A Comparison of Outpatient Treatment of Three Medical Groups with Fetal Death in the First Trimester of Pregnancy during the COVID-19 Pandemic: A Randomized, Controlled, Double-Blind Clinical Trial

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March 30, 2022

Abstract

Objective: To evaluate the efficacy and side effects of each medication regime, a comparison was drawn between the administration of misoprostol with the combined use of misoprostol plus oxytocin and misoprostol plus methylergometrine for full expulsion of retained intrauterine tissues in patients who underwent a miscarriage. Design: randomized, double-blind, clinical trial Setting: gynecology and obstetrics clinic in Jahrom, Southern Iran Population: 90 patients with gestational age below 12 weeks and having undergone a recent miscarriage. Methods: They were randomly allocated into three groups after being screened for underlying diseases and coagulative blood disorders. For the first group, labeled as the control group, misoprostol was administered alone, while as, the combination of misoprostol plus methylergometrine and misoprostol plus oxytocin was prescribed for the second and third groups, respectively. Main Outcome Measures: Primary: Expulsion of retained products of conception; Secondary: Pain, Hemorrhage Results: Despite no significant statistical difference being observed in the expulsion of retained products of conception (RPOC)by the administration of misoprostol alone or with combined medical therapy of misoprostol with oxytocin or methylergometrine (P-value$<$ 0.329), all of them showed a successful treatment. Additionally, the patients treated with misoprostol and oxytocin showed good results in expelling the RPOC(P=0.013); while as, those treated by misoprostol plus methylergometrine reported controlled pain and hemorrhage after an abortion (P=0.004). Conclusion: The course of medications viz. methylergometrine, oxytocin, and misoprostol indicated a successful outpatient treatment in patients that had experienced a miscarriage or an incomplete abortion. They are cost-effective and have shown lesser side effects.

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Short title: Outpatient Treatment of Fetal Death

Abstract

Objective: To evaluate the efficacy and side effects of each medication regime, a comparison was drawn between the administration of misoprostol with the combined use of misoprostol plus oxytocin and misoprostol plus methylergometrine for full expulsion of retained intrauterine tissues in patients who underwent a miscarriage.

Design: randomized, double-blind, clinical trial

Setting: gynecology and obstetrics clinic in Jahrom, Southern Iran

Population: 90 patients with gestational age below 12 weeks and having undergone a recent miscarriage.

Methods: They were randomly allocated into three groups after being screened for underlying diseases and coagulative blood disorders. For the first group, labeled as the control group, misoprostol was administered alone, while as, the combination of misoprostol plus methylergometrine and misoprostol plus oxytocin was prescribed for the second and third groups, respectively.

Main Outcome Measures: Primary: Expulsion of retained products of conception; Secondary: Pain, Hemorrhage

Results: Despite no significant statistical difference being observed in the expulsion of retained products of conception (RPOC)by the administration of misoprostol alone or with combined medical therapy of misoprostol with oxytocin or methylergometrine (P-value$<$ 0.329), all of them showed a successful treatment. Additionally, the patients treated with misoprostol and oxytocin showed good results in expelling the RPOC(P=0.013); while as, those treated by misoprostol plus methylergometrine reported controlled pain and hemorrhage after an abortion fiP=0.004).

Conclusion: The course of medications viz. methylergometrine, oxytocin, and misoprostol indicated a successful outpatient treatment in patients that had experienced a miscarriage or an incomplete abortion. They are cost-effective and have shown lesser side effects.

Keywords: Outpatient treatment, medical abortion, miscarriage, first trimester, retained products of conception (PROC)

Introduction

Globally, the complications succeeding a spontaneous or an unsafe abortion have been recognized as an impediment to women's general well-being [1]. A systematic and analytical study from the World Health Organization (WHO) conducted in 2014 estimated a mortality rate of 7.9% in mothers who take on an unsafe or spontaneous abortion [2]. Another study from 2017 revealed that 18% of all the pregnancies in the USA wereabortedwith80% of them being related to a gestational age of fewer than 10 weeks [3].

The prevalent long-term complications of intrauterine tissue retention include infertility, hemorrhage, intrauterine adhesion, coagulation disorders, infection, and finally death which are in a linear relationship with age advancement [4]. In contrast to curettage and manual vacuum aspiration, medical therapy by misoprostol, also known as prostaglandin, is considered a safe, non-invasive, and effective alternative method in the management of intrauterine fetal death [5-7]. In a study released in 2004 by Kehinde et al., it was illustrated that 600 micrograms of oral misoprostol intake could lead to full expulsion of retained tissue [8].

