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The effect of Dilapan-s *vs.* Misoprostol as a cervical ripening agent in 2nd trimesteric abortion with scarred uterus

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SUMMARY

AUTHORS' CONTRIBUTION: (A) Study Design · **(B)** Data Collection . **(C)** Statistical Analysis · **(D)** Data Interpretation · **(E)** Manuscript Preparation · **(F)** Literature Search · **(G)** No Fund Collection

Background: Mid-trimester abortions account for 10% to 15% of all abortions but account for two-thirds of all serious complications. In the second trimester, termination of pregnancy can be achievied by induction of abortion, D&E, hysterotomy, and hysterectomy. Cervical laceration and uterine perforation are reduced when the cervix is prepared prior to surgery. Osmotic dilators can be used to prepare the cervix.

Aim of the work: The aim of the study is to compare the effectiveness of Dilapan-s *vs.* misoprostol as a cervical ripening agent in second trimester abortions between 13 and 18 weeks of gestation.

Patients & Methods: This prospective, randomized comparative clinical trial was conducted at tertiary care hospital at Ain Shams University Maternity hospital, labor ward from June 2020 till August 2021 and performed on total 56 women with previous one cesarean section with second trimester abortion between 13 and 18 weeks of gestation fulfilling the study's eligibility criteria.

Results: Time interval from start of procedure to the start of expulsion and complete expulsion of fetus statistically was non-significantly shorter among Dilapan group than among Misoprostol group (p value=0.397, 0.105 respectively). There was no significant statistical difference between the study groups regarding successful abortion and need for surgical evacuation (p value=0.567, 0.149 respectively), with no statistically significant complications (nausea, vomiting, fever rupture uterus and post-abortive bleeding) between the study groups. The Hospital stay duration statistically was non-significantly different among the studied groups (p value=0.341). The Pain experienced was statistically non-significantly different among the studied groups (p value=0.106) and all the studied cases of both groups needed analgesics.

Conclusion: Dilapan is an insignificant agent for cervical ripening prior to abortion induction when compared to misoprostol.

Keywords: Dilapan-s; Cervical ripening agent; Second trimester abortion

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INTRODUCTION

Dilatation and evacuation (D&E) is the most effective way of terminating a pregnancy in the second trimester. When compared to medical induction, an increasing body of evidence shows that D&E is safer, quicker, less costly, and favored by women [1].

During D&E the forceps is employed to remove the fetus and placenta via an artificially dilated cervix. Cervical preparation, which involves the use of necessary agents to dilate or soften the cervix prior to the procedure, facilitates and may eliminate the need for rigid dilation during D&E. This method has been found to lower the incidence of surgical abortion complications [1]. Most forceps used for D&E require a minimum dilatation of 14 to 19 mm, while larger dilation is frequently necessary to remove products of conception at advanced gestations. [2].

Cervical preparation is an essential part of safe abortion at all stages of pregnancy. Cervical and uterine trauma are associated with forceful cervical dilatation, which may result in unfavorable reproductive outcomes such as pregnancy loss, cervical weakening, and premature delivery [3].

However, the best cervical preparation strategy has yet to be determined. Prostaglandin analogues, mifepristone (an anti-progesterone), and osmotic dilators are examples of cervical preparation agents. The two osmotic dilators now available are Dilapan-S and laminaria. Maximum dilatation of Laminaria tents manufactured from dehydrated seaweed takes 12-24 hours [2].

Dilapan-S is a hygroscopic osmotic cervical dilator that is free of pharmacological drugs. It is constructed of an anisotropic xerogel AQUACRYL® linked to a polypropylene handle with a polyamide string to be inserted inside the cervical canal. Its diameter expands from 4 to 10-12 mm in 4-8 hours as it adsorbs cervical secretions. It also causes the local release of prostaglandins, which aids in cervical ripening [4].

Dilapan-S is sterile and expands faster than laminaria. Dilapan-S also has the advantage of being constant in length and form, resulting in more anticipated outcomes [3].

Misoprostol, a synthetic prostaglandin E1 analogue, is usually considered safe and effective; nonetheless, it induces less dilatation than nightly osmotic tents [1].

