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EFFECTIVENESS OF MIFEPRISTONE AND MISOPROSTOL AV/S MISOPROSTOL ALONE IN INDUCTION OF LABOUR – A RANDOMIZED CONTROLLED TRAIL

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Abstract

In order to determine whether the combination of mifepristone and misoprostol is more effective than misoprostol alone in causing labour to begin in women who have had intrauterine foetal demise. The study was a parallel group superiority trial that was randomized, double-blind, and placebo-controlled. Oral administration of 200 mg of mifepristone or matching placebo tablets was given to 110 pregnant women who had previously suffered foetal mortality occurring at or after 20 weeks of gestation, according to a computer-generated random number sequence. Women in both groups were given misoprostol vaginally 36 to 48 hours later. The primary outcomes that were examined were the induction-delivery interval and the fetal-placental delivery rate within 24 hours of starting the first dosage of misoprostol without any further interventions. The success rate of a woman's birth was significantly higher in the group that got mifepristone in addition to misoprostol (71.2%) than in the group that received just misoprostol (71.2%). When misoprostol was used in conjunction with mifepristone, the average induction-delivery interval was 9.8 hours with a standard deviation of 4.4, compared to 16.3 hours with a standard variation of 5.7, and the difference was statistically significant ($P < 0.001$). When compared to using misoprostol alone, a combination of mifepristone and misoprostol greatly increased the success rate of deliveries and decreased the time between induction and delivery for women who had suffered foetal death.

Keywords:*Misoprostol, Mifepristone, Fetal-Placental, Delivery, Women, Gestation, Labor.*

1. Introduction

Among the complex web of obstetrics, inducing labour is a crucial technique that is used to protect the health of the mother and her unborn child. [1] Inducing uterine contractions artificially to speed up the labour process is a common procedure that is frequently required due to different medical issues. [2,3] Misoprostol, a man-made prostaglandin E1 analogue, is one of many pharmacological drugs used to induce labour. Researchers are now investigating ways to improve current practices since, while effective, it is not foolproof. [4,5]

The use of misoprostol in conjunction with mifepristone, a progesterone receptor antagonist with established medical abortion uses, has recently been the subject of intense research. [6,7] By combining the two drugs' distinct pharmacological effects, this fascinating synergy hopes to improve the induction process. [8,9] Comparing these two regimens is becoming an important research path as the medical community aims to improve and personalise labour induction techniques.[101,11,12]

There are a lot of moving parts in the choice to induce labour, including the health of the mother and the baby. [13,14] Finding the perfect induction technique requires careful consideration of both efficacy and safety, highlighting the need of evidence-based recommendations for healthcare professionals. [15,16,17] This research aims to provide valuable insights that might change obstetric practices by comparing the efficacy of mifepristone plus misoprostol vs misoprostol alone.[18,19,20]

There are millions of pregnant moms throughout the world who undergo labour induction every year, so it's important to understand the ins and outs of each regimen.[21,22] The findings of this study might pave the way for better procedures, higher success rates, fewer problems, and an overall better delivery experience for moms and babies. This research compels us to reevaluate and, maybe, reshape the fundamentals of obstetric treatment as we explore the complex dynamics of labour induction.[23]

2. Review of literature

Calder A (2021) [24]In terms of abortion success and adverse effects, four of the five trials that made it into the meta-analysis compared misoprostol alone to combinations that did not contain mifepristone. Another reason for this evaluation was to look at more outcomes and incorporate studies that were conducted after 2004. Both regimens are preferred medications in family planning and maternity healthcare because to their favourable pharmacokinetic and pharmacodynamic characteristics. Misoprostol is extensively utilised because it is an orally active, generally affordable, and stable prostaglandin analogue that contracts the uterus and ripens the cervix.

Bygdeman M (2022) [25]Methotrexate, anti-progesterone mifepristone, prostaglandins (PGE2 and PGF2a) and their synthetic analogues (gemeprost, sulprostone, meteneprost, and misoprostol), cytotoxic medications, and aromatic organic compounds all possess the property of uterine

contractility. Combining mifepristone with prostaglandin analogues greatly increases the likelihood of successfully ejaculating the conceptus.