Frequent studies have been carried out to ascertain the expulsion rate of persistent placental or trophoblastic tissue, to compare oxytocin efficacy on uterine smooth muscle contractions, and also to relate the prophylactic

effects of methylergometrine on postpartum hemorrhage[9-12]. These studies have compared different forms of drug choices such as single drug administration or a combined medical therapy during hospitalization. But unfortunately, no record of outpatient treatment for residual tissue expulsion in patients with first-trimester incomplete abortion was found.

This study has been carried keeping in mind the significance of full expulsion of the retained products of conception (RPOC) after a miscarriage to avoid hospitalization during the COVID-19 crisis. To evaluate the efficacy and side effects of each medication regime, a comparison was drawn between the administration of misoprostol with the combined use of misoprostol plus oxytocin and misoprostol plus methylergometrine for full expulsion of retained intrauterine tissues in patients who underwent a miscarriage. The outcome was used to evaluate whether outpatient treatment could be substituted with a surgical approach as a safe maneuver.

Method

Study Design

This double-blind clinical trial was performed on patients who referred to the gynecology and obstetrics clinic affiliated to Jahrom University of Medical Sciences with miscarriage and a gestational age being below 12 weeks from March to July in 2020.

After taking a comprehensive history from each patient, the data obtained was registered in the relevant code sheets. After being matched in terms of gestational age, the next step involved the random categorization of patients into three distinctive groups. To follow the double-blind study format, none of the patients were given details of the category they were allotted. Furthermore, the radiologist examined the images without prior knowledge about the status of these patients. Subsequently, the patients were checked for the status of success rates of pregnancy tissue expulsion.

Participants

According to a study conducted by Paris et al in 2020[13], a sample size of90 patients was obtained, estimating a standard deviation of 0.85, confidence interval of 95%, and power of 80%; utilizing Altman nomogram for matching sample sizes of these groups estimateda15 percent dropout rate (using G-Power software for sample size determination). Therefore, 90 patients were selected for the study and were randomly allocated into three different groups.

The eligibility criteria assigned for the patients to enter the study were as follows: gestational period below 12 weeks as confirmed by sonography & LMP; spontaneous and/or incomplete abortion diagnosed by sonography; and vaginal bleeding history in the current pregnancy that encouraged patients to pursue outpatient treatment to expel RPOC. However, the exclusion criteria that disqualified the patients for the study were following: hypersensitivity to misoprostol or certain prostaglandins; drug limitations for taking prostaglandins in patients with asthma, glaucoma and hypertension, hepatic disorders, seizure history, history and/or presence of thromboembolism; smoking habits; IUD; Hb <10 mg/dl; temperature> 38^{o} C and finally, pelvic infection or sepsis that caused patient's discontentment for outpatient treatment. Moreover, an unstable hemodynamic status was considered among the exclusion criteria.

Intervention

A thorough and organized history was obtained from the patients who met the criteria to participate in the study. Additionally, they received a special written consent form to acquaint them with the research objectives and were thereof categorized into three different groups in terms of gestational age. The first group of the patients was designated to be the control group and was given misoprostol 200 mg (Misoglandin, Samisaz Co, Mashhad, Iran) every 6 hours sublingually and 3 suppositories through the posterior vaginal fornix per night[14,15].

The second and third groups followed different medication regimes as their treatment. in the third group, misoprostol 200 mg was prescribed in the form of sublingual tablet intake every 6 hours and 3 suppositories

through the posterior vaginal fornix combined with intramuscular methylergometrine 0.2 mg (Minoo Co, Tehran, Iran) thrice a day. These groups were also advised to refer to the closest clinic to take the injection cautiously [15].

On the other hand, the third group was prescribed misoprostol 200 mg sublingually every 6 hours and 3 suppositories through the posterior vaginal fornix every night. Also, this group was simultaneously administered with oxytocin (Vetocin, Aburaihan Pharma Co., Tehran, Iran), 30 units in the morning, and 30 units intramuscularly in the afternoon, and was advised to refer to the nearest health care center for taking these injections [15].