Although there is minimal evidence to support its use, mifepristone, a progesterone receptor blocker, is also beneficial for cervical preparation prior to D&E [5].

Up to 18 weeks' gestation, Fox and Krajewski [2] suggest same-day cervical preparation using misoprostol or Dilapan-S. Senior trained doctors may try same-day protocols at later gestations after 18 weeks using serial misoprostol dosages or a mix of osmotic and pharmacological treatments. Misoprostol is not substantially effective as an adjuvant to nightly osmotic dilatation before 19 weeks of gestation [2].

To reduce the likelihood of problems during a D&E, the Society of Family Planning suggests pre-operative cervical preparation [2]. And as there is no consensus on which agent should be used, this study aimed to compare the efficacy of Dilapan-S *vs.* Misoprostol as a cervical ripening agent in second trimester abortion.

AIM OF THE WORK

The aim of the study is to compare the effectiveness of Dilapan-s *vs.* misoprostol as a cervical ripening agent in second trimester abortions between 13 and 18 weeks of gestation.

PATIENTS AND METHODS

This Prospective randomized comparative clinical trial was conducted on a total of 56 pregnant women with second trimester abortion at 13 to 18 weeks of gestation with history of previous one cesarean section who were admitted for induction of abortion and willing to participate in the study at Ain Shams University Maternity hospital, labor ward starting from June 2020 till August 2021, following ethical committee approval and informed consent from the patients prior to enrollment.

Study population: All participants were submitted to the following assessment to check for eligibility.

Complete medical history: Including age, previous obstetric history and number of previous cesarian deliveries, menstrual history for estimation of gestational age using Naegele's rule, history of previous manipulations by any uterotonics, history of current pregnancy to clarify indication for elective termination.

Physical Examination: Including General examination as vital data assessment, Abdominal examination as fundal level measurement, evidence of uterine contractions, scars of previous laparotomies and Local examination to assess cervical state (dilatation, consistency, effacement, station, position and presenting part) and state of the membranes either intact or ruptured with leakage of liquor.

Ultrasound Examination: To assess cs scar thickness, confirmation of gestational age calculated from menstrual history, Amniotic fluid index, cervical state and any evident fetal malformations.

Inclusion criteria:

- Maternal age above 18 years with no upper age limit.
- Singleton pregnancy.
- Pregnancies indicated for elective termination as negative fetal life or lethal fetal malformation.
- Gestational age between 13+0 and 17+6 weeks on day of D&E with ultrasound confirmation of gestational age.
- Scarred uterus which includes only previous one cesarean section.
- Intact membranes.

Exclusion criteria:

- History of previous traumatic delivery.
- Women with signs or symptoms of spontaneous abortion (vaginal bleeding and/or contractions).
- Known allergy or contraindication to misoprostol.
- Signs of chorioamnionitis or clinical infection at enrollment.
- Clinically evident vaginal infections.
- Serious medical conditions such as poorly-controlled asthma, cardiovascular disease, uncontrolled hypertension or diabetes, liver or kidney dysfunction, seizure disorders, glaucoma, uncontrolled hyperthyroidism

Sample size: The mean of procedure time of termination with both cervical ripening agents (Dilapan-s and Misoprostol) was used to calculate sample size. According to Wilson's prior study from 2011 [6], the mean abortion time with misoprostol was around 10.2 ± 4.3 minutes, whereas the Dilapan-s group was approximately 14.4 ± 6.4 minutes. As a result, we estimated that the least suitable sample size for rejecting the null hypothesis with 80% power at the = 0.05 level using the Chi-square test for independent samples was 28 individuals in each group. MedCalc® Statistical Software version 19.5.3 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020) was used to calculate sample size.

Randomization and Allocation: A computer-generated random allocation sequence was used to allocate patients into either of the study groups:

Group A: (Dilapan group):

- Group A comprised 28 women whose abortions were initiated with Dilapan-S (Spectrum Pharma, Czech Republic).
- Procedure included vaginal preparation with Povidone Iodine as an antiseptic, then a sterile speculum was placed and the cervical anterior lip was grasped with a ring forceps to choose the suitable Dilapan rod size (3mmx55mm or 4mmx55mm or 4mmx65mm).
- Then the chosen suitable Dilapan-S was inserted into the cervical canal followed by upper vaginal packing with sterile gauze to maintain the dilator in place for 8 hours.

