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Mifepristone Plus Misoprostol Versus Misoprostol Alone In Missed Abortion: A Retrospective Study

Minnu Ann Mohan[1] , Alasandra Rose M S [2] , Jobin Kunjumon Vilapurathu*[3], Silda Raphel[4]
[1,2,4]Intern , [3]Associate Professor
Department Of Pharmacy Practice,
Nirmala College Of Pharmacy, Muvattupuzha, Ernakulam

***Corresponding Author:**
Jobin Kunjumon Vilapurathu
Associate Professor,Department Of Pharmacy Practice,
Nirmala College Of Pharmacy, Muvattupuzha, Ernakulam

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Abstract

Introduction: Abortion is defined as the termination of pregnancy which includes the expulsion of the products of conception from the uterus. Miscarriage is common among pregnant women affecting almost one in five pregnancies and is associated with complications like excessive bleeding and high chances of infection,and causes substantial psychological harm,which includes anxiety, depression, and post-traumatic stress disorder. Medical abortion can be carried out with abortifacient agents; prostaglandin analogs and antiprogestogens having the most important role. Although there are many alternative drugs available to induce abortion, the combination of Mifepristone and Misoprostol is the most widely used among all.

Aim: The aim of the study was to compare the effectiveness of misoprostol alone versus mifepristone plus misoprostol in missed abortion.

Methodology:

A retrospective study was conducted where the case reports of women diagnosed with missed abortion in the previous 2 years were collected from the Medical Records Department of Caritas Hospital, Kottayam. A total of 102 cases were studied. The data was collected,analyzed and interpreted.

Results:

Majority of the patients had termination of pregnancy with a lower induction- abortion interval when the combination of Mifepristone and Misoprostol was given. The need for surgical management was also lower when the combination was given. 2) The most common risk factor found in women diagnosed with missed abortion was hypothyroidism. 3) Higher success rate of abortion was found to be in women treated with the combination regimen where the success of the treatment was analysed by checking the number of cases that went into surgery. The results concluded that 28.9% (n=11) had to undergo surgery when treated with misoprostol alone and 21.8% (n=14) had to undergo surgery when treated with the combination of Mifepristone plus Misoprostol.

Conclusion:

The combination of Mifepristone plus Misoprostol was found to be more effective than administering Misoprostol alone to the patients as it showed a decreased induction – abortion interval, increased success rates and a faster rate of completion of abortion.

Keywords: Missed Abortion, Induction-Abortion Interval, Comorbidity, Misoprostol, Mifepristone

Introduction

Missed abortion or missed miscarriage is defined as an inviable growth of the fetus which does not get expelled and the products of pregnancy remains in the uterus. It is synonymous to fetal demise intrauterine. A missed miscarriage is diagnosed when an ultrasound scan reports a non-viable pregnancy during the first 14 weeks of gestation. Women who have missed miscarriage usually present with no symptoms or they may have small amounts of vaginal bleeding or abdominal pain before the diagnosis is made. [1,2,3] In a missed miscarriage, all pregnancy tissue is retained in the uterus.[1]

Missed abortion is usually associated with inhibition of uterine contractions, hormonal imbalance and intrauterine infections. Other causes includes embryonic anomalies, uterine anomalies, maternal disease, fetal chromosomal abnormalities and placental abnormalities. Anembryonic gestation also known as blighted ovum where a gestational sac develops with the absence of an embryo is also a major cause for missed abortion.

In most of the cases, miscarriage occur before the 12th week of pregnancy. It is usually associated with mild symptoms like vaginal bleeding or spotting, abdominal cramping or pain, pain in the lower back, fluid or tissue passing from the vagina.

The management of first trimester missed miscarriage or missed abortion includes expectant, medical, or surgical methods.[2] The primary aim of all these methods is the complete expulsion of the pregnancy tissue and to prevent the presence of any retained products of conception. If expectant management is not successful or is not acceptable to the woman, then the preferred method is medical management. Many women opts for MTP (Medical termination of pregnancy) as a solution for missed abortion.

