The Effect of a Single Preoperative Dose of Sublingual Misoprostol in Reducing Intraoperative Blood Loss After Total Abdominal Hysterectomy: A Single-Blind Randomized Controlled Trial

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Introduction

A total abdominal hysterectomy (TAH) is one of the most common gynecological surgeries in the world. It is estimated that 45% of women under 65 years of age have experienced hysterectomies (1). According to the world health report (WHR) published in 2002, a total of 146,422 women had undergone hysterectomies in Iran (2). This surgery is performed with a variety of approaches, such as abdominal, vaginal, or laparoscopic surgery. Hemorrhage requiring a blood transfusion is one of the complications of this surgery, which occurs in 2 to 12% of cases (3-5).

Different methods have been used to reduce blood loss during a TAH. One of the most commonly used methods is a preoperative prescription (for a few months before the surgery) of gonadotropin-releasing hormones (GnRH and mifepristone) that are effective in reducing the size of the vasculature (6). However, significant side effects, such as flushing and osteoporosis, have also been reported after use. Furthermore, the cost of the GnRH hormone is high (7, 8). A vasopressin injection in the lower parts of the uterus has also been used for this purpose, which, despite its favorable results, was associated with severe complications (9-11).

ABSTRACT

Background & Objective: Postoperative hemorrhage is one of the most frequently cited complications of total abdominal hysterectomy (TAH). This study aimed to investigate the effect of a single preoperative dose of sublingual misoprostol on reducing blood loss during total abdominal hysterectomies.

Materials & Methods: This study was a single-blind randomized controlled trial (RCT). The statistical population included all women who were candidates of hysterectomy in 2017 and 2018. A total of 132 patients were randomly selected and classified into two groups of misoprostol (N=66) and placebo (N=66). Examining intraoperative blood loss was considered a primary outcome. Moreover, levels of hemoglobin before and 24 hours after the surgery, the need for a blood transfusion, febrile morbidity, and the duration of hospitalization were regarded as secondary outcomes. The means of bleeding in the two groups were compared using a t-test.

Results: There were no significant differences between the two groups in the baseline characteristics (P>0.05). After the surgery, the mean of hemoglobin values was lower in the placebo group compared to the misoprostol one, and this difference was statistically significant (P<0.001). There was a significant difference in intraoperative blood loss between the two groups, and it was significantly higher in the placebo group (P<0.001).

Conclusion: Taking a single preoperative dose of sublingual misoprostol is effective in reducing intraoperative blood loss after total abdominal hysterectomies. Additionally, this intervention led to a decline in hemoglobin.

Keywords: Misoprostol, Hysterectomy, Post Hysterectomy Hemorrhage, Randomized Controlled Trial
caused by long-term use of non-steroidal anti-inflammatory drugs (12), but also applies as a treatment for uterine atonic. However, studies have also confirmed its crucial role in reducing postpartum hemorrhage and bleeding after undergoing surgical procedures (13). Misoprostol can lead to a direct contraction of the vessels in the uterus (14), and this feature is most likely to be useful in reducing blood loss during a TAH. In addition to the low cost of this drug, it accompanies with few side effects (15). This drug is used in different doses to prepare the cervix before a dilatation, during a dilatation, a curettage or hysteroscopy. Unlike drugs, such as methionine and carboprost, misoprostol can also be prescribed to women with hypertension and asthma (16).

Although the oral form of this drug has a stronger and faster effect (15), recent pharmacological studies have shown that bioavailability of sublingual misoprostol was higher than oral, rectal, and vaginal misoprostol (17). As far as the researchers investigated, no studies have been carried out to investigate the effect of misoprostol on bleeding during a hysterectomy in Iran yet. Therefore, this study aimed to evaluate the effect of a single dose of sublingual misoprostol before a hysterectomy on reducing intraoperative blood loss.

