World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-14, September 2022
ISSN: 2749-3644

INTRAUTERINE EXTRA AMNIOTIC MISOPROSTOL VERSUS VAGINAL MISOPROSTOL FOR TERMINATION OF SECOND TRIMESTER MISCARRIAGE.

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Article history:

Received: July 20th 2022
Accepted: August 20th 2022
Published: September 30th 2022

Abstract:

The study aims to compare the efficacy and safety of two different routes of administration of misoprostol; the intrauterine extra-amniotic route and vaginal route of misoprostol in a dose of 200 microgram of misoprostol every 4 hours for the termination of pregnancy in cases of second-trimester miscarriage

The study was conducted as a prospective randomized trial from the 1st of February 2017 to the 15th of December 2017 at Salah AL Din General Hospital –Tikrit –Salahuddin Province–Iraq

The patients who participate in this study include those pregnant females with gestational age (13-24 weeks) who attended to the consultant clinic of the hospital with a missed miscarriage

The demographic characteristic of each patient includes body weight, height, BMI, gravidity, parity, history of previous miscarriage, and the mode of delivery of her previous pregnancies. Two different documented ultrasounds scan from two different radiologist, blood group and Rhesus factor, CBC, liver function tests

The data were collected and analyzed using the Statistical Package for Social Science (SPSS Inc., Chicago, version 21) the demographic data were compared between treatment groups

The study resulted in 2 outcomes; st outcome of this study was the mean duration from the initial use of misoprostol until the fetal expulsion was completed (induction-expulsion interval). The 2ndoutcomes included the dose of misoprostol, the patient's need for analgesia, the need for surgical intervention in cases of retained placenta, and the occurrence of side effects.

Group A was significantly less than group B in developing nausea with the result ((3 (6.1)) versus. 19 (38.1)) respectively with p-value=0.000; group A also was significantly less than group B in developing vomiting with results ((2 (3.9) vrs. 8 (15.9)) in both groups respectively with p-value 0.005; group A was significantly less than group B in developing diarrhea with results ((1 (1.9) versus 3(6))) in both groups respectively & p-value =0.001; while fever developed in group A with value 4 (7.8) while in group B value was 0(0) and p-value not significant; chills developed in both groups but results show no significance in difference with value ((1(2) versus 12 (23.8)).

Keywords: Misoprostol, Miscarriage, Amniotic, Vaginal, and Trimester

INTRODUCTION

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ISSN: 2749-3644

Missed Miscarriage is a term used to describe the condition when the fetus or embryo died but is retained in the uterus [1]. There are various definitions of Miscarriage depending on the criteria for viability or survival of the fetus. According to the RCOG, Miscarriage is a pregnancy that is ends spontaneously before a fetus has reached a viable gestational age; at present, the legal definition of Miscarriage in the United Kingdom is a spontaneous loss of pregnancy at or before 24 weeks of gestation [2]. Missed Miscarriage is defined as a Miscarriage occurring in the absence of symptoms or minimal symptoms where the pregnancy is still visible within the uterus, with the ultra sound finding of crown-rump length > 6 mm, no fetal heart movement, or empty gestational sac with mean diameter >20 mm [3].

According to the WHO and ACOG, miscarriage is defined as any pregnancy terminated (induced or spontaneously) prior to 20 weeks gestation or with a fetus born weighing less than 500 g [4]; the term missed miscarriage was used to describes the death of embryo or fetus but the POC are retained in utero. Symptoms of pregnancy disappear, and there may be a brownish vaginal discharge but no free bleeding. Pain and tenderness are absent, the cervix is semi-firm and closed or only slightly patulous, the uterus becomes smaller and irregularly softened, and the adnexa are normal. Miscarriage, in general, is spontaneous or induced termination of pregnancy. Spontaneous miscarriage can be classified clinically in a number of ways. Commonly used subgroups include threatened, inevitable, incomplete, septic, recurrent, and missed miscarriage [1].

Second-trimester pregnancy loss has been defined as miscarriage diagnosed between the duration of gestation of 13–24 weeks (5).

Although the causes of miscarriage in the first and second trimester appear different, there is inevitably some overlap (3).

In the second trimester, the uterus can be emptied by dilation and evacuation (D & E) or induction of labor with intravaginal prostaglandin E 2 (PGE2) or misoprostol. D & E is an extension of the traditional D & C and vacuum curettage. It is especially appropriate at 13 to 16 weeks gestation, although many proponents use this procedure through 20 weeks. The cervix is usually first prepared using misoprostol or passively dilated with laminaria to avoid trauma, and the fetus and placenta are mechanically removed with suction and instruments by an experienced surgical hand (6,7).

