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Use of Misoprostol in Missed Abortion – A Double Edged Sword in Anemia Prevailing Countries

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Objective: *To identify the efficacy of oral misoprostol (600 µg) for the management of missed abortion.*
Method: *A prospective study was conducted at the Gynecology Department of Muhammad Medical College Hospital (MMCH) over a period of two year from January, 2013 till December 2014. Eligible women satisfying the inclusion and exclusion criteria were recruited after written informed consent and given 600 µg of misoprostol orally at six hour interval, with a maximum of 4 doses. Patients were monitored for 24 hours following complete abortion or surgical evacuation and then discharged. The primary outcome of the 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 were also recorded. The data was analysed using SPSS version 21 (IBM, Chicago, IL).*
Result: *Among four hundred and eighty five participants, success in abortion with Misoprostol was observed in 157 (32.4%) of patients with majority (92.4%) success being achieved with two doses. Women where failure was documented, excessive bleeding (61%) was most prevalent followed by incomplete abortion (36%). The most common side effects observed were severe bleeding (41.1%), cramping/ abdominal pain (16.4%), increased bleeding (13.8%) and nausea/ vomiting (8.8%).*
Conclusion: *High failure rate and increased bleeding with the use of 600 µg of oral misoprostol for missed abortion was identified thus should only be a consideration for prescription to patients once admitted in hospital settings.*
Keywords: *anaemia, bleeding, pregnancy, oral, misoprostol, surgical evacuation,*

I. Introduction

Termination of pregnancy on account different maternal factors or due to foetal condition is a common obstetrical problem. Missed abortion during the first trimester is characterized by the foetal development arrest with ultrasound findings reporting an empty gestational sac or fetus with no cardiac activity [1]. It occurs in 11% of clinically recognized pregnancies and is not only associated with substantial healthcare and financial burden but non continuing pregnancy is upsetting for mother [2]. The percentage of missed abortion is increasing having diagnosed on routine ultrasound screening [3, 4]. Majority of missed abortion occurs spontaneously however some pregnancies simply stop growing without any obvious symptoms, with a deferment in expulsion of conceptus [5].

Similarly to the effective care required during labor for child birth, safe induction of abortion is sensitive and requires effective and high quality of meticulous medical care. Different surgical and medical methods are available for the termination of pregnancy however medical methods are preferred considering demonstrated lower rates of maternal morbidity and mortality. Surgical evacuation, irrespective of being quick and effective procedure when performed by a well-trained physician, however carries a risk of injury, bleeding and infection, along with possible complications from the anesthesia [6]. Misoprostol is a Prostaglandin analogue being widely used for termination of pregnancy, considering it efficacious, low cost and long shelf life (2 years) at room temperature [7, 8]. Though both oral and vaginal route of admisntration are present but women however prefer oral route as to avoid inconvenience due to vaginal examination.

In developing country like Pakistan, majority of women resides in rural areas where appropriate health facilities are not accessible. Moreover, a high prevalence of anaemia during first trimester of pregnancy is significant health problem. Therefore, the prospective study was conducted to evaluate the efficacy of oral misoprostol (600 µg) for the management of missed abortion.

II. Methods

The prospective study was conducted at the Gynecology Department of Muhammad Medical College Hospital (MMCH) over a period of two year from January, 2013 till December 2014. Muhammad Medical College Hospital having established in 1999, located 6 km just outside Mirpurkhas, Sindh. The hospital has a

well established Gynecological department and women residing in both rural and urban areas nearby visits 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 prospective study. Women with history of inflammatory bowel disease, asthma or liver diseases, hemodynamically unstable, severe infection (assessed by the presence of at least one of the following; fever above 38 ^{0}C, foul smelly discharge and uterine tenderness), deranged coagulation profile (Prothrombin index ≤ 85%), ectopic pregnancy and contraindicated to prostaglandin use were excluded.

After baseline investigation and ultrasonographic confirmation of missed abortion data on age, parity and gestational week were recorded. All women eligible to be recruited in this study were admitted in hospital and given 600 µg of misoprostol orally at six hour interval, with a maximum of 4 doses. The pills were swallowed with sip of water in the presence of clinician. The outcome was assessed after 12 hours following the last dose of misoprostol. 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). Patients were monitored for 24 hours following complete abortion or surgical evacuation and then discharged. They were prescribed analgesics and prophylactic antibiotics for 5 days.

The first follow-up visit was at one week after discharge to confirm their clinical status. In the event of continued heavy bleeding, enlarged uterus, or suspicion of ectopic pregnancy, women were referred for ultrasound and follow-up care. In the event of continued incomplete abortion surgical evacuation was performed. Such cases were considered as failure on account of the recourse of surgery. Finally, all participants recruited in this prospective study were advised to visit hospital anytime for any query or complication.

For the present study ethical approval was granted by the institutional ethical review committee of Muhammad Medical College Hospital (MMCH), Pakistan. Written informed consent was obtained from all participants prior to recruitment having explained comprehensively the process involved, intervention given (Misoprostol) and benefits/ risks of being the part this research. It was ensured that anonymity and confidentiality of recruited participant's data was maintained throughout the research and no unauthorized person had an access to the data. The participants had a right to withdraw at any point of this prospective study.

The data was analysed using SPSS version 21 (IBM, Chicago, IL). Descriptive statistics were performed. The qualitative variables were presented as frequency/ percentage whereas the quantitative variables were presented as mean ± SD.

III. Results

The table 1 gives characteristics of the study participants enrolled. The mean (SD) age in years was 28.47 (5.2) with majority (53%) were in age category 26-34 years. The mean gestational age in weeks and parity were 10.01 weeks and 2.41 respectively. Majority (83.7%) had gestational age as less than or equal to 10 weeks while the highest proportion of patients (51.8%) had parity 2 to 3.

