin management of first trimester missed abortion.

Study Design: Quasi experimental study.

Place and Duration of Study: This study was conducted at the Gynecology Department, Muhammad Medical College Hospital, Mirpurkhas from January 2013 - December 2014.

Materials and Methods: Eligible women satisfying inclusion/exclusion criteria were recruited after written informed consent and given 600 µg of misoprostol vaginally/orally with a maximum of 3 doses. Patients were monitored for 24 hours following complete abortion or surgical evacuation and then discharged. The primary outcome of study was defined as Success (non surgical evacuation of product of conception) or Failure (excessive bleeding with retained product of conception where surgical evacuation was performed). Associated adverse events, patient satisfaction and acceptability to treatment were also recorded and compared. The data was analysed using SPSS version 21 (IBM, Chicago, IL).

Results: Both vaginal and oral routes were highly effective, however greater proportion of patients receiving vaginal Misoprostol had success compared to those receiving oral Misoprostol (88% Vs. 71%; p-value = 0.005). Moreover, greater proportion of patients receiving vaginal Misoprostol had induction – expulsion interval within 12 hours compared to those receiving oral Misoprostol (50% vs. 39.44%; p-value = 0.041). Fewer side-effects were observed among participants receiving Vaginal Misoprostol than Oral Misoprostol. There was no significant difference in patient's satisfaction and acceptability in participants of both groups.

Conclusion: Vaginal misoprostol is more effective than oral misoprostol for first trimester missed abortion.

Keywords: First trimester, Missed abortion, Misoprostol.

Citation of article: Kafil N, Arain FR. Comparison of Efficacy of Vaginal VS Oral Prostaglandin E1 Analogue (Misoprostol) in Management of First Trimester Missed Abortion. Med Forum 2017; 28(11):45-49.

INTRODUCTION

Termination of pregnancy due to different maternal factors or on account of foetal condition is a prevalent obstetrical problem[1,2]. Missed abortion in the first trimester of pregnancy is characterized by development arrest of fetus along with ultrasound findings reporting an empty gestational sac or no cardiac activity of fetus[1,2,3]. Slightly more than 10% of clinically recognized pregnancies have reported termination of pregnancy[3]. This not only imposed significant healthcare and financial burden on cost of care but non continuing pregnancy also psychologically affects mothers. Studies have reported increased diagnosis of missed abortion on routine ultrasound screening[3,4,5].

A significant proportion of missed abortion occurs simultaneously, however some pregnancies simply stop growing without any obvious symptoms with end fate as deferment in expulsion of conceptus[6,7].

Safe induction of abortion is of immense clinical importance requiring effective and high quality medical care. Different surgical/medical methods are available for termination of pregnancy however medical methods are preferred demonstrated by lower rates of maternal morbidity/mortality[8,9]. Surgical evacuation, although quick and effective procedure when performed by a well-trained physician, carries a risk of injury, bleeding and infection, and possible complications from anesthesia[10,11]. Misoprostol is a Prostaglandin analogue widely used for termination of pregnancy, considering it efficaciousness, low cost and long shelf life (2 years) at room temperature[8,12,13]. Both oral and vaginal routes are available but oralroute is associated

1. Department of Pharmacology, Muhammad Medical College, Mirpurkhas.
2. Department of Obstetrics & Gynecology, Taif Medical College, Taif, KSA

Correspondence: Dr. Nighat Kafil, Professor Pharmacology, Muhammad Medical College, Mirpurkhas, Pakistan.
Contact No: 0323-8226979
Email: nhafil@hotmail.com

Received: June 15, 2017; Accepted: August 19, 2017

with disadvantages like decreased bioavailability, increased gastrointestinal side-effects[9,14,15].

Present study was conducted to compare the efficacy and safety of Misoprostol(i.e. 600 µg) administered intravaginally/ orally in missed abortion up to 12 weeks of gestation among patients visiting Gynecology Department of Muhammad Medical College Hospital (MMCH). Only a few studies have been conducted to compare the efficacy and safety of oral/vaginal Misoprostol in missed abortion at equal dosage (i.e. 600 µg) globally, and to the best of our knowledge first in Pakistan.