MATERIAL AND METHOD

The study was conducted as a prospective randomized trial from the 1st of February 2017 to the 15th of December 2017 at Sallah AL Din General Hospital – Tikrit –Sallahidin Provence–Iraq. The study aims to compare in two different methods of misoprostol administration intra uterine- extra amniotic route versus intra-vaginal route in terms of the safety and efficacy. This study was approved by The Scientific Council of Obstetrics and Gynecology as a requirement of Fellowship of The Iraqi Board of Obstetrics and Gynecology.

The patients who participate in this study include those pregnant females with gestational age (13-24 weeks) who attended to the consultant clinic of the hospital with a missed miscarriage, were interviewed and invited to participate in the study as a method of termination of their pregnancy after description the possible benefit and side effect of misoprostol with verbal consent. All those patients had a detailed history with a full medical and gynecological examination. They had an uneventful history with the normal general examination. The result of the Gynecological examination revealed an enlarged uterus with no any vaginal bleeding or vaginal discharge and no dilatation of the internal os of the cervix.

The demographic characteristic of each patient includes the body weight, height, BMI, gravidity, parity, history of previous miscarriage, and the mode of delivery of her previous pregnancies. Two different documented ultrasounds scan from two different radiologist, blood group and Rhesus factor, CBC, liver function tests, clotting profile, blood sugar, viral screen for hepatitis and HIV, and a sample of blood saved for the cross match were estimated for patients under study.

The diagnosis of missed miscarriage and the gestational age was confirmed by depending on a reliable last menstrual history and an ultrasound examination; the ultrasound scan reports show the fetal demise with absence of fetal cardiac activity approved by two different radiologists.

The total number of eligible are 116 patients randomly collected, with seven patients with abnormal results of the investigation (3 cases with increased serum fibrinogen level, 1 case with low platelet count, and 3 cases with low Hb level), and four patients refuse to participate in the study. Four patients with a history of C-sections. And lastly, one patient was a heavy smoker, those 16 patients were excluded from the study, and only 100 patients fulfilled the criteria of inclusion.

All participants were randomly allocated to one of two groups; The Group A (intrauterine-extra amniotic

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misopristol). This group includes 50 patients who received one tablet of misoprostol (CYTOTEC, Pf IZER), each one containing 200 mcg crushed and placed in normal saline dissolute solution through intra uterine Foley's catheter (18 french) inserted for every patient for every 4 hours. Group B (vaginal misoprostol) received one tablet of misoprostol vaginally placed at the posterior fornix every 4 hours, include 50 patients.

Monitoring of blood pressure, temperature side effects, including (nausea, vomiting, diarrhea, chills & fever), and uterine contraction, assessed clinically ((manually)) because the tocometer was not available in the department during the time of the study, the dilatation of cervix assessed by vaginal examination and bleeding were occurred every 4 hrs after initiation of misoprostol. Analgesia like DICLOFENAC SODIUM, either oral or intramuscular, or TRAMADOL given either intramuscular or intravenous together with anti-emetics (METACLOPROMIDE).

The procedure was considered completed with a successful outcome when the products of conception were expelled completely (including the placenta membrane) within 24 hrs of the beginning use of the dose of misoprostol, so no any further interventions were needed if fetal expulsion did not occur within 24 hours from starting of misoprostol, induction was considered a failed, and the woman was offered standard evacuation method, however, if the fetus was expelled but the placenta partly or completely retained in the uterus after an additional 30 min.

STATISTICAL ANALYSIS

The data were collected and analyzed using the Statistical Package for Social Science (SPSS Inc., Chicago, version 21) the demographic data were compared between treatment groups. The outcome variables were calculated using a student t-test to compare continuous variables. For dichotomous variable, χP2P was used toestimatethe significance value. For analysisp, <0.05 was considered to be significant.

RESULTS

The demographic characteristics of the two groups include (age in years.), parity, BMI (kg/$m^{2)}$, gestational age (weeks), pulse (b/min), and Bood Pressure (mmHg). There was no statistically significance in the difference between the two groups. Maternal age means (31.161 ± 5.181yrs versus 30.432 ± 5.232yrs) for groups A & B, respectively. The parity means (2.552 ± 1.712 versus 2.551 ± 1.541) for groups A & B, respectively. BMI means (26.353 ± 3.622 versus 26.112 ± 1.211) for groups A & B, respectively. Gestational age means (17.871 ± 2.791 versus 17.600 ± 2.691) for both groups, respectively. Pulse (b/min) mean (78.700 ± 6.141 versus 78.481 ± 5.931) for both groups, respectively. Systolic Bood Pressure (mmHg) mean (120.330 ± 15.920 versus 120.442 ± 14.010) for both groups, respectively. Diastolic Bood Pressure (mmHg) (68.022 ± 15.133 versus 68.401 ± 9.480) for both groups, respectively.

