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Use of hyoscine as an adjuvant treatment on shortening the time of abortion induction in second trimester: randomized controlled clinical trial

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ABSTRACT

Objective. The aim of this study was to determine whether using hyoscine as an adjuvant treatment with vaginal misoprostol versus vaginal misoprostol only in the induction of abortion in the second trimester can shorten the time of abortion and therefore the duration of hospital stay.

Materials and Methods. This study was a randomized controlled trial conducted on 40 women underwent induction of abortion between 13 and 24 weeks with positive foetal pulsation during the period from December 2022 until June 2023. Patients were randomized into two equal groups as follows: group I included 20 patients who were given only vaginal misoprostol 400 μg, and group II included 20 patients in which women were given vaginal misoprostol 400 μg plus intramuscular administration of hyoscine N-butyl bromide.

Results. There was a statistically significant shorter mean time of abortion induction (hours) of 19.00±8.95 with a P-value ($p = 0.029$) and hospital stay (days) of 1.65 ± 1.13 with a P-value ($p = 0.031$) in the intervention group compared to the control group 35.48 ± 16.60 and 2.85 ± 1.43 respectively. According to oxytocin infusion, there was a higher frequency of oxytocin infusion in the control group of 4 women (20%), while there was no oxytocin infusion in the intervention group, with a P-value ($p = 0.035$).

Conclusions. In comparison to misoprostol alone, we found that hyoscine N-butyl bromide plus misoprostol significantly shortens the time required to induce an abortion in the second trimester without the requirement for an oxytocin infusion and reduces the length of hospital stay.

INTRODUCTION

Induction of abortion (IOA) is done in pregnant women due to medical causes or foetal disorders. Currently, severe anatomical, metabolic, or mental abnormalities are the most common indications for it. Failure of abortion induction in the presence of an unripened cervix may lead to surgical termination of the pregnancy. Therefore, the use of prostaglandins is helpful for cervical ripening [1].
Cervical dilatation and effacement are the two main factors that determine the duration of labour. Mecha-

nical, pharmacological, and non-pharmacological factors can facilitate cervical dilatation. Prostaglandins, oxytocin, analgesics, and smooth muscle relaxants are examples of pharmacological agents [2].
Misoprostol, a prostaglandin E1 analogue, has gained popularity as an IOA agent in recent years [3-4]. Misoprostol has some potential benefits over other prostaglandins. It is stable at room temperature, cheap, and can be given orally, vaginally, sublingually, and buccal. To this day, no unique dosage or administration method has been recorded without causing such side effects [4-5].
Hyoscine N-butyl-bromide (HBB) belongs to the parasympatholytic group of drugs and is an effective antispasmodic drug without the untoward side effects of atropine [6]. Hyoscine with misoprostol may also reduce the duration of abortion induction due to increased cervical dilatation. According to prior studies, due to its spasmolytic effect and effectiveness on cervical dilatation, hyoscine is effective in reducing active labour duration. Use of hyoscine in doses up to 30 mg, has no significant side effects [1].
The aim of this study was to evaluate the effect of misoprostol in combination with hyoscine, compared with misoprostol alone in reducing the duration of abortion induction and shortening induction delivery interval.

MATERIALS AND METHODS

Study design

This study was a randomized controlled trial conducted on 40 women with positive foetal pulsation during the period from December 1, 2022, to June 30, 2023, at Ain Shams University Maternity Hospital in Egypt to determine whether using hyoscine as an adjuvant treatment with vaginal misoprostol versus vaginal misoprostol only in the IOA in the second trimester can shorten the time of abortion and therefore the duration of hospital stay, as well as the total dose of misoprostol used in the induction.