Likewise, in those patients with negative Rh, intramuscular Rhogam 300 mg injection was prescribed for preventing iso-immunization[16]. So, all the patients received treatment in the outpatient setting. After a 3-day interval, sonography was performed on each group to check the size of residual mass to assess the success rate of the undergoing outpatient treatment. The sonography was performed by an expert radiologist which was blinded to the therapeutic regime of the patient. Moreover, the course of the medication regime was repeated three times in the case of sonographic detection of endometrial mass. At last, a failure of the study was ascertained even with a slight detection of tissue residue under sonography, and patients with medical treatment failure were then advised to undergo other approaches such as surgery or curettage to remove the RPOC.

Data Collection

A demographic questionnaire used to gather information about age, sex, weight, blood pressure, existing underlying diseases, and the gestational age of the patients was given to the patients to fill in. Also, sonographic studies were employed to confirm intrauterine death.

After a 3-day outpatient intervention, the patients were asked to refer to the gynecology and obstetrics clinic affiliated to Jahrom University of Medical Sciences for further follow up. In this follow-up session, data such as spotting in pregnancy, pain, bleeding, and finally successful expulsion of RPOC were asked and recorded carefully in relevant code-sheets. For the assessment of the pain severity in the patients, the Visual Analogue Scale system (VAS), a 10 cm scaled ruler was used to show the degree of the pain in these patients; such that 0 and 10 were its two extremes representing no pain and worst pain, respectively. Data during follow-up were recorded in a blinded fashion and by using forms that were prepared in advance. Furthermore, 1-3 score denoted a relative pain, 4-6 a moderate pain, and 7-10 a severe pain overall [17]. Several internationally published papers have confirmed the reliability and durability of the VAS scale[18,20], as have many Iranian national publications confirmed its durability with a correlation coefficient of R: 0.88[21].

Statistical Analysis

The data attained in the present study were analyzed by descriptive and inferential indices through a repeated measurement method and utilization of a one-way ANOVA test and SPSS v.22. The Wilcoxon signed-rank test was used to compare population mean ranks. Also, for the comparison between the different groups, Chi-square and independent-sample t-test were employed and a significance level was considered when P-value was$<$0.05.

Ethical Considerations

Before entering the study, all the patients were informed about the process and research objectives and were requested to fill in a written consent form subjectively. Also, all of them were given referral letters for rapid and unconditional hospitalization in case they witnessed any severe complications during the outpatient treatment such as severe bleeding, severe pain, nausea, and vomiting. All the study's procedures were conducted under the Declaration of Helsinki, and the medical files of the patients were kept confidential. All the cost in this study was bored by the research team and no additional costs were requested from the patients. Fortunately, none of the patients in this study experienced intolerable pain, severe hemorrhage, and other complications. Additionally, all patients received a follow-up for treatment control. This research was approved by the ethical committee of Jahrom University of Medical Sciences issued with code No.:

IR.JUMS.REC.1396.143, and it was further registered in the Iranian registry of clinical trials with code ID of IRCT20200122046221N1.

Results

Descriptive Findings

In the current study, among the 110 eligible patients, 90 patients were evaluated and randomly allocated into three distinctive groups, each consisting of 30 participants. The first, second, and third groups received a dose of misoprostol, misoprostol plus methylergometrine, and misoprostol plus oxytocin, respectively, and were thus named accordingly (Figure 1).

[INSERT FIGURE 1]

The mean age of all the patients, as well as mean gestational age, attained29.76±5.53 and 8.23±2.29, respectively. The data including weight, height, age, and blood pressure has been presented inTable-1. To avoid variables that could alter the outcome, a study design was devised that allowed us to choose common demographic variables among the patients. These demographic data demonstrated no statistical significance between the variables in the patients utilizing the ANOVA test in which the significance value appeared to be above 0.05 (Table-1).

[INSERT TABLE 1]

Inferential Analysis

The clinical complications following pregnancy tissue expulsion were classified into different groups, and the data has been put together in Table-2. Mild to moderate post-abortion hemorrhage was treated with misoprostol accompanied by methylergometrine, and this group constituted the majority of the patients (83.3%), the only exception to this being two patients who reported acute painful misoprostol bleeding (more painful than severe menstrual cramps). Whereas, the groups that received misoprostol plus oxytocin and misoprostol alone complained of mild to severe pains, and constituted 80% and 73.3% of the study sample, respectively. Further, with regards to the distribution of bleeding onset, no statistical significance could be established (P=0.627) (Table2).