Surgical methods are usually least preferred because of patient discomfort and the complications associated with it. Medical management is non invasive and only involves administration of the drug which is comparatively easier than surgical interventions. Medical management of missed abortion is recommended on the International Clinical Guidelines and is the best preferred option for most of the women.[1]

Medical management of missed abortion usually consists of administration of abortifacient agents. The most frequently used agents includes oxytocin which are given in large doses for its abortifacient action, intravenous infusions of prostaglandin e2 (PGE2) or single intraamniotic injection of 15-methyl-PGF2alpha. [18] Misoprostol is a prostaglandin analogue and is the commonly used drug for the medical management of miscarriage. It works by inducing myometrial contractions which helps in the expulsion of pregnancy tissue. [4] It has not been found to be always effective, and in most cases an additional dose of misoprostol was to be added for the treatment to be successful. [5,6,7,8,9] Routes of administration of misoprostol includes oral, vaginal and sublingual routes, The doses ranges from 100 micrograms to 800 micrograms. National Institute for Health and Care Excellence (NICE) guidelines recommends a single dose of 800 micrograms of misoprostol orally or vaginally.

Mifepristone is a competitive progesterone receptor antagonist that functions by priming the myometrium before prostaglandin exposure and is sometimes used in combination with misoprostol to improve the effects of misoprostol.[4] The standard method of administration of mifepristone is 200mg orally 24to 48 hrs before the administration of misoprostol.

A combination of mifepristone plus misoprostol is now widely been given rather than administering misoprostol alone .A single tablet of mifepristone of the dosage 200 mg is given 24 to 48 hours prior to the administration of misoprostol. Reports from previous clinical trials showed that when mifepristone and misoprostol were given in combination, the effectiveness has ranged from 64% to 84%.[10,11,12] It is said that mifepristone has an added advantage that increases the myometrial contractions induced by misoprostol. In the year 2012,The National Institute for Health and Care Excellence (NICE) guideline (clinical guidance 154) recommended not offering mifepristone as a treatment for missed miscarriage as it was found to have no benefit based on the findings of a randomised trial of 115 women in the UK. [10,13] Therefore, the standard practice adopted in the UK is to offer misoprostol alone vaginally at a dose of 800 µg for women diagnosed with incomplete or missed miscarriage.[1]

Volume 6, Issue 2; March-April 2023; Page No 90-95
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In India, both the combination of mifepristone plus misoprostol and misoprostol alone are considered as treatment options for missed abortion. [18] Studying the induction-abortion interval and rate of completion of abortion helps to choose the better treatment option that is either misoprostol alone or the combination of mifepristone plus misoprostol.

In this study, we compared whether the treatment with the combination of mifepristone plus misoprostol would result in a lower induction – abortion interval and higher success rates of missed abortion compared to when administering misoprostol alone.

Methods

A retrospective study was conducted in a tertiary care hospital in Kottayam, where cases from July 2019 to December 2021 was collected from the gynaecology department of the hospital . The study subjects included women diagnosed with missed abortion on ultrasound scan in the first 20 weeks of pregnancy. Women diagnosed with missed abortion after first 20 weeks of pregnancy were excluded from the study. There was no age exclusion in our study. All eligible participants during the time period were consecutively selected and a total of 102 cases were identified.

The data was collected from the case charts from the Medical Records Department in a data collection form. The demographic characteristics like age of the patient, gestational age , co morbidities like diabetes,hypertension,polycystic ovary disease,hypothyroidism,previous LSCS,the treatment given and whether the patient underwent surgery were recorded. . The cases were analysed and the treatment regimen was compared mainly focussing on the induction-abortion interval and the rate of completion of abortion. The data information from the data collection forms was entered into an Excel sheet. The IBM SPSS version 23 was used to conduct the analysis. Frequency and percentage were used to express the categorical variables.

Results

In the study, a total of 102 cases of missed abortion was reported in the study period. The data on age of the patients, gestational age, comorbidities, induction abortion interval, failure of medical management and the success rates were collected. The treatment result was considered as complete, incomplete and failure based on the prescence of RPOC. If no RPOC was found, the abortion was considered complete. If RPOC was found positive, the abortion was considered incomplete. The treatment was considered failure when the patients had to undergo surgery.