Materials and Methods

The present study was a single-blind randomized controlled trial (RCT). The population of the study included all women who were candidates for having abdominal hysterectomies due to benign gynecologic diseases in two hospitals of Tehran, Iran (Rasoul-e-Akram and Firoozgar Hospitals) between 2017 and 2018. The indications were the same for all of participants. The inclusion criterion was women who were candidates for undergoing abdominal hysterectomies due to benign gynecologic diseases. Moreover, women who were not able to take misoprostol due to such reasons as mitral stenosis, cardiovascular diseases, glaucoma, sickle cell anemia, severe hypertension, diastolic pressure higher than 100 mm/hg, severe asthma, and known sensitivity to prostaglandin, were excluded from the study. In addition, patients with known history of pelvic endometriosis or active internal disease, diabetes, obesity (BMI>30), previous myomectomies, and preoperative GnRH agonists and patients with invasive endometrial cancer, cervical cancer, and ovarian tumors were excluded from the study.

Based on previous studies conducted on women who underwent TAHs, the mean blood loss during TAHs was 510 mL (9). Therefore, for a 90% confidence level and a significance level of 5%, the required sample size was calculated to include at least 132 women (66 people per group).

Randomization Method

The patients were divided into two groups using a permuted block randomization (PBR). To create random sequences in a randomized block approach, the following website was used: https://www.sealedenvelope.com. Non-transparent envelopes were also used to hide the allocation concealment such that the type of intervention was written on some cards. The cards were then sealed inside the non-transparent envelopes. For each envelope, in accordance with the random sequence created, a number (code) was defined and placed on the envelope.

Intervention

The patients were randomly assigned to either the misoprostol group or the placebo one. In the misoprostol group, a 200-microgram tablet of misoprostol was sublingually prescribed an hour before the surgery. Meanwhile, a vitamin B6 tablet was sublingually prescribed an hour before the operation to the patients in the control group (placebo). The patients were blinded concerning the type of intervention.

Outcomes

The primary outcome included measuring intraoperative blood loss by calculating the collected blood in the suction bottles and the difference in the number of wet gas. The duration of the surgery was derived from the time of incision until the end of suturing the skin. Additionally, levels of hemoglobin were recorded before and 24 hours after the surgery. Moreover, febrile morbidity, the need for a blood transfusion, and the duration of hospitalization were examined as secondary outcomes in both the intervention and placebo groups using a predesigned questionnaire. The researchers performed all the surgeries.

Other Variables

Age, sex, and BMI were also measured.

Ethical Considerations

The IRI’s Committee on Ethics ratified this research plan under the following code: IR.IUMS.FMD.REC 1396.9311290001. This study was also registered at the Iranian Clinical Practice Center. Initially, the main objectives and methods of implementing this study were explained to the patients. A written consent letter was obtained from all participants. In the event of any side effects, all stages of the treatment were taken place for the patient. All patient information remained confidential. At all stages of conducting this study, the researchers followed the principles of the Helsinki Treaty and the Ethics Committee of Iran University of Medical Sciences. Also, IRCT registration code is “IRCT20180821040844N1”.

Statistical Analyses

Frequencies and percentages were used to characterize the qualitative variables, and for the quantitative variables, standard deviations were applied. A Chi-square test was used to compare qualitative variables, and an independent t-test was employed to examine the means of the two groups. P-value<0.05 was considered a significant level.
Data were analyzed using SPSS 22 (SPSS Inc., Chicago, Illinois, USA).

**Results**

A total of 132 people entered the study (66 (50%) intervention and 66 (50%) placebo). The mean age of the intervention group was 43.72 years (with a standard deviation of 6.33), and the mean age of the placebo group was 44.8 (with a standard deviation of 6.61). The difference in the mean age of the two groups was not statistically significant ($P=0.35$). There was no significant difference between the two groups regarding body mass index (BMI) and hemoglobin before the surgery (Table 1).