As for pain severity, the VAS score was compared in the three groups' post-abortion and after medication misoprostol intake. The outcome for the three groups that comprised of those given misoprostol plus oxytocin, misoprostol plus methylergonovine and misoprostol alone, the median and first, second and third quantiles (percentiles of 25^{th}, 50^{th}, and 75^{th}) were obtained [3 (interquartile range (IQR) of 2.75-5.25), 2 (IQR: 1.75-4) and 4.5 (IQR: 2.75-6)] with a P-value of 0.014, respectively (Figure 2). Notably, the median score of VAS in the group that received a compound of misoprostol plus methylergonovine was less than that of the group treated by misoprostol alone, with P=0.011. On the other hand, there was no evidence of a remarkable statistical significance in the median VAS score between those patients who received misoprostol plus methylergonovine and misoprostol plus oxytocin. Similar observations were reported in the group treated with combined therapy of oxytocin plus misoprostol and misoprostol alone, with P>0.05 (Table 2)

[INSERT FIGURE 2]

Regarding spotting after abortion and medical therapy, the group that received misoprostol and oxytocin constituted the majority, being 13.3% of the total. Although, no statistical significance in the normal distribution of spotting between other groups of the study was observed(P=0.894).

[INSERT TABLE 2]

Assessing the rate of RPOC expulsion, no significant difference was seen before the intake of different medications(P=0.434). However, great statistical differences were detected(P=0.013) after patients' exposure to these medications. The groups were given misoprostol plus oxytocin demonstrated a greater efficacy to expel the RPOC compared to the patients prescribed with misoprostol alone (P=0.015). Also, table 3illustratespositive results on all groups with regards to prescribed drug dose to expel the RPOC(P=0.001).

[**INSERT TABLE 3**]

Finally, the outcomes demonstrated an 83.33% success rate in those patients treated by misoprostol alone. While those groups treated by misoprostol plus oxytocin and misoprostol plus methylergonovine illustrated a success rate of 93.333%. The net results showed neither any statistical significance in the three different medication therapies (P=0.329) nor any adverse effects associated with them.

Discussion

The result obtained in the present study confirms an improved efficacy of the medical therapy of misoprostol either combined with oxytocin or with methylergonovine in successful expulsion of the RPOC. Although treatment by misoprostol alone (83.3%) has not resulted in remarkable statistical significance, greater therapeutic efficacy was reported in the groups (93.33%) treated by a combination of misoprostol plus oxytocin or misoprostol plus methylergonovine. Moreover, by designating the degree of persistent residual tissues in the patients, it was concluded that those patients treated with misoprostol plus oxytocin had the best outcome compared to the other groups. Likewise, all the patients treated with other medications showed a sufficient successful rate of RPOC expulsion.

Kaviani et al. in 2006 concluded that 'the efficacy of methylergonovine in the successful expulsion of retained pregnancy tissues in patients with incomplete abortion showed to be 94.6%'. Additionally, Niroumanesh et al. reported results similar to our findings [12]. Another study carried out by Petca et al. in 2019 compared the effectiveness of simultaneous administration of misoprostol and oxytocin (M&O) versus misoprostol and mifepristone (M&M) on abortion in the second trimester in over 108 patients. Their study further illustrated that administering M&M simultaneously resulted in greater expulsion rates within 12 hours compared to M&O, with the latter regimen demonstrating synergistic benefits, with lower expenses and satisfactory I-AI [22]. This study, like the previous one, is in coherence with our study.

Misoprostol is a prostaglandin E1 analog which is a uterotonic pharmacological agent and functions either by contracting the uterine smooth muscles or by dilation of the uterine cervix[23]. On the other hand, by increasing the permeability of uterine myofibrils to sodium, oxytocin causes uterine smooth muscle contraction. That is why this compound is frequently used to induce labor [24]. Overall, these beneficiary medications aid to dilate the cervix gently which results in a drastic reduction in the subsequent complications of cervical dilation i.e. uterus perforation, cervix rupture, hemorrhage, incomplete fetal-placental delivery and infection, and pregnancy products expulsion. Besides, these medications help to avoid anesthesia and its complications in cases where complete abortion is necessary [25].

Although the mean age of all the patients in this study was 29.76±5.53 with no statistical significance in the three different groups, we discovered that age-related physiological factors have the potential to alter the outcomes. Niroumanesh et al. concluded that older multiparous patients with several histories of previous pregnancies were found to have more tendencies for surgical and curettage approaches as compared to the other patients [26].