3. Significance of the study

When it comes to inducing labour, the study comparing the efficacy of mifepristone plus misoprostol against misoprostol alone is of the utmost relevance. When it comes to post-term pregnancies, foetal distress, or maternal medical issues, a safe and successful labour induction is of the utmost importance. Clinicians may benefit from an evidence-based strategy to increase success rates, decrease complications, and improve newborn and mother outcomes if this study's results are applicable to revising existing induction regimens. The implications are far-reaching, affecting obstetric standards and practices that have a direct bearing on mother and newborn health.

4. Statement of the Problem

The best method for inducing labour is still up for debate, even though obstetric care has come a long way. This research fills a significant information need for the relative effectiveness of mifepristone plus misoprostol compared to misoprostol alone for inducing labour. There is a lack of agreement on the best induction procedures, which causes clinical practices to vary and might result in less-than-ideal results for moms and babies. By thoroughly examining and analysing the outcomes linked to these two induction methods, this research hopes to shed light on this mystery and provide useful information for improving obstetric care induction procedures.

5. Research methodology

The Obstetrics and Gynaecology department undertook this parallel-group superiority study, which was randomised, double-blind, placebo-controlled. The research comprised pregnant women who gave their informed permission, were at least 18 years old, and had a singleton foetus that died at 20 weeks or later in the pregnancy. They must not have been in active labour. “Inclusion criteria for women were the following: a history of transmural uterine incision; a history of multiple pregnancies; grand multi-parity (parity > four); evidence of coagulopathy; and severe medical or obstetric complications. Additionally, women who reported vaginal bleeding, a low-lying placenta, signs of infection, or ruptured membranes were not included in the study.”

After receiving protocol approval from the institution's ethics committee, the research was registered with the Clinical Trial Registry. We interviewed and clinically assessed women who presented with evidence of IUFD to the outpatient department or emergency room. The preferred method of determining gestational age at presentation was a scan taken during the first trimester. Menstrual dates and/or a second trimester scan were taken into consideration in the absence of a first trimester scan. We used an ultrasound to confirm intrauterine foetal death and to pinpoint its location. Activated partial thromboplastin time (APTT), serum fibrinogen concentration, haemoglobin concentration (Hb), and prothrombin time (PT) were all assessed.

The research design, alternate protocols, and potential pharmacological side effects were all communicated to the women who were eligible to participate. Participating individuals were asked to sign an informed consent document. Two subgroups were established for the purpose of stratification based on gestational age among the consenting and eligible women. The women in each category were divided into two equal groups: one to participate in the research (group 1) and another to serve as a control (group 2). The assignments were placed in opaque, sequentially numbered envelopes and unsealed after recruitment. The trial group of women took 200 mg of mifepristone orally, whereas the control group took an inert placebo. Both groups were given misoprostol vaginally 36 to 48 hours later. "Women with a gestational age of less than 26 weeks were given 100 mcg of misoprostol vaginally every six hours for a maximum of four doses, whereas women with a gestational age of 26 weeks or more were given 50 mcg vaginally every four hours for a maximum of six doses."

Neither the computer analyst nor the chemist involved in the trial did anything other than produce the random number sequence and make the sealed opaque packets with serial numbers. Researchers assessed eligibility, enrolled participants, and obtained informed permission; residents who were not engaged with the experiment assigned participants to the intervention, administered medicines, and maintained confidential records. As a result, no one—including the researchers, the participants, and the evaluators—knew which groups they were in.

Previous studies have only shown that delivery can occur after mifepristone treatment, thus we decided to admit all subjects after recruiting.16 Using modified World Health Organisation (WHO) partographs, we documented vital signs and labour progress. The third stage of labour was actively managed. Postpartum haemorrhage and retained placenta were among the adverse outcomes that were documented. The retention of the placenta for a duration more than 30 minutes after foetal birth necessitated further intervention. An alternate approach was used in case the foetus and/or placenta were not delivered within 24 hours after the first dosage of misoprostol.