MATERIALS AND METHODS

The Quasi experimental study was conducted at Gynecology Department of Muhammad Medical College Hospital, Mirpurkhas over a period of two years from January 2013 - December 2014. Muhammad Medical College Hospital was established in 1999, located 6 km outside Mirpurkhas, Sindh. The hospital has a well-established Gynecological department with women from both rural and urban areas visiting for routine ante natal checkups, deliveries and gynecological problems.

Women with confirmed diagnosis of missed abortion on ultrasound, age duration 18-45 years, gestational age ≤ 12 weeks, closed cervix on bimanual pelvic examination and hemoglobin ≥ 9 gm/dl, place of residence within 20 km from hospital, willingness to abstain from intercourse for first two weeks after intervention given and comply with the follow-up schedule were invited to participate in this study. Women with history of inflammatory bowel disease, asthma or liver diseases, hemodynamically unstable, severe infection (assessed by presence of fever/foul smelly discharge/uterine tenderness), deranged coagulation profile (Prothrombin index ≤ 85%), ectopic pregnancy and contraindicated to prostaglandin use were excluded.

After satisfying the inclusion/exclusion criteria, baseline investigations and ultrasonographic confirmation of missed abortion, participants were recruited in this study. Participants were non-randomly allocated to treatment Group A (Vaginal Misoprostol) and treatment Group B (Oral Misoprostol). Patients in the treatment Group A received 600µg of misoprostol having soaked in normal saline solution intra-vaginally into posterior fornix, repeated six hourly up to a maximum of three doses. Prior to insertion, vaginal cleansing was performed with 10% povidone iodine, following insertion women remained fully recumbent for at least 3 hours. Patients in treatment Group B were admitted in hospital and given 600 µg of misoprostol orally with water at six hour interval, with a maximum of 3 dosesin the presence of clinician.

Data on characteristics of participants i.e. age, place of residence, parity, gestational age in weeks, previous spontaneous abortion and previous caesarian section were collected. The primary outcome of the study was defined as Success (non surgical evacuation of product of conception confirmed on ultrasound) or Failure (incomplete expulsion of products of conception or excessive bleeding with retained product of conception where surgical evacuation was performed). The other clinical outcomes assessed were number of doses, induction – expulsion intervals in hours and cervical permeability (good cervical permeability was defined as the ability to pass #8 Hegar dilator) in both treatment groups. Patients in both groups were monitored for 24 hours following complete abortion or surgical evacuation and then discharged with analgesics and prophylactic antibiotics for 5 days.

The first follow-up visit was one week after discharge. Any adverse events i.e. nausea/ vomiting, severe crampy pain, dizziness, headache, diarrhea, fever with chills, excessive bleeding, discharge per vaginum, cervical tear and uterine rupture were recorded and managed accordingly. Moreover data on patient's satisfaction, acceptability and preference to recommend to others were also collected at follow-up visit.

For this clinical study ethical approval was obtained by the institutional ethical review committee of Muhammad Medical College Hospital. Prior to enrollment in the study, written informed consent was obtained from all participants having explained the process involved, intervention given (oral or vaginal Misoprostol) and benefits/ risks of recruitment in this research. Anonymity and confidentiality of participant's data was maintained throughout the research with only investigators having access to the data.

Data was analyzed using SPSS version 21 (IBM, Chicago, IL). The qualitative variables were presented as frequency/percentage. The baseline characteristics of the study participants receiving vaginal/oral Misoprostol were compared using chi square statistics. Importantly, the clinical outcomes (success proportion, number of doses, induction – expulsion intervals in hours and cervical permeability), adverse events, patient's satisfaction and acceptability observed among the study participants receiving Vaginal Misoprostol (Group A) and Oral Misoprostol (Group B) were also compared using chi-square statistics. For the purpose of inferential statistics p-value ≤ 0.05 was considered significant.

RESULTS

Table 1 compared the baseline characteristics of the study participants receiving vaginal or oral Misoprostol. There was no significant difference in baseline characteristics among patients non-randomly allocated to receive Group A/Group B.

Table 2 gives details of comparison of the clinical outcomes amongst Group A and Group B. Significant difference was only found in success proportion and

induction – expulsion intervals among patients non-randomly allocated inboth groups. Greater proportion of patients receiving vaginal Misoprostol had success compared to those receiving oral Misoprostol (88% Vs. 71%; p-value = 0.005).