Another conclusive point with regards to the mean age of the patient is that younger aged patients experiencing abortion need to be educated thoroughly about contraceptives and preventive methods, unlike the other age groups. However, this perspective might appear irrelevant to the current study aim.

Abnormal weight in the mothers has a crucial impact on fertility and sanitizations during a healthy pregnancy; that is why determining factors like BMI like weight and height can play a substantial role in abortion physiology. For this matter, all the patients were examined for BMI and blood pressure, but no statistical significance in these variables was noted that might have altered the outcomes. These findings were compatible with a study conducted by Ghasemi et al.in 2018[27].

After the prescription of drugs in the different groups, hemorrhage, pain, and spotting which are considered as pregnancy tissue expulsion associated complications were carefully evaluated. A persistent postpartum hemorrhage after fetus abortion signifies small fragments of trophoblast and decidua still retained in the uterus after fetal death or RPOC expulsion [28]. There are various medical protocols developed to prevent

bleeding after surgical abortion or labor. However, these protocols are continuously being modified to achieve better outcomes and higher rates of success[29-31]. Even though there is no evidence of significant difference regarding the severity of hemorrhage in three different groups in our study, but those given misoprostol plus methylergonovine showed very mild bleeding as compared to the other groups.

A causal-comparative study was conducted by Whitehouse et al. to compare the efficacy of medical management for bleeding prevention after surgical abortion in over 336 patients with a history of recent abortion in 2018. Their study discovered that 72% of the patients used contraceptive drugs to prevent bleeding, and among them, 83% preferred vasopressin over other drugs. Likewise, scientists declared that these patients also showed willingness for the intake of methylergonovine during the second trimester to control severe bleeding and then preferred misoprostol [15]. Whitehouse et al's discoveries are consistent with our findings. A year later, they conducted another study to illustrate oxytocin potency on the reduction of frequency rate of hemorrhage and blood loss and concluded that oxytocin as prophylaxis for bleeding does not result in a reduced number of interventions required to control the bleeding during dilation and evacuation (D&E) period between 18-24 week of gestation. However, it does reduce the bleeding intensity and hemorrhage frequency which was also in harmony with our study.

Methylergonovine and oxytocin are stimulators of uterine contraction which act directly on uterine smooth muscle and peripheral vasculature, especially uterine vessels, and thus reduce hemorrhage[33,34]. This topic supports our study by demonstrating that there is no significant statistical difference between oxytocin efficacy and other drugs used for the mentioned purpose.

Similarly, regarding spotting manifestation after abortion and medication intake, the analysis proved no significant difference in the manifestation of spotting between different study groups. This fact confirms the results obtained from the degree of hemorrhage reported from the participants.

Considering medication intake and postpartum pain followed by fetal abortion, our study has discovered that the combination of misoprostol plus methylergonovine showed the best efficacy in pain management. A varied number of guidelines published for pain management by various medical associations have recommended only a normal dosage of common analgesics [35,36]. But, most of these guidelines describe neither specific medication type nor specific dosage in this scope. Moreover, the efficacy of analgesic protocols is limitedly studied in the literature, especially the protocols discussing the prevention and treatment of pain occurring post-miscarriage.

Although the World Health Organization (WHO) strongly recommends controlling, monitoring, and measuring the pain [37], even then they have not specified pain measurement methods in women with miscarriage during the first trimester.

A study conducted by Kemppainen et al. with the purpose of pain scaling during a medical abortion in early pregnancy reported VAS score of 75, and 91-54 for median and interquartile range respectively, in over 140 teenage and adult patients. Of all the women, 57.7% of them experienced severe pain (VAS=70) during abortion care. Also, 93.5% of these women needed additional opioid analgesics such as tramadol or oxycodone despite being administered with regular analgesics for prophylactic pain medication, like ibuprofen and paracetamol. Even though the misoprostol administration did not reduce the risk of pain recurrence, but even then, patients treated with misoprostol reported satisfaction[38]. According to Kari Braaten et al[39], intravenous injections of sedatives were not useful to reduce the pain in patients with surgical abortion during the first trimester, in contrast to their study, due to administration of combined misoprostol and methylergonovine, severe pain remained uncovered and its manifestation occurred in none of the patients. It is noteworthy to mention that, methylergometrine can be also used to modulate the pain of origins except miscarriage; for example, Niño-Maldonado et al. reported positive efficacy of methylergometrine for migraine pain modulation in emergency settings [40].