Population

A total of 75 women were recruited and evaluated for eligibility to participate in the study. Twenty patients did not fit the criteria for inclusion, and fifteen patients declined the intervention for religious reasons or because they were unwilling to participate in the study. The computer-generated system randomly assigned forty eligible patients, meeting our inclusion criteria, in a single-blind fashion to one of two treatment arms. The following criteria had to be met for a woman to be eligible: she had to be between 13 and 24 weeks gestational age (confirmed by the patient's last menstrual period or serial ultrasound if she did not have sure dating) with a singleton living fetus (confirmed by pregnancy ultrasound before IOA), and if she had a surgical history of one or two previous cesarean sections only. We excluded all women who had abortions between 13 and 24 weeks with no fetal pulsation, multiple gestations, uterine anomalies, or who had had more than two caesarean sections (**Figure 1**).
After taking informed written consent, the recruited patients were subjected to a detailed history taking and thorough examination, including a pelvic examination to assess cervical dilatation, effacement, consistency, and any other pelvic abnormalities. In addition, laboratory tests, including a complete blood picture, blood group, and urine analysis, were performed. Ultrasound was done transabdominally using a MEDISON R5 ultrasound machine equipped with a 3.5 MHz convex probe to evaluate the foetal biometry, placental site, foetal weight, congenital foetal malformation (CFMF), and amount of liquor.
The sample size was calculated using the PASS 11 program for sample size calculation, setting power at 80% and alpha error at 0.05. It is estimated that a sample size of 20 women per group can detect the difference between two groups regarding time

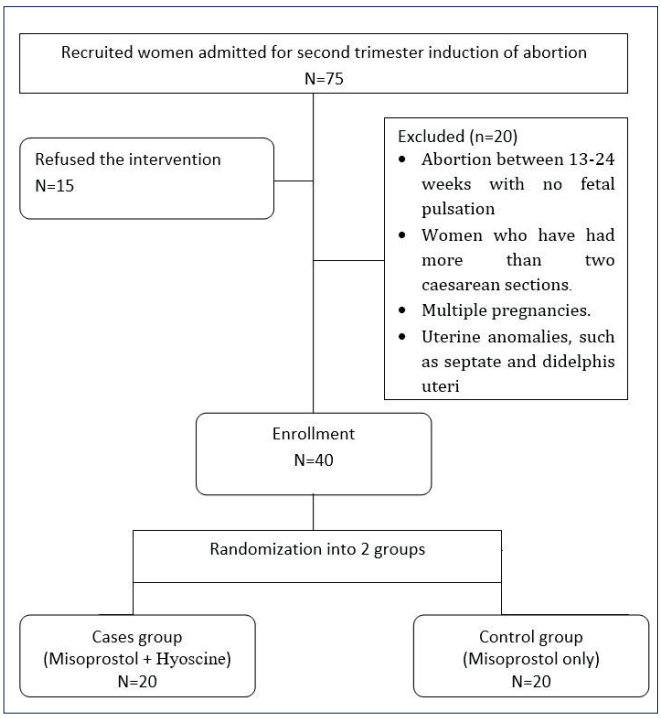

Figure 1. *Flow chart of the study.*

to abortion, assuming that time in the intervention group is 653.38 + 80.386 min and time in the control group is 726.29 + 64.56 min.

Patients were randomly assigned to two groups: group I (the control group) received only vaginal misoprostol 400 μg (Misotac, manufactured by Sigma Pharmaceutical Company), and group II (the intervention group) received vaginal misoprostol 400 μg (Misotac) with intramuscular administration of 20 milligrams of hyoscine N-butyl bromide (Spasmofen ampoule, manufactured by Amarya Company). Misoprostol was administered every 4 hours to both groups for a maximum of five doses per day. Supervisors and expert staff supplied the repeated doses, evaluated the patients, and conducted the abortions. Neither the women nor the staff knew whether the patient under observation had been assigned to misoprostol alone or with hyoscine N-butyl bromide. The end point of the study was the initiation of abortion.

The allocation concealment mechanism uses consecutive numbers on opaque sealed envelopes with a letter of "A" or "B" according to the sequence generated through the computer sequentially numbered opaque sealed envelope system, with each envelope containing a letter corresponding to a number in the randomization list. Participating women were allocated to each group according to the letter inside the envelope.

Statistical methods

Recorded data were analysed using the statistical package for social sciences, version 23.0 (SPSS Inc., Chicago, Illinois, USA). The quantitative data were presented as mean± standard deviation and ranges when their distribution was parametric (normal), while non-normally distributed variables (non-parametric data) were presented as median with inter-quartile range (IQR). Also, qualitative variables were presented as numbers and percentages. Data were explored for normality using the Kolmogorov-Smirnov and Shapiro-Wilk tests.