Table No.1: Comparison of baseline characteristics of the study participants receiving Vaginal Misoprostol (Group A) and Oral Misoprostol (Group B)

Baseline Characteristics	Group A (n = 100) n (%)	Group B (n = 100) n (%)	P-value
Age categories (years)			
18-20 years	15 (15)	16 (16)	0.906
21-25 years	43 (43)	47 (47)	
26-30 years	31 (31)	28 (28)	
> 31 years	11 (11)	9 (9)	
Residence			
Rural	33(33)	37 (37)	0.654
Urban	67 (67)	63 (63)	
Parity			
Primigravida	70 (70)	74 (74)	0.639
Multigravida	30 (30)	26 (26)	
Gestational age (weeks)			
< 6 weeks	8 (8)	5 (5)	0.565
6-12 weeks	92 (92)	95 (95)	
Previous spontaneous abortion			
Yes	39 (39)	41 (41)	0.887
No	61 (61)	59 (59)	
Previous caesarian section			
Yes	18 (18)	22 (22)	0.597
No	82 (82)	78 (78)	

Table No.2: Comparison of clinical outcome among the study participants receiving Vaginal Misoprostol (Group A) and Oral Misoprostol (Group B)

Clinical Outcomes	Group A (n = 100) n (%)	Group B (n = 100) n (%)	P-value
Success			
Yes	88 (88)	71 (71)	0.005
No	12 (12)	29 (29)	
Number of Doses			
One	10 (11.36)	2 (2.82)	0.064
Two	38 (43.18)	27 (38.03)	
Three	40 (45.45)	42 (59.15)	
Induction-Expulsion Interval (hours)			
≤ 6 hours	10 (11.36)	0 (0)	0.041
7-12 hours	34 (38.64)	28 (39.44)	
13-18 hours	41 (46.59)	36 (50.70)	
> 18 hours	3 (3.4)	3 (4.23)	
Cervical Permeability			
Permeable	12 (12)	25 (86.20)	0.439
Non-Permeable	0 (0)	4 (13.80)	

Moreover, greater proportion of patients receiving vaginal Misoprostol had induction – expulsion interval within 12 hours compared to those receiving oral Misoprostol (50% vs. 39.44%; p-value = 0.041). Importantly, none of the patients receiving oral Misoprostol had induction – expulsion interval less than or equal to 6 hours. Table 3 gives details of comparison of side effects observed among the study participants of Group A and Group B. Comparatively, the incidence of side-effects were more in patients receiving the oral Misoprostol than vaginal Misoprostol.

Table No.3: Comparison of side effects observed among the study participants receiving Vaginal Misoprostol (Group A) and Oral Misoprostol (Group B)

Side-Effects	Group A (n = 100) n (%)	Group B (n = 100) n (%)
Nausea/ Vomiting (Requiring anti-emetics)	61 (61)	71 (71)
Dizziness	22 (22)	27 (27)
Headache (Requiring analgesics)	19 (19)	22 (22)
Severe crampy pain (Requiring analgesics/ anti-spasmodic)	33 (33)	51 (51)
Diarrhea	14 (14)	17 (17)
Fever with chills (Requiring anti-pyretic)	5 (5)	9 (9)
Excessive bleeding	4 (4)	7 (7)
Discharge per vaginum	3 (3)	5 (5)
Cervical tear	0 (0)	0 (0)
Uterine rupture	0 (0)	0 (0)
Death	0 (0)	0 (0)

Table No.4: Comparison of patient satisfaction and acceptability to treatment observed among the study participants receiving Vaginal Misoprostol (Group A) and Oral Misoprostol (Group B)

Patient satisfaction and Acceptability	Group A (n = 100) n (%)	Group B (n = 100) n (%)	P-value
Patient satisfaction			
Satisfied	74 (74)	72 (72)	0.923
Unsatisfied	22 (22)	23 (23)	
Neither satisfied nor unsatisfied	4 (4)	5 (5)	
Acceptability			
Would choose again	77 (77)	74 (74)	0.740
Would not choose again	23 (23)	26 (26)	
Recommendations			
Would recommend to others	76 (76)	73 (73)	0.740
Would not recommend to others	24 (24)	27 (27)	

Table 4 gives details of comparison of patient's satisfaction and acceptability observed among the study participants in Group A and Group B. There was no significant difference in all criteria between the 2 groups, however, patients receiving Vaginal Misoprostol showed comparatively a slightly greater extent of patient's satisfaction, acceptability and preference to recommend to others compared to Oral

Misoprostol; however the difference was not statistically significant.