Limitations

Short-term follow-up and small sample size were among the barriers that limited the present study. Hence, to

increase the accuracy rate of the findings in the detection of the postpartum hemorrhages, other researchers are recommended not only to assess the severity or volume of the hemorrhage but also, they are also encouraged to analyze the mean number of days with hemorrhage throughout the intervention.

Conclusion

Outpatient treatment in patients with miscarriage can be carried out by the administration of oxytocin and methylergometrine in combination with misoprostol. This form of medical therapy has demonstrated positive impacts on the expulsion of retained products of conception (RPOC) during the first trimester and was more cost-effective compared to surgical and hospitalization approaches. Moreover, outpatient treatments in cases of medical abortion and avoidance of hospitalization are advantageous, especially during the Covid-19 pandemic. Not only it preserves the medical care resources, service management, and effectively improve women's status of physical and mental health, but it is also more convenient for the patients to manage the pain at ease as they receive psychological support from their families at home. Besides, these patients with outpatient treatment often find the opportunity to handle housework affairs and can also meet other children's needs at home. Thereby, patients' tendency toward outpatient treatments motivated us to apply certain therapeutic methods to manage intrauterine fetal death during the first trimester. We believe that this medical therapy is more cost-effective and it is a safer therapeutic approach for the patients compared to surgical methods. Thus, we suggest all medical experts continue with outpatient treatment.

Declarations

Ethical approval of the study

Written inform consent was obtained from the patients in our study. The purpose of this research was completely explained to the patient and was assured that their information will be kept confidential by the researcher. This research was approved by the ethical committee of Jahrom University of Medical Sciences issued with code No.: IR.JUMS.REC.1396.143, and it was further registered in the Iranian registry of clinical trials with code ID of IRCT20200122046221N1.

Consent for publication

Consent was obtained from the patients regarding the publication of this study.

Availability of data and materials

SPSS data of the participant can be requested from the authors. Please write to the corresponding author if you are interested in such data.

Competing interests

The authors declare that they have no competing interests.

Funding

No financial support was received for this study.

Acknowledgments

We would like to express our sincere gratitude to the Clinical Research Development Unit of Peymanieh Educational and Research and Therapeutic Center affiliated to Jahrom University of Medical Sciences for providing suitable environmental facilities and research requirements.

Authors contribution

AR designed the study. AM and ZZ collected the data, NT drafted the manuscript and RS revised and edited the manuscript. All authors proof read and approved the final version of the manuscript.

References

1. Obstetricians, A.C.o. and Gynecologists, ACOG Committee Opinion No. 427: Misoprostol for postabortion care. Obstet. Gynecol, 2009. 113(2 Pt 1): p. 465.

2. Say, L., et al., Global causes of maternal death: a WHO systematic analysis. Lancet Glob. Health, 2014. 2(6): p. e323-e333.

3. Jones, R.K. and J. Jerman, Abortion incidence and service availability in the United States, 2014. Perspect. Sex. Reprod. Health, 2017. 49(1): p. 17-27.

4. Hooker, A.B., et al., Long-term complications and reproductive outcome after the management of retained products of conception: a systematic review. Fertil. Steril., 2016. 105(1): p. 156-164. e2.

5. Ambusaidi, Q. and A. Zutshi, Effectiveness of Misoprostol for Induction of First-Trimester Miscarriages: Experience at a single tertiary care centre in Oman. Sultan Qaboos Univ. Med. J, 2015. 15(4): p. e534.

6. Raymond, E.G., et al., Mortality of induced abortion, other outpatient surgical procedures and common activities in the United States. Contraception, 2014. 90(5): p. 476-479.

7. Thiebaut, M., et al., Retrospective assessment of the influence of gestational age on the first trimester medical abortion efficiency. Rev Med Liege, 2017. 72(4): p. 193-198.

8. Ibiyemi, K.F., A.I. Munir'deen, and K.T. Adesina, Randomised Trial of Oral Misoprostol Versus Manual Vacuum Aspiration for the Treatment of Incomplete Abortion at a Nigerian Tertiary Hospital. Sultan Qaboos Univ. Med. J, 2019. 19(1): p. e38.

9. Hernández-Martínez, A., et al., Oxytocin discontinuation after the active phase of induced labor: A systematic review. Women Birth, 2019. 32(2): p. 112-118.

10. Budden, A., L.J. Chen, and A. Henry, High-dose versus low-dose oxytocin infusion regimens for induction of labour at term. Cochrane Database Syst. Rev, 2014(10).