The following tests were done:

The independent-samples t-test of significance was used when comparing between two means, and the Mann-Whitney U test was used for two-group comparisons in non-parametric data.

The comparison between groups with qualitative data was done by using the Chi-square test and Fisher's exact test instead of the Chi-square test only when the expected count in any cell was less than 5.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as follows:

Probability (P-value)

- A P-value < 0.05 was considered significant.
- A P-value < 0.001 was considered highly significant.
- A P-value > 0.05 was considered insignificant.

Table 1. *Baseline characteristics.*

Baseline characteristics	Control group (n = 20)	Intervention group (n = 20)	Test value	P-value	Sig.
Age (years)					
Mean ± SD	27.00 ± 6.87	26.25 ± 4.42	0.168	0.684	NS
Range	15-39	20-36			
Gestational age					
Mean ± SD	18.05 ± 2.84	18.65 ± 3.05	0.416	0.523	NS
Range	13-23.7	12.7-24			
Gravidity					
Median (IQR)	3 (1-3)	3 (1-3)	0.112	0.740	NS
Range	0-9	1-7			
Parity					
Median (IQR)	2 (0-2)	2 (0-2)	1.442	0.237	NS
Range	0-4	0-3			
Number of caesarean sections					
Median (IQR)	1 (1-1)	2 (2-2)	1.519	0.101	NS
Range	1-2	1-2			
Number of vaginal deliveries					
Median (IQR)	2 (1-3)	2 (1-3)	0.036	0.854	NS
Range	1-4	1-3			

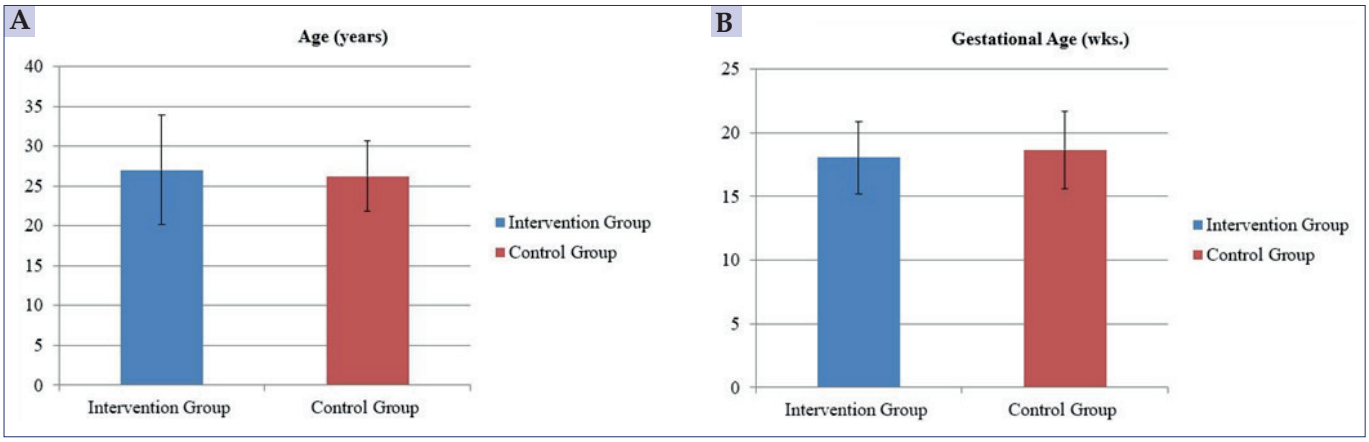

Figure 2. ***(A)*** *Comparison between the intervention group and the control group according to age (years);* ***(B)*** *Comparison between the intervention group and the control group according to gestational age (wks.).*

Table 2. *The most common causes of induction of abortion in the second trimester.*

	Control group (n = 20)	Interven-tion group (n = 20)	Test value	P-value	Sig.
Anhydramnios	11 (55.0%)	9 (45.0%)	6.112	0.548	NS
CFMF	7 (35.0%)	11 (55.0%)	0.406	0.524	NS
Heart Failure	1 (5.0%)	0 (0.0%)	1.000	0.317	NS
HELLP Syndrome	1 (5.0%)	0 (0.0%)	1.000	0.317	NS