Table (1) Demographic characteristics of patients

Variables	***(Group A)***	***(Group B)***	***P- value***
Age (yrs)	**31.161 ± 5.181**	**30.432 ± 5.232**	**0.223**
Parity	**2.552 ± 1.712**	**2.551 ± 1.541**	**0.431**
BMI (Kg/m2)	**26.353 ±3.622**	**26.112±1.211**	**0.323**
Gestational age (wks)	**17.871 ± 2.791**	**17.600 ± 2.691**	**0.515**
Pulse (beats/min)	**78.700 ± 6.141**	**78.481 ± 5.931**	**0.805**
Systolic BP (mmHg)	**120.330 ± 15.920**	**120.442 ± 14.010**	**0.960**
Diastolic BP (mmHg)	**68.022 ± 15.133**	**68.401 ± 9.480**	**0.841**

Data are presented as mean ±SD (n=50).

A T-test was used to determine the p-value between groups A & B.

Table 2: This table shows the primary and secondary outcomes of the study; the mean duration of the induction expulsion interval was (4.22 ± 3.40) in group A (intra uterine-extra amniotic misoprostol), which was significantly shorter than the mean duration in group B(vaginal misoprostol) which was(8.72 ± 2.17) and p-value = (0.001).The mean dose of misoprostol in (mcg) until expulsion (259 ± 215.8 versus 511 ± 198.2)in group A & B respectively with p-value =(0.000).There was a statistically significant difference in the number of patients need surgical evacuation due to retained conception products between groups A & B ((4 (8%) versus 12 (24%) respectively)) and p-value=0.005.

There was a significant difference in no. of patients need analgesic drugs during the study between groups A & B ((5 (10%) versus 16 (32%) respectively & p-value=0.005))

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Volume-14, September 2022
ISSN: 2749-3644

Table (2) Effect of misoprostol

Outcomes	**group (A)**	**group(B)**	**p-value**
Induction-expulsion time interval (hrs)[a]	**4.22 ± 3.40**	**8.72 ± 2.17**	**0.001**
Dose of misoprostol until expulsion (µg) [a]	**259 ± 215.8**	**511 ± 198.2**	**0.000**
No. of women needs surgical evacuation, up to 17 weeks (%) [b]	**4 (8%)**	**12 (24%)**	**0.005**
No. of women needs analgesics, (%) [b]	**5 (10%)**	**16 (32%)**	**0.005**

[a] Data are presented as Mean±SD (n=50)
[b] Data are presented as n (%)
The T-test in quantitative data was used to determine the p-value & Chi-square test in qualitative data was used to determine the p-value.

Table 3: show the difference in side effect of misoprostol in both groups as seen by assessment medically & patients' complaints; there was a difference in nausea, vomiting & diarrhea between both groups

Table (3) Side effects of misoprostol

Side effects (%)	**group (A)**	**group(B)**	**p-value**
Nausea	**3(6.1)**	**19 (38.1)**	**0.000**
Vomiting	**2 (3.9)**	**8 (15.9)**	**0.005**
Diarrhea	**1 (1.9)**	**3 (6)**	**0.001**
Fever	**4(7.8)**	**0(0)**	***
Chills	**1 (2)**	**12 (23.8)**	***

DISCUSSION

Miscarriage is a common event in the life of women. Medical management of miscarriage and induced abortion has become the gold standard in clinical practice in several northern of European countries. But, the treatment of second-trimester miscarriage has been addressed in only a few research studies [(8)].

Misoprostol is readily available, stable at room temperature, less expensive, and has an acceptable profile of safety. It has been administered in different routes in several treatment regimens for medical abortion with varying results of success. The main disadvantage of the oral or buccal and sublingual routes is the frequent gastrointestinal side effects, including nausea, vomiting, shivering, and hyperthermia [(9)].

Intravaginal use of misoprostol has been used largely to terminate second-trimester pregnancies. Intracervical route of misoprostol is an alternative method of termination of pregnancy for women at that period of gestation [(10).]

Intracervical routes of administration of misoprostol appear to be effective and well-tolerated, with less side effects and no complications [(10)].