Table 1: Characteristics of the study participants

	Mean ± SD or n (%)
Age in years	28.47 ± 5.2
Age categories	
≤ 25 years	137 (28.2)
26-34 years	257 (53)
≥ 35 years	91 (18.8)
Gestational age in weeks	10.01 ± 1.4
Gestational age categories	
≤ 10 weeks	406 (83.7)
11-12 weeks	79 (16.3)
Mean parity	2.41 ± 1.4
Parity	
≤ 1	125 (25.8)
2-3	251 (51.8)
≥ 4	109 (22.5)

The mean (SD) dose of Misoprostol given were 2.21 (0.53), with seventeen participants (3.5%) received one dose, three hundred and fifty nine (74%) received two doses and one hundred and nine (22.5%) received 3-4 doses.

The most common side effects observed with Misoprostol dose of 600 µg was severe bleeding (41.1%), followed by cramping/ abdominal pain (16.4%), increased bleeding (13.8%), nausea/ vomiting (8.8%), fever/ chills (5.1%), headache (4.3%) and diarrhea (3.7%) as shown in *table 2.*

Table 2: Side effects observed among patients

Side Effects	n (%)
Profuse (Severe) bleeding	200 (41.1)
Increased bleeding (but not profuse)	67 (13.8)
Cramping/ abdominal pain	80 (16.4)
Nausea/ Vomiting	43 (8.8)
Fever/ chills	25 (5.1)
Diarrhea	18 (3.7)
Headache	21 (4.3)

Among four hundred and eighty five participants, success in abortion with Misoprostol was observed in 157 (32.4%) of patients with majority (92.4%) success being achieved with two doses *(Table 3)*. Among three hundred and twenty eight patients where failure was documented, excessive bleeding (61%) was most prevalent followed by incomplete abortion (36%) and patient request (3%).

Table 3: Clinical Outcomes among patients

Clinical Outcomes	Mean ± SD or n (%)
Efficacy of Misoprostol	
Success	157 (32.4)
Failure	328 (67.6)
Success with respect to doses (n = 157)	
One dose	1 (0.6)
Two doses	145 (92.4)
Three to four doses	11 (7)
Failure where surgical evacuation performed (n = 328)	
Incomplete abortion	118 (36)
Excessive bleeding	200 (61)
Patient request	10 (3)
Mean hospital stay (hours)	38.5 ± 4.9

IV. Discussion

The results of the prospective study reported a low efficacy of Misoprostol with failure rate as around sixty eight percent. Excessive bleeding was highlighted as the most common reason as being reported in around 61% of patients. Other adverse events being reported were cramping/ abdominal pain, increased bleeding, nausea/ vomiting, fever/ chills, headache and diarrhea.

The findings of the current study varied to some extent with the evidence in literature reporting the efficacy of Misoprostol. A prospective clinical study from Yemen, where patient received single dose of oral misoprostol 600 µg reported a success rate as 75%, while 40% women required surgical evacuation within the first 48 hours due to considerable vaginal bleeding and 60% of evacuation after 7 days due to incomplete miscarriage [9]. Another clinical study reported a success rate as around 61% within the first 48 hours of receiving a single dose of oral misoprostol 600 µg while around 39% of women recruited required further surgical evacuation during the same period [10]. Another clinical trial reported a higher success rate 97.9% in the first 72 hours and this may be accounted due to using of single dose of oral misoprostol in the management of incomplete abortion not missed abortion as in our study [11]. A clinical study that compared the two regimens of oral misoprostol, single dose (600 µg) and repeated dose (1200 µg) in the treatment of incomplete abortion reported an overall success rate as 87% [12].

Related to side effects, the study [9] by Sakkaf (2016), reported the most common side effect was related to gastrointestinal tract, in the form of nausea (20%), diarrhea (20%) and vomiting (5%). This study by Benchamanon and Phupong reported a higher incidence of gastrointestinal side effects as diarrhea (61.55%), nausea (41.85%), and vomiting in slightly less than 6 percent of patients [10]. The increased incidence of gastrointestinal side effects is related to the route of admisntration. As in oral route the gastrointestinal side effects are more likely. A previous study reported that the route of administration affects the side effects rate more than the dosage [13].

In the present study among three hundred and twenty eight patients where failure was documented, excessive bleeding (61%) was most prevalent reason identified. Not many clinical studies have reported a high incidence of bleeding shortly after misoprostol admisntration. A prospective clinical study from Nigeria reported that Cramping/abdominal pain (14.4%) and increased vaginal bleeding (12.3%) were the

symptoms most commonly reported by women shortly after administration of misoprostol [14]. The prospective clinical study has certain limitations. The study had only one follow-up visit at two week. A multiple follow-up at fourth and six week would have been beneficial in terms of identifying time for resumption of menses and any further side effects (i.e. post-abortal bleeding duration and amount) experienced.

Moreover, acceptability and tolerance of oral Misoprostol received was not inquired. Therefore, in future a prospective study with multiple follow-ups while considering other important variables of interest should be conducted.

Recommendation

Though Misoprostol is a very efficacious drug being 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. Misoprostol could be used in medical termination of pregnancy in missed abortion but clinicians should be very cautious in prescribing it as should be 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 or vaginal Misoprostol tablets as there are adverse event 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 as will lead to morbidity and mortality in women.

V. Conclusion

The study highlighted high failure rate and increased bleeding with the use of 600 µg of oral misoprostol for missed abortion. It should only be prescribed to patients once admitted in hospital settings. Its prescription for missed at primary healthcare facilities where appropriate healthcare management are frequently not available could result in high morbidity and mortality especially in developing countries i.e. Pakistan where prevalence of anaemia is already high among pregnant women during first trimester of pregnancy.

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