Table 3. *Number of doses of Misotac.*

	Control group (n = 20)	Intervention group (n = 20)	Test value	P-value	Sig.
Number of doses of Misotac (Tabs)					
Median (IQR)	6 (3-10)	6 (4-12)	1.223[a]	0.276	NS
Range	1-15	2-24			

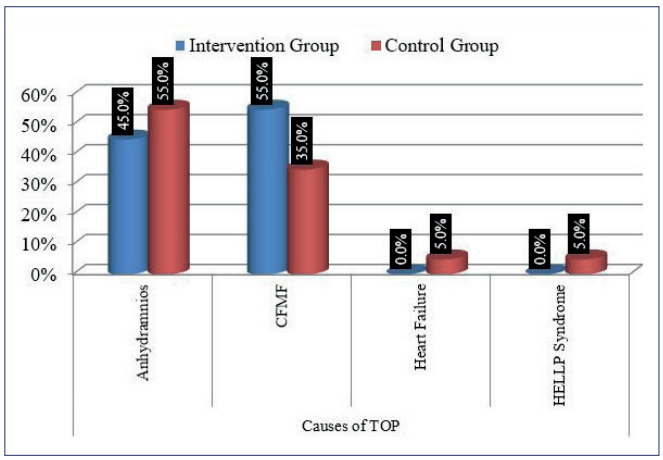

Figure 3. *Comparison between the intervention group and the control group according to causes of TOP.*

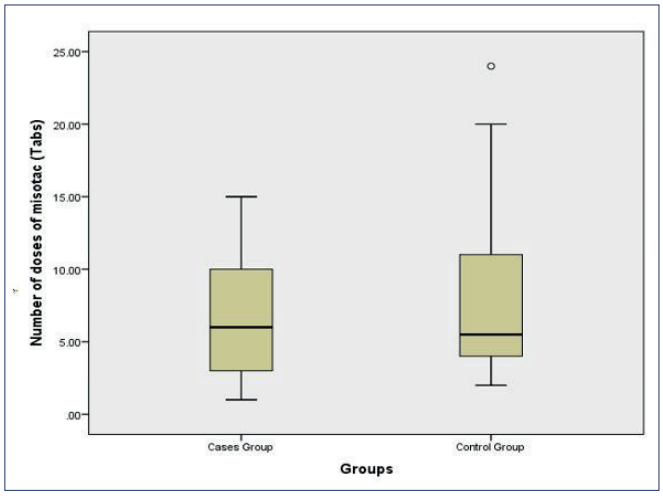

Figure 4. *Box plot between the intervention group and the control group according to the number of doses of misotac (tabs).*

RESULTS

Baseline characteristics are summarized in **Table 1** and **Figure 2A,B**. This table shows no statistically significant difference between groups according to demographic data about age (years), gestational age (weeks.), gravidity, parity, number of caesarean sections, and number of vaginal deliveries, with a P-value > 0.05.

The most common causes of induction of abortion in the second trimester are summarized in **Table 2** and **Figure 3**: anhydramnios in 20 women (50%), including 9 patients (45%) in the intervention group compared to 11 patients (55%) in the control group; CFMF in 18 women (45%), including 11 patients (55%) in the intervention group compared to 7 patients (35%) in the control group; and medical causes in 2 patients (10%) in the control group. There was no statistically significant difference between the two groups with a P-value > 0.05.

Table 4. *Time of abortion induction, hospital stay, and oxytocin infusion.*

	Control group (n = 20)	Intervention group (n = 20)	Test value	P-value	Sig.
Time of abortion induction (hrs)					
Mean ± SD	19.00 ± 8.95	35.48 ± 16.60	2.859	0.029[a]	S
Range	3-60	9-120			
Hospital stays "days"					
Mean ± SD	1.65 ± 1.13	2.85 ± 1.43	2.335	0.031[a]	S
Range	1-8	0-10			
Oxytocin infusion					
No	20 (100.0%)	16 (80.0%)	4.444	0.035[b]	S
Yes	0 (0.0%)	4 (20.0%)			

Regarding Misotac doses, **Table 3** and **Figure 4** show that the higher median value of the number of doses of Misotac (Tabs) in the control group was 6 (4-12) compared to the intervention group was 6 (3-10), but there was an insignificant difference between the groups, with a P-value > 0.05.