Abdulrahim A. Rouzi et al. in 2014 is one of the study groups that study the (Efficacy of intra-cervical misoprostol in the management of early pregnancy failure) the results of the study show that 9 (45%) women received one dose, and eleven (55%) women received two doses of intracervical misoprostol. Miscarriage within 24 hours of treatment initiation occurred in sixteen (80%) women. Complete miscarriage within 24 hours occurred in 14 (70%) women [(41)].

Desai GS et al. in 2016 is one of the study groups that study the efficacy and safety of combined intracervical

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Available Online at: https://www.scholarexpress.net
Volume-14, September 2022
ISSN: 2749-3644

and intravaginal misoprostol in the management of mid-trimester medical termination of pregnancy and to compare it with intravaginal misoprostol. Induction-abortion interval, need for surgical evacuation, completeness of abortion, and side effects, if any, were documented. Mean induction-abortion interval for the intravaginal group and combination group was comparable (t = 7.9 ± 1.8 and 6.5 ± 3.5 h, respectively). Three patients required surgical evacuation for incomplete abortion (n = 2 after vaginal misoprostol and one after intracervical-intravaginal misoprostol). Number of patients aborting within six h was more in the intracervical-intravaginal group (36.3 %). Patients with intracervical misoprostol complained of abdominal pain more often than those in other groups. Excessive bleeding and uterine rupture were not seen in any patient [(11)].

In our study, we do a comparison between two different routes, intrauterine-extra amniotic & vaginal routes, although there was few research about the intrauterine route.

One of study that was done by using the intrauterine extra amniotic route done *by Mitwaly et al. 2016* [(12)]; this was the first reported study to compare and investigates the effect of misoprostol dissolute in saline solution by using the intrauterine extra' amniotic route for termination of the second-trimester miscarriage. This study proved that the use of misoprostol via intra uterine extra 'amniotic route with a dose of 200 mcg every 4 hours is more effective and more safe than the vaginal misoprostol .in this study, the investigator used A prospective randomized open-labeled clinical trial that include 180 women with 2nd trimester missed miscarriage in gestational age between 13 and 24 wks. Patients were randomized to receive doses of 200 mcg misoprostol every 4 hours either intra uterine extra-amniotic route by Foley catheter or by vaginal route; this study support and aids our study.

Our study results show no significant difference between the intrauterine extra amniotic rout and vaginal group in the effect of the demographic characteristic of patients in each group to misoprostol action, which agrees with *Mitwally et al., Abdulrahim A. Rouzi et al., and Desai GS et al. studies.* ; The mean duration for the induction and expulsion interval was (4.22 ± 3.40) in group A (intra uterine extra amniotic group) which was significantly shorter than mean duration in group B (vaginal group) which was (8.72 ± 2.17) and p-value (0.001) action which agrees with *Mitwally et al.* but not agrees with *Desai GS et al*. The mean of misoprostol in (mcg) until the expulsion of the fetus ((259 ± 215.8 versus 511 ± 198.2) in groups A & B, respectively, with a p-value (0.000). There were significant differences in the number of patients who needs surgical evacuation due to retained conception product between groups A & B ((4 (8%) versus. 12 (24%) respectively)) and a p-value of 0.005 that was supported by *Mitwally et al.* and Desai *GS et al.* studies. The need for analgesic drugs was different with significances in both groups A & B ((5 (10%) versus .16 (32%) & p-value: 0.02)); there was a difference in nausea, vomiting & diarrhea between the two groups; group A was significantly less than group B in developing nausea with result ((3 (6.1) vrs. 19 (38.1)) respectively with p-value 0.000; group A also was significantly less than group B in developing vomiting with results ((2 (3.9) vrs. 8 (15.9)) in both groups respectively with p-value 0.005 that agree with *Mitwally et al and* Desai *GS et al*; group A was significantly less than group B in developing diarrhea with results ((1 (1.9) vrs. 3 (6)) in both groups respectively & p-value 0.001; while fever developed in group A with value 4(7.8) while in group B value was 0(0) and p-value not significant; chills developed in both groups but results show no significance in difference with value ((1 (2) versus 12(24)) respectively that are agree with *Desai GS et al* but differ from results of *Mitwally et al* study.

CONCLUSION

According to the results of our study, we concluded that the intrauterine-extra amniotic ally used misoprostol solution appear as more effective as a method of termination of missed miscarriage at 2nd trimester of pregnancy with a short duration from induction till expulsion & with a much little need to use surgical evacuation.

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ISSN: 2749-3644

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