DISCUSSION

The present Quasi experimental study highlighted that vaginal misoprostol is more effective than oral misoprostol as demonstrated with increase success rate, fewer dosages with lesser side effects. Moreover, patients receiving vaginal Misoprostol demonstrated increased patient's satisfaction, acceptability, and recommendation to others.

In this study, the patients non-randomly allocated to Group A (Vaginal Misoprostol) and Group B (Oral Misoprostol) showed no significant difference in baseline characteristics (i.e. age, residence, parity, gestational age, previous spontaneous abortion and caesarian section) was observed thus implying that the two groups were comparable. Importantly, the success rate with vaginal Misoprostol was significantly higher(88%) compared to oral Misoprostol (71%).Evidence from the literature also demonstrated the greater efficacy of vaginal Misoprostol compared to the administration by oral route. A prospective, non-blinded, randomized clinical trial[16] that recruited twenty participants to compare efficacy of misoprostol given as 400 µg orally (group 1) or 800 µg vaginally (group 2) reported significantly higher success rate with vaginal misoprostol (88%) compared to administration through oral route (25%). Another, prospective randomized controlled trial was conducted to compare the efficacy and side-effects of vaginal versus oral misoprostol given in equal dose of 800 µg found no significant difference in vaginal and oral misoprostol administration (61.1% Vs. 64.4%); however significantly decreased incidence of diarrhea was identified (13.6% Vs. 65.3%, $P < 0.01$) with the use of vaginal misoprostol[17]. This is consistent with the findings of the recent study where fewer incidences of side-effects were being observed with vaginal Misoprostol compared to oral Misoprostol. Another clinical study[18]comparing misoprostol administration (oral and vaginalin equal dose of 800 µg) for treatment of missed abortion reported no significant difference (89% Vs. 92%). A randomized prospective trial[19], comparing the efficacy of misoprostol given vaginally or orally in 400 µg to a maximum of three doses six hours apart reported both routes were highly effective (vaginal=92%, oral= 74%, p=0.032).

Though, no significant difference was observed in patient's satisfaction and acceptability with the use of vaginal or oral Misoprostol; slightly higher proportion of patients were satisfied and showed greater acceptability with the vaginal use. The results of a recently published systemic review and meta-analysis that included 18 studies with 1802 participants reported that in terms of tolerability, vaginal misoprostol of 400ug was reported with fewer side effects and oral misoprostol of 600 ug was reported with more side effects[20].

CONCLUSION

Our study concluded that first trimester missed abortion can be medically managed with the use of oral or vaginal Misoprostol. They are suitable practical alternatives to conventional surgical evacuation with higher success rates. However, vaginal administration of Misoprostol should be preferred due to increased success rate, decreased side effects, increased tolerability and patients acceptance compared to oral administration.

Recommendations: Though Misoprostol both orally and vaginallyis very efficacious, commonly used in early missed abortion and termination of pregnancy, but its safety is a concern for pregnant women living in remote areas or villages receiving it in outpatient settings. Clinicians should be very cautious in prescribing it, recommended only if the patient is living nearby the hospital facility. In cases where Misoprostol is indicated for patients living in remote areas, they should be admitted first and given oral/vaginal Misoprostol as there are adverse events i.e. bleeding after its use. Considering the high prevalence of anaemia during pregnancy, the use of Misoprostol is not safe for women with health facilities inaccessible. Moreover, it should only be offered by trained clinicians in established clinical settings to provide surgical treatment in case of failed abortion or excessive bleeding.