- Then the gauze and the rod were withdrawn and oxytocin infusion was started to achieve adequate uterine contractions till expulsion of contents.

Group B: (Misoprostol group):

- Group B comprised 28 women whose abortions were initiated with Misoprostol (Cytotec 200 microgram tablet, Pfizer).
- Misoprostol was administered through vaginal route with a dosage form 400 microgram / 3-4 hours according to the FIGO misoprostol only recommended regimens 2017 chart, to achieve adequate uterine contractions till expulsion of contents.

Allocation Concealment: Sequentially numbered, opaque and sealed envelopes were used to ensure allocation concealment.

Outcome measures:

Primary outcome: Time interval from start of procedure to start of expulsion of fetus.

Secondary outcomes:

1. Time interval from start of procedure to complete expulsion of uterine content.
2. Incidence of surgical Evacuation for incomplete abortion.
3. Duration of hospital stays.
4. Amount of blood loss.
5. Need for analgesics.
6. Complications as nausea and vomiting, chills, fever and rupture uterus. Fever was defined as a temperature ≥ 37.6°C on two consecutive measurements or ≥ 38.0°C on one measurement and paracetamol was given to women with fever, cramps, or headache.
7. The pain experienced was assessed using a visual analogue scale and the maximum score was recorded.

Failure rate:

In Dilapan group: Failure was considered if dilatation of the cervix could not be achieved, or if there was no response to oxytocin within 36 hours.

In Misoprostol group: Failure was considered if uterine contractions and start of expulsion had not occurred within 36 hours from initiation of therapy.

Ethical Considerations: The patients' data were anonymous. Data presentation was not achieved by the patient's name but by diagnosis and patient confidentiality was protected. An informed consent was taken from all participants, it was in Arabic language and confirmed by date and time. confidentiality was preserved by assigning a number to patients initials and only the investigator knew it

Conflict of interest: the candidate declared that there was no conflict of interest and the cost of the study was paid by the candidate (no funding third-party was available for this study).

Statistical analysis: IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0, IBM Corp., Chicago, USA, 2013, and Microsoft Office Excel 2007 were used to code, tabulate, and statistically analyze the obtained data. The level of significance was set at P value 0.050, which indicates that the data is significant; otherwise, it is not.

RESULTS

78 patients were evaluated for eligibility in this trial, and 56 were accepted (28 in each group). Based on the exclusion criteria, 19 individuals were rejected from this study, while three patients declined to participate.

Finally, the analysis was based on the data of 56 women separated into two groups: Dilapan and Misoprostol.

*No patients were lost during intervention, as all patients were admitted at Ain Shams University Maternity hospital, labor ward.

No significant statistical differences were found between the study groups regarding demographic characteristics; age (p 0.188), body mass index (p 0.149), parity (p 0.979) and gestational age (p 0.647) (not tabulated).

Tab. 1. shows that time interval from start of procedure to start of expulsion of fetus statistically was non-significantly shorter among Dilapan group than among Misoprostol group. **Tab. 2.** shows that time interval from start of procedure to complete of expulsion of fetus in in successful cases was statistically non-significantly shorter among Dilapan group than among Misoprostol group. **Tab. 3.** shows that there was no significant statistical difference between the study groups regarding failure rate.

It is worthy to mention that all failed cases among Dilapan group were attributed to failed response to oxytocin within 36 hours rather than failure of cervical dilatation, as all cases among Dilapan group achieved cervical dilatation after removal of the Dialapan.

Tab. 4. shows There were no significant statistical differences between the study groups regarding incomplete abortion that required surgical evacuation.

There were no statistically significant differences among study groups regarding: (not tabulated)

1. Blood loss volume (p 0.149).
2. Pain experienced assessed by VAS (p 0.106).
3. Need for analgesia, as all patients among studied groups required analgesics.
4. Hospital-stay duration (p 0.341).