In **Table 4** there was a statistically significant higher mean value for time of abortion induction (calculated from the initiation dose of drugs up to the descent of the foetus) in the control group was 35.48 ± 16.60 compared to the intervention group was 19.00 ± 8.95, with P-value (p = 0.029) (**Figure 5A**), for hospital stay "days" in the control group was 2.85 ± 1.43 compared to intervention group was 1.65 ± 1.13, with P-value (p = 0.031) (**Figure 5A**), and for oxytocin infusion in the control group was 4 women (20%), while there was no oxytocin infusion in intervention group, with P-value (p = 0.035) (**Figure 5C**).

With regards to complications of IOA (**Table 5**), during the study there were no complications like uterine rupture, as we were very strict with the FIGO recommendation of misoprostol doses for induction of abortion [7-8]. Reports of adverse effects of misoprostol include nausea (**Figure 6A**), affecting approximately 35% of women in each group with a P-value of p = 1, fever (**Figure 6B**), affecting about 30% of women in the control group and 35% in the intervention group with a P-value of p = 0.736, diarrhoea (**Figure 6C**), affecting approximately 30% of women in each group with a p-value of p = 1, abdominal pain, and headache, all of which are dose-dependent. In pregnant women, shivering and fever are more commonly reported side effects [9]. Fever up to 38.50 °C is associated with a higher dose of misoprostol, shorter intervals, and oral or sublingual routes. However, fever is transient and easily disappears after cooling and