Prevalence of age in missed abortion

We compared the age and gestational age of the patients diagnosed with missed abortion to identify the most prevalent age group. 55.88% of patients diagnosed with missed abortion was in the age group of 21-30.Patients in the age group of 31-40 (40.19) also showed higher rates of incidence and the age group of 41-50 and 18-20 had lower rates of incidence.

Gestational age of patients with missed abortion

Gestational age is measured in weeks, and is used to describe how far along the pregnancy is.It is measured from the first day of the woman's last menstrual cycle to the current date. A normal pregnancy can range from 38 to 42 weeks. A comparison on the incidence of missed abortion with gestational age was done.

66.66% of women diagnosed with missed abortion were in the GA of 6 to 10 weeks.

Comorbidities associated with missed abortion

Patients diagnosed with missed abortion were also found to have comorbidities including hypertension, hypothyroidism, PCOD, DM etc. Previous LSCS was also considered a comorbidity.

The most common comorbidity associated with MA was found to be hypothyroidism.18.62% of women who had hypothyroidism had the incidence of missed abortion.11 patients who underwent previous LSCS (10.78%) were also found to be diagnosed with missed abortion. Other comorbidities include : 5.88% patients with DM, 3.92% patients with HTN and PCOD .The reason for MA could be due to such underlying conditions or may be due to other reasons.

In our study,37.25% patients were treated with misoprostol alone and 62.75% patients were given the combination of mifepristone plus misoprostol. Both of the regimens are used to treat missed abortion.

Dose of Mifepristone

Volume 6, Issue 2; March-April 2023; Page No 90-95
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The prescribed doses of mifepristone were 200mg,400mg,600mg. Out of these doses,400 mg was the most prescribed dose.39.21% patients were prescribed with 400 mg of mifepristone on the day of admission. Misoprostol was given 24 hours after mifepristone was given. 13.72% were prescribed with 600 mg and 9.80% were prescribed with 200 mg. Most patients received 400 mg of mifepristone.

Induction-Abortion Interval

The induction abortion interval in both the regimens were compared. Time taken for abortion after starting the drug was noted and it was reported in hours. The difference in the time taken to achieve complete abortion after initiating both the regimens were compared. The I-A interval was found to be lower with the combination of mifepristone plus misoprostol compared with misoprostol alone.

Failed medical treatment was considered if the patient underwent surgery. This indicates that treatment with medicine has failed the patient require surgery for the removal of retained products of conception.The number of patients who received surgical management are as follows:

Surgical management

It was observed that 11 out of 38 patients (28.9%) who were treated with Miso alone had to undergo surgery for complete abortion. 14 out of 64 patients (28.9%) who were treated with Mife plus Miso had to undergo surgery for complete abortion. The results concluded that lower number of patients had to undergo surgery when treated with the combination group compared to misoprostol alone.

CHARACTERISTICS	FREQUENCY	PERCENTAGE
AGE		
18-20	1	0.98
21-30	57	55.88
31-40	41	40.19
41-50	3	2.94
GESTATIONAL AGE		
0-5	1	0.98
6-10	68	66.66
11-15	21	20.58
16-20	12	11.76
COMORBIDITIES		
HYPOTHYROIDISM	19	18.62
DIABETES MELITUS	6	5.88
HYPERTENSION	4	3.92
PREVIOUS LSCS	11	10.78
PCOD	4	3.92
TREATMENT		
MISOPROSTOL ALONE	38	37.25
MIFEPRISTONE PLUS	64	62.74

Volume 6, Issue 2; March-April 2023; Page No 90-95
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MISOPROSTOL		
SURGICAL MANAGEMENT		
MISOPROSTOL	11	28.9
MIFEPRISTONE PLUS MISOPROSTOL	14	21.8

Discussion

The medical management of missed abortion can be done by either giving misoprostol alone or following a combination regimen of Mifepristone plus misoprostol. The effectiveness of both the regimen were compared in this study. The study was a retrospective study and cases from the past 2 years were analysed.