11. Schaider, J.J., et al., Rosen & Barkin's 5-minute emergency medicine consult. Vol. 4. 2012: Lippincott Williams & Wilkins.

12. Kaviani, M., et al., Comparison of the Effects of Simultaneous Use of Methylergonovine and Combined Low-dose (LD) Contraceptive Pills on Hemorrhage Due to Retained Pregnancy Products after Abortion. Int. J. Curr. Microbiol. App. Sci, 2016. 5(11): p. 499-507.

13. Paris, A.E., et al., Mifepristone and misoprostol compared to osmotic dilators for cervical preparation prior to surgical abortion at 15–18 weeks' gestation: a randomised controlled non-inferiority trial. BMJ Sex. Reprod. Health, 2020. 46(1): p. 67-72.

14. Guilbert, E.R., et al., First-trimester medical abortion practices in Canada: National survey. Can Fam Physician, 2016. 62(4): p. e201-e208.

15. Whitehouse, K., et al., Use of medications to decrease bleeding during surgical abortion: a survey of abortion providers' practices in the United States. Contraception, 2018. 97(6): p. 500-503.

16. Jahangir, M., et al., Efficacy of vaginal Misoprostol for terminating missed abortion. KAUMS Journal (FEYZ), 2005. 9(2): p. 1-5.

17. Wewers, M.E. and N.K. Lowe, A critical review of visual analogue scales in the measurement of clinical phenomena. Res Nurs Health, 1990. 13(4): p. 227-236.

18. Feng, X., et al., Transcutaneous acupoint electrical stimulation pain management after surgical abortion: A cohort study. Int J Surg, 2016. 30: p. 104-108.

19. Conti, J.A., et al., Self-administered lidocaine gel for pain control with first-trimester surgical abortion. Obstetrics & Gynecology, 2016. 128(2): p. 297-303.

20. Thaxton, L., et al., Nitrous Oxide Compared with Intravenous Sedation for Second-Trimester Abortion: A Randomized Controlled Trial. Obstetrics & Gynecology, 2018. 132(5): p. 1192-1197.

21. Rezvani Amin, M., et al., Correlation between visual analogue scale and short form of McGill questionnaire in patients with chronic low back pain. Qom University of Medical Sciences Journal, 2011. 5(1): p. 31-34.

22. Petca, A., et al., second trimester abortion: mifepristone plus misoprostol vs. misoprostol plus oxytocin. Farmacia, 2019. 67(5): p. 850-856.

23. Bakker, R., S. Pierce, and D. Myers, The role of prostaglandins E1 and E2, dinoprostone, and misoprostol in cervical ripening and the induction of labor: a mechanistic approach. Arch Gynecol Obstet, 2017. 296(2): p. 167-179.

24. Huffmeijer, R., et al., Salivary levels of oxytocin remain elevated for more than two hours after intranasal oxytocin administration. Neuro endocrinology letters, 2012. 33(1): p. 21-25.

25. Tehranian, A., et al., The effect of adding hyoscine to vaginal misoprostol on abortion induction success rate. Tehran Univ. Med. J, 2010. 68(4).

26. Niroumanesh, S. and N. Azadbeh, Use of vaginal Misoprostol tablets in the management of missed abortion in pregnant women. J Adv Med Biomed Res, 2002. 10(341):p 1-7.

27. Ghasemi, M., et al., Comparison of two dosing regimens of intravaginal misoporostol for second-trimester abortion. The Iranian Journal of Obstetrics, Gynecology and Infertility, 2018. 21(4): p. 19-24.

28. Sang, G.-w., et al., Termination of early pregnancy by two regimens of mifepristone with misoprostol and mifepristone with PG05—a multicentre randomized clinical trial in China. Contraception, 1994. 50(6): p. 501-510.

29. Jain, R., et al., Comparison of intramuscular methylergometrine, rectal misoprostol, and low-dose intravenousoxytocin in active management of the third stage of labor. Tzu Chi Med. J., 2019. 31(3): p. 158.

30. Tan, J., et al., Misoprostol versus ergometrine-oxytocin for preventing postpartum haemorrhage: a systematic review and meta-analysis of randomized controlled trials. Evid Based Med, 2016. 9(4): p. 194-204.

31. Dabbaghi Gale, T., et al., Comparison of intravenous oxytocin and oral misoprostol in reduction of postpartum hemorrhage. ZUMS Journal, 2012. 20(81): p. 1-8.