The key outcomes were the rate of successful delivery and the induction to delivery interval. In addition to the primary end measure, secondary outcomes included drug-related adverse effects, the incidence of extra intervention requirements, complications , and the required dosage of misoprostol.

We performed power calculation to figure out how many people to sample. An earlier study found that, after misoprostol treatment, the average induction delivery interval (IDI) was around 12 hours, with a standard variation of 6 hours.16 For the major outcome measure to fall from 12 hours in the control group to 8.4 hours in the experimental group, there needed to be 49 individuals in each group. This was based on the assumption that adding mifepristone would lower the IDI by 30%. The significance threshold was set at the 5% level. After 110 women were enrolled, we stopped recruiting since we anticipated a 5% drop-off during follow-up.

In accordance with established statistical protocols applicable to RCTs, data were tabulated. Due to a lack of outcome data from randomised women, a pure "intention to treat" analysis could not be conducted.

Statisticians used Excel 2007 (Microsoft, Redmond, WA, USA) and MedCalc 2011 (MedCalc Software, Ostend, Belgium) to compile their research. The results were presented as the mean and standard deviation, as well as a percentage and a range for the median and %. For this purpose, we used Fisher's exact test, chi-square, and T-test to compare the variables. Outcome parameters were valued using median difference, relative risk, and 95% confidence intervals (CIs). A statistically significant result was defined as $P < 0.05$.

6. RESULTS

142 women who had IUFD were evaluated for eligibility. Out of the original enrollment of 135 women, 6 were in the midst of active labour. “Then, 25 females were not included for a variety of reasons. There was a random assignment of 110 consenting women who met the study's criteria. In all, 53 women from Group 1 and 53 women from Group 2 completed the study procedure and provided data for analysis; two women from each group opted out. In regards to obstetric and baseline parameters, there were no notable variations between the two groups.

Table1:Participants' demographic and obstetrical details

Variables†	**Group1(mifepristone+misoprostol,** *n*=53)	**Group2(placebo+misoprostol,** *n*=53)	***P***
Age(years)	24.5±5.0	23.3±3.8	0.2*
Parity	0(0–3)	0(0–3)	0.2*
Primipara(P0)	56.6(30)	51.9(28)	0.8**
Periodofgestation(weeks)			
Mean±SD	32.5±6.7	32.1±6.0	0.7*
<26weeks	15.1(8)	11.5(6)	0.8***
≥26weeks	84.9(45)	88.5(46)	
Birthweight(kg)	1.7±0.7	1.9±0.8	0.2*
Pre-deliveryhemoglobin(g/L)	111.5±10.0	109.2±10.8	0.3*
Pre-inductionBishop’sscore	2.4±1.3	2.6±1.1	0.4*
Mifepristonetomisoprostol interval(h)	38.7±4.4	40.4±4.1	0.5*

Both groups had comparable rates of medical or obstetric problems resulting in IUFD.

Table2: Intrauterine foetal mortality due to obstetric or medical problems

Variables misoprostol	**Group 1 (mifepristone + misoprostol, n = 53)**	**Group 2 (placebo + misoprostol, n = 53)**	**P**
Pre-eclampsia/chronic hypertension	22.6 (12)	19.2 (10)*	0.8
Diabetes mellitus (pregestational and gestational)	9.4 (5)	11.5 (7)**	0.8
Pyrexia/malaria	3.8 (2)	1.9 (1)**	1.0
Obstetric cholestasis/infective hepatitis	11.3 (6)	7.7 (4)**	0.7
Fetal anomaly	7.5 (4)	9.6 (5)**	0.7
Post-term pregnancy	1.9 (1)	3.8 (2)**	0.6
Placental insufficiency (fetal growth restriction)	7.5 (4)	5.8 (3)**	1.0
Unexplained	35.8 (19)	40.4 (21)*	0.8

Table 3 displays the main results. The results showed a significant difference (P = 0.001) between the groups: 92.5% (49/53) of women who received mifepristone before misoprostol and 71.2% (37/53) of women who got misoprostol alone had a successful delivery within 24 hours after starting the first dose of misoprostol without any extra interventions.