Author's Contribution:

Concept & Design of Study:	Nighat Kafil
Drafting:	Nighat Kafil, Farzana Rizwan Arain
Data Analysis:	Farzana Rizwan Arain
Revisiting Critically:	Nighat Kafil, Farzana Rizwan Arain
Final Approval of version:	Nighat Kafil

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

REFERENCES

1. Gemzell-Danielsson K, Ho PC, Gómez Ponce de León R, Weeks A, Winikoff B. Misoprostol to treat missed abortion in the firsttrimester. Int J Gynecol Obstet 2007;99:182-185.
2. Nybo Andersen A-, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: Population based register linkagestudy. Br Med J 2000;320(7251):1708-12.
3. Zikopoulos KA,Papanikolaou EG,Kalantaridou SN, Tsanadis GD, Plachouras NI, Dalkalitsis NA, et.al. Early pregnancy termination with vaginal

misoprostol before and after 42 days gestation. Human Repro 2002;17:3079-3083.

4. Wagaarachchi PT, Ashok PW,Narvekar N, Smith NC, Templeton A. Medical management of early fetal demise using a combination of mifepristone and misoprostol. Human Repro 2001;16:1849–1853.
5. Sifakis S, Angelakis E, Vardaki E, Fragouli Y, Koumantakis E. High-dose misoprostol used in outpatient management of first trimester spontaneous abortion. Archives Gyne Obs 2005; 272:183–186.
6. Shah N, Azam SI, Khan NH. Sublingual versus vaginal misoprostol in the management of missed miscarriage. J Pak Med Assoc 2010;60:113-116.
7. Abdul MA, Palmer HO, Aminu B, Ismail H, Kadas A. Experiences in the use of misoprostol in the management of first trimester missed abortion in a low resource setting. Trop J Obstet Gynaecol 2016;33:201-4.
8. Rizwan N, Farhanuddin S. Medical treatment of the complication of first trimester pregnancy loss with Misoprostol. Int J Med Med Sci 2014;6:211-214.
9. Honemeyer U, Kurjak A, Monni G. Normal and abnormal early pregnancy. Donald Sch J Ultrasound Obstet Gynecol 2011;5(4):356-84.
10. Yigiter AB. Early normal and abnormal pregnancy. Donald Sch J Ultrasound Obstet Gynecol 2011; 5(4):385-404.
11. Marwah S, Gupta S, Batra NP, Bhasin V, Sarna V, Kaur N. A comparative study to evaluate the efficacy of vaginal vs oralprostaglandin E1analogue (misoprostol) in management of first trimester missed abortion. J Clin Diagn Res 2016; 10(5):QC14-8.
12. Niinimäki M, Suhonen S, Mentula M, Hemminki E, Heikinheimo O, Gissler M. Comparison of rates of adverse events inadolescent and adult women undergoing medical abortion: Population Register Based Study. BMJ 2011;342(7804).
13. Petersen SG, Perkins AR, Gibbons KS, Bertolone BI, Mahomed K. The medical management of missed miscarriage: Outcomesfrom a prospective, single-centre, australian cohort. Med J Aust 2013; 199(5):341-6.
14. Sagili H, Divers M. Economic evaluation of alternative management methods of first-trimester miscarriage based on results fromthe miscarriage treatment (MIST) trial by petrou, et al. BJOG Int J Obstet Gynaecol 2007;114(1):116-7.
15. Singh K, Fong YF, Prasad RN, Dong F. Randomised trial to determine optimal dose of vaginal misoprostol for pre-abortion cervical priming. Obstet Gynaecol 1998; 92:795-8.
16. Creinin MD, Moyer R, Guido R. Misoprostol for medical evacuation of early pregnancy failure. Obstet Gynecol 1997;89(5):768-72.
17. Pang MW, Lee TS, Chung TKH. Incomplete miscarriage: A randomized controlled trial comparing oral with vaginal misoprostol for medical evacuation. Hum Reprod 2001;16(11): 2283-7.
18. Ngoc NTN, Blum J, Westheimer E, Quan TTV, Winikoff B. Medical treatment of missed abortion using misoprostol. Int J Gynecol Obstet 2004; 87(2):138-42.
19. Marwah S, Gupta S, Batra NP, Bhasin V, Sarna V, Kaur N. A comparative study to evaluate the efficacy of vaginal vs oral prostaglandin E1analogue (Misoprostol) in management of first trimester missed abortion. J ClinDiagn Res 2016; 10(5): QC14-QC18.
20. Wu H-, Marwah S, Wang P, Wang Q-, Chen X-. Misoprostol for medical treatment of missed abortion: A systematic review and network meta-analysis. Sci Rep 2017;7(1).