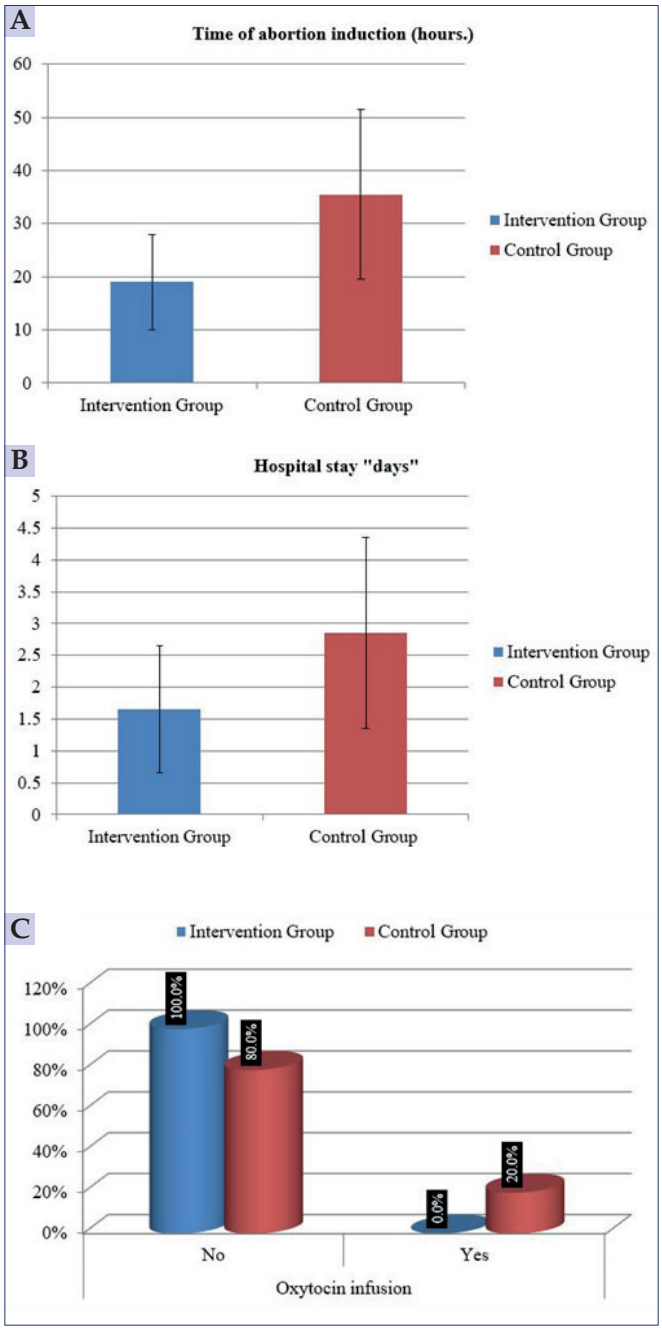

Figure 5. ***(A)*** *Comparison between the intervention group and the control group according to time of abortion induction (hours);* ***(B)*** *Comparison between the intervention group and the control group according to hospital stay;* ***(C)*** *Comparison between the intervention group and the control group according to oxytocin infusion.*

antipyretics. Diarrhoea is another common adverse reaction; fortunately, it is mild and self-limited even without any management [9-10].

DISCUSSION

IOA should be used when the benefits of abortion outweigh the risks of continuing, for example, in the setting of maternal or foetal medical compli-

Table 5. *Complications and adverse effects of misoprostol.*

	Control group (n = 20)	Intervention group (n = 20)	Test value	P-value	Sig.
Nausea					
Yes	7 (35.0%)	7 (35.0%)	0.000	1.000	Ns
No	13(65.0%)	13 (65.0%)			
Fever					
Yes	7 (35.0%)	6 (30.0%)	0.114	0.736	NS
No	13(65.0%)	14(70.0%)			
Diarrhoea					
Yes	6 (30.0%)	6 (30.0%)	0.000	1.000	NS
No	14 (70.0%)	14(70.0%)			

cations or multiple CFMFs incompatible with life. These decisions should always be made in conjunction with the patient and their preferences. In the current study, the characteristics of the patients were nearly similar in both arms of the study. This excludes the possibility of the presence of any confounding factors that might affect the study results and interpretation. Our findings as regards the time of abortion induction (hours) are significant. It was less in intervention group compared with control group (19.00 ± 8.95 min, with 35.48 ±**1** 6.60 min) (P-value was < 0.029) and also the length of hospital stays (1.65 ± 1.13, with 2.85 ± 1.43) (P-value was < 0.031), but in oxytocin infusion there was a statistically significant higher frequency in control group, while there is no oxytocin infusion in intervention group (P-value was < 0.035).

There was not any significant result regarding causes of induction of abortion, ultrasound findings, medical or obstetrics condition related to the current pregnancy or Misotac doses.

In our study, we found that there was significant difference between abortion induction time in both groups. This agrees with Javadi *et al.* [1] who compared the effect of misoprostol in combination with hyoscine versus misoprostol alone in reducing the duration of abortion induction in a clinical trial on 126 pregnant women with gestational age below 20 weeks elected for abortion.

They found the mean duration of abortion induction in intravenous (IV) administration of 20 mg Hyoscine with 400 μg vaginal misoprostol represented statistically significant decrease compared with misoprostol (653.38 ± 80.386 min, with 726.29 ± 64.56 min) ($p \leq 0.001$).

To the best of our knowledge, no other studies (apart from the one mentioned above in the previous paragraph) have been conducted on the use of hyoscine to induce second-trimester abortion. Other studies, however, have found that hyoscine is effective in the first, second, and third phases of labour.

Our findings were consistent with those of Maged *et al.* [11], who conducted a study on 120 primigravida admitted in active labor stage and divided wo-