Tab. 1. Time interval from start of procedure to start of expulsion of fetus (hours) in successful cases among studied groups.

Measures	Dilapan (N=28)	Misoprostol (N=28)	p-value	Effect size Mean ± SE 95% CI
Mean ± SD	16.1 ± 4.8	17.3 ± 5.2	0.397	-1.1 ± 1.3
Range	8.0–28.0	10.0–28.0		-3.8–1.5

Tab. 2. Time interval from start of procedure to start of expulsion of fetus (hours) in successful cases among studied groups.

Measures	Dilapan (N=20)	Misoprostol (N=18)	p-value	Effect size Mean ± SE 95% CI
Mean ± SD	23.5 ± 4.9	25.9 ± 4.3	0.105	-2.5 ± 1.5
Range	17.0–34.0	19.0–33.0		-5.5–0.5

Tab. 3. Failure rate among the studied groups.

Abortion	Dilapan (N=28)	Misoprostol (N=28)	p-value	Effect size RR (95% CI)
Successful	20 (71.4%)	18 (64.3%)	#0.567	1.39 (0.45–4.29)
Failure	8 (28.6%)	10 (35.7%)		

Tab. 4. Incomplete abortion among the studied groups necessitating surgical evacuation

Abortion	Dilapan (N=28)	Misoprostol (N=28)	p-value	Effect size RR (95% CI)
Incomplete	8 (28.6%)	10 (35.7%)	#0.567	0.72 (0.23–2.22)
Complete	20 (71.4%)	18 (64.3%)		

5. Complications as Nausea (p 0.237), Vomiting (p 0.408) and Fever (p 0.0.592).

DISCUSSION

This Prospective randomized comparative clinical trial was conducted on a total of 56 pregnant women with second trimester abortion at 13 to 18 weeks of gestation with history of previous one cesarean section who were admitted for induction of abortion at Ain Shams University Maternity hospital, labor ward starting from June 2020 till August 2021.

78 patients were evaluated for eligibility in this trial, and 56 were accepted (28 in each group). Based on the exclusion criteria, 19 individuals were rejected from this study, while three patients declined to participate. The analysis was based on the data of 56 women separated into two groups: Dilapan and Misoprostol.

The current study found no statistically significant differences between the study groups in terms of demographic variables such as age, BMI, parity, and gestational age (p values = 0.188, 0.149, 0.979, 0.647) respectively.

According to our findings, the time gap between starting of the intervention and the start of expulsion and the total expulsion of the fetus was statistically non-significantly shorter in the dilapan group than in the Misoprostol group (p value=0.397, 0.105).

Vincienne and his colleagues in 2018 [7] conducted a retrospective study enrolling a total of 270 pregnant women at their second trimester (after 16 weeks) seeking termination of pregnancy (TOP) for medical reasons. He randomized his study groups, where one group used Dilapan-S (164 women) and the other (106 women) not, to study the effectiveness of Dilapan-S in shortening the induction-to-delivery interval (IDI).

In contrast with our results, Vincienne [7] revealed that induction-to-delivery interval (IDI) which started with misoprostol in both groups, was shorter in the Dilapan group (5 h 48 min *vs.* 10 h 18 min in the other, ($p < 0.001$). Vincienne also reported that amniotomy was achieved after the first misoprostol dose more rapidly in the Dilapan group: a mean of 47 min *vs.* 4 h 30 min ($p < 0.001$) and rates of expulsion before 12 and 24 h were more in the Dilapan group: 94.5 and 100%, respectively, *vs.* 68.9 and 91.5% ($p < 0.001$).

Our study procedures differed from that of Vincienne, as patients in our study had no combination regimens of misoprostol and Dilapan, where one group received Dilapan only (in conjunction with oxytocin), while the other received Misoprostol only. This huge difference in our study procedures can explain the difference between our results.

Wilson and his colleagues in 2011 [6] conducted a retrospective observational cohort study evaluating 554 women at their 12 to 18 weeks of gestation, who had a cervical preparation using Dilapan-S or Misoprostol prior to surgical evacuation. Wilson aimed to investigate the safety and efficacy of using misoprostol and Dilapan-S.