Surgical management was considered an option after failed medical management of missed abortion. From the data collected, a total of 25 women underwent surgery. Surgical management usually involves suction evacuation to remove the RPOC. The study showed a reduced number of surgical intervention in women treated with Mifepristone plus Misoprostol combination compared to Misoprostol alone. 28.9% of the patients treated with misoprostol alone had to undergo surgery and 21.8% of patients treated with Mifepristone plus Misoprostol combination had to undergo surgery. The results conclude that Mifepristone plus Misoprostol is a better option than Misoprostol alone.

A vast number of studies were conducted comparing the effectiveness of both the regimens : misoprostol alone versus mifepristone plus misoprostol. Most of the studies concluded that the combination regimen of Mifepristone plus Misoprostol was more effective than giving Misoprostol alone. The combination led to a decreased I-A interval and decreased need for surgical management. Some studies concluded that adding Mifepristone to Misoprostol did not increase the effectiveness and that Misoprostol alone is capable of completing the abortion.

Among the 102 cases collected,the most prevalent age group in women with missed abortion was found to be 21-30. The age group of 31-40 also showed higher prevalence. The study conducted by A M Anderson et al.,[14] and M C Magnus et al.,[15] concluded that missed abortion was more common in women aged greater than 30 years.

Among the cases collected,hypothyroidism was found to be a comorbidity in women diagnosed with missed abortion (18.62%). Previous LSCS was also found to be a risk factor (10.78%). DM,HTN and PCOD were also found to be other risk factors. A study conducted by M Abalovich et al.,[16] stated that women with hypothyroidism have an increased risk of abortion.

The I – A interval was found to be lower in women treated with the combination of mifepristone plus misoprostol. Similarly K Mrudula et al.,[17] conducted a study and compared the I-A interval and it was found to be 6 hours for the combination and 12 hours when misoprostol was given alone.

This study aimed to compare the effectiveness and identify the better option: Misoprostol alone versus Mifepristone plus Misoprostol. This study is a retrospective study where data from previous 2 years was collected and analysed. The induction-abortion interval was found to be lower in women treated with the combination of mifepristone plus misoprostol compared to misoprostol alone.

The results obtained from our study concluded that the combination regimen of Mifepristone plus Misoprostol had a better rate of completion of abortion, had a decreased I-A interval and had a decreased need for surgical intervention.

The results are supported by the study conducted by J J Chu[18]which concluded that the combination is more effective than administering misoprostol alone. The results of the trial showed that while mifepristone plus misoprostol was given, it resulted in a higher rate of resolution by 7 days compared with misoprostol alone. Therefore, they recommend that women with missed abortion should be offered mifepristone pretreatment before misoprostol to

Volume 6, Issue 2; March-April 2023; Page No 90-95
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increase the chance of successful management, while reducing the need for surgery. From our study, we observed that the combination of mifepristone plus misoprostol showed a higher rate of completion of abortion, decreased I-A interval and reduced need of surgery compared to misoprostol alone.

Conclusion:

In our study, we aimed to conclude on which is the better treatment option: giving misoprostol alone or in combination with mifepristone. We compared the I-A interval and the rate of completion of abortion in both the regimen and concluded that the combination of mifepristone plus misoprostol had a better rate of completion of abortion and a lower I-A interval.

Abbreviations:

GA: Gestational age , **RPOC:** Retained products of conception , **I-A:** Induction-Abortion , **HTN:** Hypertension , **LSCS:** Lower segment caesarean section , **PCOD:** Polycystic ovarian disease , **DM:** Diabetes Mellitus

Mife: Mifepristone , **Miso:** Misoprostol

Declarations

Funding

No funds, grants or other support was received

Ethical Approval

The study was approved by the Institutional Review Board and Ethics Committee of Nirmala college of Pharmacy, Muvattupuzha and Caritas Hospital, Kottayam.

Guarantor

Jobin Kunjumon

Contributorship

Jobin Kunjumon, contributed to the study conception and design. Data collection and analysis were performed by Alasandra Rose, Minnu Ann Mohan and Silda Raphel. The first draft of the manuscript the manuscript was written by Jobin Kunjumon , Minnu Ann Mohan and Alasandra Rose . All authors read and approved the final manuscript.

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Patient Consent

Patient consent was weaved off as this is a retrospective study.

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Volume 6, Issue 2; March-April 2023; Page No 90-95

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