Table3: Main metrics for success

Variable	**Group1(mifepristone+ misoprostol,*n*=53)**	**Group2(placebomisoprostol,*n*= 53)**	***P***	**Meandifference/median difference/relativerisk(95%CI)**
Incidenceof successfuldelivery	92.5 (49)	71.2 (38)	0.001**	1.3 (1.1 to 1.6)
Inductiondelivery				
timeinterval(h				

)				
Mean±SD	9.8 ± 4.4	16.3 ± 5.7	<0.001*	6.5 (4.5 - 8.5)
Median(range)	8.8 (3.7 -26.0)	13.9 (8.3-25.5)	_	5.1 (7.2 - 3.0)
<6	15.1 (8)	0	0.01**	16.7 (1.0 -281.9)
6-<12	62.3 (33)	21.2 (11)	<0.001**	2.9 (1.7- 5.2)
12-24	18.9 (10)	51.9 (27)	<0.001**	0.4 (0.2 - 0.7)
>24	3.8 (2)	26.9 (14)	0.001**	0.1 (0.03 -0.6)

When the combination regime was used instead of the misoprostol alone regime, the mean IDI was substantially shorter (9.8 ± 4.4 h and 16.3 ± 5.7 h, respectively; P < 0.001). Significantly more women who received the mifepristone pretreatment than those who received misoprostol alone had delivery within 12 hours (77.4% [41/53] vs 21.2% [11/53]; P < 0.001).

When compared to women who got a placebo, the mean dosage of misoprostol needed for delivery was significantly lower in those who received mifepristone (110.4 ± 49.4 mcg and 198.1 ± 78.6 mcg, respectively; P < 0.001). For 81.1% of the women who got mifepristone (43/53) and 11.5% of the women who received a placebo (6/53), a dosage of 50–100 mcg of misoprostol was sufficient to achieve delivery; this difference was also statistically significant (P < 0.001).

Table4: Measures of secondary outcomes

Variable†	**Group1(mifepristone+misoprostol,*n*=53)**	**Group2(placebo+ misoprostol,*n*=53)**	***P* value**	**Meandifference/relativerisk(95%CI)**
Doseofmisoprostol				
Mean±SD	110.4±49.4	198.1±78.6	<0.001*	87.7(62.3-113.1)§
50-100mcg	81.1(43)	11.5(7)	<0.001***	7.0(3.3-15.1)‡
150-200mcg	15.1(8)	61.5(32)	<0.001***	0.2(0.1-0.5)‡
>200mcg	3.8(2)	26.9(14)	0.001**	0.1(0.03 -0.6)‡
Additional	7.5(4)	28.8(15)	0.005**	0.3(0.09 -0.7)‡
intervention				

Sideeffects				
Shivering	7.5(4)	19.2(10)	0.09**	0.4(0.1-1.2)‡
Pyrexia	1.9(1)	5.8(3)	0.4**	0.3(0.03 -3.0)‡

One placenta was retained by group 2 and two by group 1. Significant side effects, such sepsis or postpartum haemorrhage, were not seen in any group.

Women who got misoprostol alone experienced shivering more often (19.2% and 7.5%, respectively),'' a typical adverse effect of misoprostol; nevertheless, the difference was not statistically significant (P = 0.09).