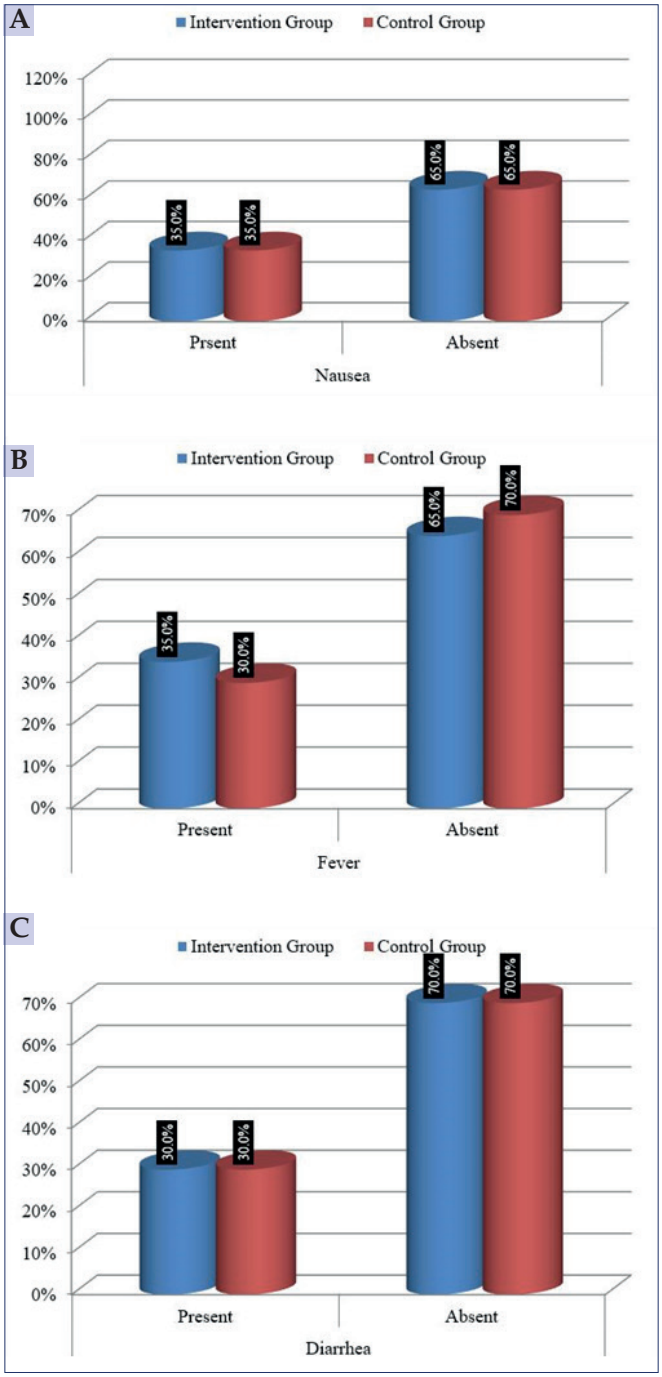

Figure 6. ***(A)*** *Comparison between the intervention group and the control group according to nausea;* ***(B)*** *Comparison between the intervention group and the control group according to fever;* ***(C)*** *Comparison between the intervention group and the control group according to diarrhoea.*

men into three equal groups. A single dose of the medication (placebo, HBB 20 mg, or HBB 40 mg) was administered slowly intravenously to groups A, B, and C, respectively.

The duration of the first stage was calculated from the time of cervical dilatation of three to four centimetres in active labour until the cervix was fully dilated. Women who received 20 or 40 mg of HBB had significantly shorter first stage durations compared to control women (187.73 ± 20.92, 186.41 ± 19.40 *vs* 231.39 ± 33.14 minutes).

Another study by Imaralu *et al*. [12] was conducted on a randomized double-blind placebo-controlled clinical trial involving 160 participants who received either intravenous Hyoscine butyl-bromide (20 mg in 1 ml; n = 80) or intravenous normal saline (1 ml; n = 80).

The mean duration of the active phase of labour was significantly shorter in the HBB group (365.11 ± 37.32 min, range = 280-490) than in the control (placebo) group (388.46 ± 51.65 min, range = 280–525) [mean difference 23.35 min, 95%CI -37.43 to -9.27, p = 0.001].

However, no significant differences were observed in the durations of the second and third stages of labour (20.46 ± 10.46 *vs* 23.38 ± 18.95 min, p = 0.43 and 8.96 ± 4.34 *vs* 9.23 ± 5.92 min, p = 0.75), respectively, between the 2 groups.