Wilson reported that there was no difference in cervical preparation time which is the mean time between agent placement to the start of surgical evacuation between both groups (p=0.17).

Wilson's study, also, differs from our study, as we did not explore the efficacy of Dilapan as a cervical preparing agent prior to surgical evacuation. We aimed to compare its efficacy to Misoprostol in terms of medical abortion rather than the need of surgical intervention.

Chodankar and his colleagues in 2018 [3] conducted a multicentric prospective observational study enrolling 483 women between 6+0 to 24+0 weeks' gestation aiming to investigate the outcomes of using Dilapan-S altogether

with misoprostol as a cervical preparing agent prior to medical or surgical abortion.

Chodankar reported that using adjunctive misoprostol was equivalent to using Dilapan-S followed by misoprostol for the aim of cervical ripening in order to achieve complete medical abortion (p = 0.238).

Our study states that there are no significant statistical differences between the study groups regarding successful abortion and need for surgical evacuation (p value=0.567, 0.149) respectively, with no statistically significant complications (nausea, vomiting, fever rupture uterus and post-abortive bleeding) between the study groups.

In addition, our study reports that both amount of blood loss and hospital stay duration were statistically non-significantly different among the studied groups (p value=0.149, 0.341) respectively.

Our results are approving that forementioned by Vincienne and his colleagues [7] in their study, which revealed that there was no significant statistical difference between the study groups regarding complications during TOP (antepartum hemorrhage, postpartum hemorrhage, rupture uterus; p value=0.54, 0.093, 0.39) respectively, with no significant difference regarding duration of hospitalization (p = 0.31).

Also, Chodankar [3] did not report major side effects with the use of Dilapan-S, and this also implies women with a previous caesarean section scar. Infection was reported in 0.9% of patients with no causal relationship established with the use of Dilapan less than 24 hours [8].

On the contrary, Wilson and his colleagues [6] revealed that eight complications during the study period (excessive bleeding, incomplete abortion and cervical laceration) were recorded in women who received cervical preparation, though, these complications occurred with no statistically significant difference between the use of misoprostol or the use of Dilapan (p value=0.32), and this also agree with our study results.

Our results revealed that the pain experienced was statistically non-significantly different among the studied groups (p value=0.106) and all the studied cases of both groups needed analgesics.

Vincienne and his colleagues [7] revealed that Dilapan shortens induction to delivery interval as before mentioned, However, they reported increase in pain experience, this was explained that Dilapan intracervical placement was painful, this in addition to painful contractions which started at the night of placement. This is not in harmony with our results, however as mentioned before, we attribute these differences to different study procedures between both studies.

Samuel and his colleagues in 2009 [8] conducted a pilot study recruiting 26 patients to study pain experience difference between 2 groups, one group receiving Dilapan-S as cervical preparing agent in conjunction with misoprostol while the other receive mifepristone altogether with misoprostol.

Samuel reported that Dilapan-S and misoprostol combined use reduces the pain experienced with medical abortion. This does not approve our finding as regard pain experience associated with Dilapan use which didn't show statistically significant improvement compared to misoprostol, however, again here study procedures are different, and sample size in smaller in Samuel's study.

It is worthy to mention, that the strength points of our study are that it is a prospective rather than retrospective study, designed as a randomized clinical trial rather than an observational one. Also, to our knowledge, it is the first study in Egypt to assess and compare efficacy of Dilapan-s vs misoprostol as cervical ripening agent in second trimester abortion with scarred uterus.

It is also important to mention that our study had some limitations, including relatively small sample size in comparison to previous studies, not encompassing multi-centers, and this represents a significant risk of publication bias. But it is important to know that pandemic covid-19 limited the availability of women involved in this research study attending our hospital.

CONCLUSION

Dilapan is an insignificant agent for cervical ripening prior to abortion induction when compared to misoprostol regimens. The current study adds to the body of knowledge and sheds some insight on future prospective studies with bigger sample sizes that demonstrate the efficacy of dilapan for cervical preparation for medical and surgical abortions.

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