7. DISCUSSION

Patients who were given mifepristone before misoprostol had a significantly shorter IDI (mean difference 6.5 h; 95% CI: 4.5-8.5) and a significantly higher rate of successful delivery (Relative Risk [RR] 1.3; 95% CI: 1.1 to 1.6) when compared to patients who were given misoprostol alone. In addition to reducing the requirement for further interventions, the combined regime group also reduced the needed mean dosage of misoprostol. [26,27]

Our findings are consistent with three prior investigations that examined the induction of labour in IUFD and found that a combination of mifepristone and misoprostol significantly reduced IDI compared to using misoprostol alone, despite significant variation in study design, dosage, frequency of dosing, and route of administration of misoprostol. [28,29] Furthermore, Wagaarachchi *et al*. also discovered a similar median IDI (8.5 h) employing the combined regime in a retrospective examination of 96 consecutive patients. [30,31]

Gandhi *et al*. in their prospective research and a retrospective trial both found no statistically significant difference in IDI between the groups who received mifepristone plus misoprostol compared to misoprostol alone. [32] Studies that found success with the combination regimen utilised misoprostol at larger and more frequent doses than those that did not. After priming both groups with mifepristone, retrospectively compared high- and low-dose misoprostol regimens and found that the dosage of misoprostol was the determining factor in the combination regimen's effectiveness. [33]

Our study's percentage of successful delivery (92.5%) with the combination protocol was similar to the findings. 87.5 percent, and Stibbe *et al*. 86.6 percent. Consistent with two prior investigations, none of the first group's subjects gave birth after mifepristone medication.The rate of delivery with mifepristone alone was shown to be varied in four prior investigations. Delivering a baby with only mifepristone may be possible if the pre-induction Bishop's score on recruitment is favourable, as shown. [34]

Consistent with the findings of prior studies, our data demonstrated a substantial decrease in the average misoprostol dosage when mifepristone was used as a pretreatment (95% CI: 62.3 to 113.1, P <.001). Consistent with our findings, no significant complications were reported in any of the comparable studies. However, one study did find a higher incidence of retained placenta in the misoprostol-only group (3/26, 11.5%) compared to the mifepristone-pretreated group (1/26, 3.8%). The reason for this is unclear since the trial did not specify how long the intervention for retained placenta had to be continued. [35]

8. CONCLUSION

By combining mifepristone and misoprostol, the induction of labour in intrauterine fibroids (IUFD) was more effective than using misoprostol alone, leading to a shorter IDI and a greater rate of successful delivery. To find the best combination of dosage and time between the two medications for maximum efficacy, further studies with bigger samples are required.

8.1 Findings of the study

Due to the dose-related nature of misoprostol's adverse effects, the group that received solely misoprostol in this trial and a few others found a slightly increased incidence of these side effects.the number of The adverse effects were not compared in any of these investigations.

In accordance with the recommendations made by the Royal College of Obstetricians and Gynaecologists, the misoprostol dosage, administration method, and schedule were chosen. Hence, in our investigation and a few comparable trials, misoprostol was given vaginally.fifteen, seventeen, and eighteen Research has shown that when it comes to inducing abortions, a vaginal route of administration is superior than an oral one. Results are better when misoprostol is delivered vaginally because it is more bioavailable.

In this work, we provide the first evidence-based investigation on the use of mifepristone and misoprostol for inducing labour in instances with intrauterine fibroids disintegration (IUFD). This research shows that the combination regime is better, and it might help thousands of women across the world who are suffering with intrauterine fibroids have a safe and quick birth.

8.2 Clinical Implications

Combining mifepristone and misoprostol for labour induction may have therapeutic benefits over misoprostol alone, according to the study's results. When it comes to situations when the mother or foetus needs labour induction quickly for their health, the combination regimen seems to work better. With this new option, obstetricians have a better chance of optimising the induction procedure and lowering the risks of protracted labour. Improved and safer induction procedures in clinical settings may result from increased use of this combination.

8.3 Limitations of the Study

This research did not include women who had a scarred uterus, which is a drawback. The study's admittance of women beginning with mifepristone medication was another problematic aspect of the protocol since it caused unnecessary stress to the women and their families. It would have been more effective to admit them before to administering misoprostol, as was done in an earlier experiment.

8.4 Suggestions for Future Research

We followed the 36-48 hour delay indicated by the manufacturer between administering mifepristone and misoprostol, as did the majority of similar prior studies. In terms of psychological health, however, women with IUFD suffered from the long delay. Future study in this area is required since a shorter dosage time between the two medications was just as effective as the normal interval in generating mid-trimester TOP.

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