32. Whitehouse, K., et al., Effects of prophylactic oxytocin on bleeding outcomes in women undergoing dilation and evacuation: a randomized controlled trial. Obstetrics & Gynecology, 2019. 133(3): p. 484-491.

33. Huh, W.K., D. Chelmow, and F.D. Malone, A double-blinded, randomized controlled trial of oxytocin at the beginning versus the end of the third stage of labor for prevention of postpartum hemorrhage. Gynecol Obstet Invest, 2004. 58(2): p. 72-76.

34. Cunningham F. G., Norman F. G., KennethJ. L., et al. abortion. Williams obstetrics. 21th Edition. New York, MC Graw Hill.2001; pp: 855-883.

35. Fiala, C., et al., Pain during medical abortion, the impact of the regimen: a neglected issue? A review. Eur J Contracept Reprod Health Care, 2014. 19(6): p. 404-419.

36. Fiala, C., et al., Pain management for up to 9 weeks medical abortion–An international survey among abortion providers. Eur. J. Obstet. Gynecol, 2018. 225: p. 181-184.

37. Suhonen, S., et al., Pain during medical abortion: predicting factors from gynecologic history and medical staff evaluation of severity. Contraception, 2011. 83(4): p. 357-361.

38. Kemppainen, V., et al., Pain during medical abortion inearly pregnancy in teenaged and adult women. Acta Obstet Gynecol Scand, 2020.

39. Braaten, K.P., et al., A randomized comparison of intravenous sedation using a dosing algorithm compared to standard care during first-trimester surgicalabortion. Contraception, 2018. 97(6): p. 490-496.

40. Nino-Maldonado, A.I., et al., Efficacy and tolerability of intravenous methylergonovine in migraine female patients attending the emergency department: a pilot open-label study. Head Face Med, 2009. 5(1): p. 21.

Table 1. Demographic variables in drug prescription based on mean and standard deviation

Variable	**Total**	**Groups Misoprostol**	**Groups Misoprostol + Methylergometrine**	**Groups Misoprostol + Oxytocin**	**P**
Age	29.76±5.53	31.47±5.83	28.13±4.8	29.67±5.57	0
Weight	66.27±11.07	64.59±9.69	65.71±10.61	68.48±12.7	0
Height	159.98±5.24	159.79±4.88	161.22±5.69	158.96±5.07	0
Min. BP	74.24±9.84	74.6±10.83	73.96±10.12	74.17±9	0
Max. BP	116.6±11.85	117.92±9.25	118.96±15.54	113.31±9.56	0
Gestational Age	8.23±2.29	8.17±2.77	7.43±1.59	9.14±2.22	0

Table 2. abortion indications in control and experimental groups

Abortion indications	**Abortion indications**	**Groups** (%)	**Groups** (%)	**Groups** (%)	**Significance value**
		Misoprostol *n=30*	**Misoprostol + Methyler-gometrine** *n=30*	**Misoprostol + Oxytocin** *n=30*	
Bleeding	*Mild*	16 (53.23(	24 (80)	19 (63.33)	0.627
	Moderate	5 (16.6%)	1 (3.33)	4 (13.33)	
	Severe	1 (3.33)	0 (0)	1 (3.33)	
Pain	*None to Mild (VAS*=0-3)*	13 (43.33)	20 (66.66)	17 (56.66)	0.004
	Moderate (VAS=4-6)	11 (36.66)	10 (33.33)	8 (26.66)	
	Severe (VAS=7-10)	6 (20)	0(0)	5 (16.66)	
Spotting	-	3 (10)	3 (10)	4 (13.3)	0.894
VAS: Visual Analogue Scale	*VAS: Visual Analogue Scale	*VAS: Visual Analogue Scale	*VAS: Visual Analogue Scale	*VAS: Visual Analogue Scale	*VAS: Visual Analogue Scale

Table 3. illustrations regarding expulsion degree of retained products of conception (RPOC) before and after medical therapy in both control and experimental groups based on mean and standard deviation.

Variable	**Total**	**Groups**
		Misoprostol
Degree of RPOC* before medication	32.49±20.38	35.38±17.22

Variable	Total	Groups
Degree of RPOC after medication	13.53±13.13	19.07±14.31
Two sample T-test Significance	0.001	0.001
RPOC: Retained products of conception	RPOC: Retained products of conception	RPOC: Retained products of concep

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