These results agree with a lot of studies about the effect of hyoscine-N-butylbromide on labour progress, *e.g*., a systemic review of three RCTs (Kandil *et al*., Barau *et al*., Ibrahim *et al*. [13-15] found a dosage of 20 mg HBB decreased the duration of the first stage of labour by 64.74 min; MD: -64.74, 95%Ci -67.97 to -61.50).

In addition, Sfregola *et al.* [16] investigated the effect of gestational age (days), maternal age (years), BMI (kg/m^2), and foetal weight on induction success of labour and stated that age and BMI results were associated with the risk of oral misoprostol induction failure. The age reported an odds ratio (OR) of 0.795 (95%CI 0.679-0.931) per each year of increased age for induction success; similarly, BMI reported an OR of 0.857 (95%CI 0.737-0.997) per each unit of BMI for induction success.

Furthermore, Etrusco *et al*. [17] conducted another study to evaluate the effect of maternal age and body mass index (BMI) on oral misoprostol induction of labour for late-term pregnancies. The study population was investigated by dividing patients based on age and BMI. The data of the study population was analysed by dividing it into two groups based on the cutoff of 35 years. Seventy-one women were > 35 years old, while 32 women were ≥ 35 years old. This analysis showed no statistically significant differences between the two analysed populations for all the investigated maternal-foetal variables.

Based on BMI, the study population was divided into two groups according to the diagnosis of obesity (BMI ≥ 30; n = 53) or non-obesity (BMI > 30, n = 51): obese women showed a longer time between the last dose of misoprostol and cervical dilation of 6 cm (p = 0.01), a longer time between the last dose of misoprostol and delivery (p = 0.04), and a higher rate of grade II vaginal lacerations (p = 0.02), whereas no significant differences were found for the other maternal-foetal variables. The practical implication of this study is that HBB can be combined with misoprostol in the induction of second-trimester abortion to reduce the time required to induce abortion and allow the patient to be discharged from the hospital without wasting time or money.

Study strength and limitations

The strength of the current study is that it is one of the few randomized controlled studies to address the use of hyoscine N-butyl bromide as an adjuvant treatment with vaginal misoprostol in the induction of abortion in the second trimester, thereby reducing abortion time and subsequently the length of hospital stay.

Furthermore, it is a prospective, randomized, controlled clinical trial with a low percent of bias. Every effort was made to ensure that all follow-up data were accurate, and only complete information was used in the data analysis. All clinical assessments, sonographic measurements, deliveries, and assessments of study outcomes were done by the same team.

Our study has limitations, including the legal and religious prohibition on terminating a pregnancy without medical reasons. Other approaches, such as mechanical routes, were not explored.

Future study perspectives and recommendations

We recommend complementary studies to evaluate more than one method, whether pharmacological or mechanical, in IOA to establish the best model to be used safely in clinical practice and validate the contradictory findings as regards the use of hyoscine in IOA.

CONCLUSIONS

This study was a randomized controlled trial to evaluate the effectiveness of hyoscine N-butyl bromide as an adjuvant treatment with vaginal misoprostol versus vaginal misoprostol only in the induction of abortion in the second trimester on shortening the time of abortion and therefore the duration of hospital stay. We found that a combination of misoprostol and hyoscine N-butyl bromide achieves a significant shortening in the time of abortion induction in the second trimester and period of hospital stay compared to misoprostol alone with no oxytocin infusion needed.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution
M.A.O.: Validation, supervision, visualization. M.E.A.: Conceptualization, data curation, investigation, methodology, validation, supervision, visualization, writing – review & editing. A.N.S.: Writing - original draft, writing - review & editing, methodology. R.G.E.: Conceptualization, data curation, formal analysis, investigation, methodology, writing – original draft.

Funding
None.

Study registration
Our study was registered on Clinicaltrial.gov. with the following number: NCT06207539.

Disclosure of interests
The authors declare that they have no conflict of interests.

Ethical approval
The study was approved by the Ethics Committee of the Department of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, with the following number: FMASU MS 714/2022. The research protocols used in this research were approved by the ethical standards of the responsible institution for human subjects and in accordance with the Declaration of Helsinki.

Informed consent
Informed written consent was obtained from all participants before recruitment for the study and after explaining the purpose and procedures of the study.

Data sharing
Data are available under reasonable request to the corresponding author.

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