| Table 1. The basic information of the participants in the study (sample size=132) |
|-----------------------------------------------|-----------------|-----------------|---------------|
|                      | Misoprostol | Placebo | $P$-value |
| Age (year)            | 43.72±6.63   | 44.80±6.61     | 0.35         |
| Body mass index (BMI) | 25.12±3.35   | 24.48±2.51     | 0.22         |
| Duration of the surgery (minute) | 138.71±34.15 | 144.24±36.95 | 0.36         |
| Hemoglobin before the surgery (mg/dl) | 11.42±0.91   | 11.57±0.77     | 0.31         |

The results showed that the mean postoperative hemoglobin concentration in the patients was 10.43 mg/dl in the misoprostol group and 9.69 mg/dl in the placebo one. The results of the t-test demonstrated that the difference in the mean hemoglobin levels of the two groups was statistically significant ($P<0.001$). Furthermore, there was a statistically significant difference in the level of hemoglobin changes between the misoprostol and placebo groups and the hemoglobin level declined more in the placebo group ($P<0.001$).

The intraoperative blood loss in the intervention group (misoprostol) was 312.98 mL and it was 448.63 mL in the placebo group. Comparing these two values, yielded that the observed difference was statistically significant ($P<0.001$) (Table 2). However, the results indicated that there was no statistically significant difference in the duration of hospitalization between the two groups ($P=0.44$).

As shown in Table 3, there was no significant difference in the need for a blood transfusion between the misoprostol and placebo groups ($P=0.46$). Also, the incidence of fever was 10.6% in the misoprostol group and 9.1% in the placebo one. There were no significant differences between the two groups in this regard ($P=0.46$).

| Table 2. The comparison of the mean postoperative hemoglobin, hemoglobin changes, blood loss and the duration of hospitalization between the two intervention and placebo groups |
|-----------------------------------------------|-----------------|-----------------|---------------|
|                      | Misoprostol | Placebo | $P$-value |
| Postoperative hemoglobin (mg/dl) | 10.43±0.88   | 9.69±0.81     | <0.001       |
| Hemoglobin changes (mg/dl) | -0.99±0.57   | -1.88±0.29     | <0.001       |
| Blood loss (mL)          | 312.98±149.83 | 448.63±130.22 | <0.001       |
| Duration of hospitalization (day) | 4.59±1.30   | 4.74±1.26     | 0.45         |

| Table 3. The comparison of the frequency of blood transfusion and the incidence of fever in the patients in the two groups using the Chi-square test |
|-----------------------------------------------|-----------------|-----------------|---------------|
|                      | Misoprostol (66 people) | Placebo (66 people) | $P$-value |
| Blood transfusion | Yes | 3 (5.4%) | 5 (7.6%) | 0.46 |
|                    | No  | 63 (95.6%) | 61 (92.4%) |
| Fever              | Yes | -7 (10.6%) | 6 (9.1%) | 0.77 |
|                    | No  | 59 (89.4%) | 60 (90.9%) |
Discussion

Overall, the results of the present study indicated that the use of a single dose of sublingual misoprostol before a hysterectomy significantly reduced intraoperative blood loss. Furthermore, the patients’ hemoglobin levels decreased significantly after the hysterectomy.

Similar to the results of the current study, the results of a study conducted by Biswas et al. showed that prescribing sublingual misoprostol significantly reduced blood loss during TAHs compared with a placebo group. Moreover, the mean postoperative hemoglobin concentration in the misoprostol group was higher than the placebo one, and postoperative hemoglobin loss was lower in the misoprostol group (18). These results are consistent with the results of the present study.

Another study examined the effect of misoprostol on lessening bleeding after a hysterectomy. Contrary to the results of the present study, the results yielded that the preoperative dose of misoprostol did not have a significant effect on reducing intraoperative bleeding (6). This might be due to the low sample size in the mentioned study compared to the present study, which could affect the statistical significance of the results.

In other studies, although the direct effect of sublingual misoprostol on postoperative bleeding has not been investigated, the effect of this drug on reducing intraoperative bleeding has been investigated in the studies related to gynecological surgery. In this regard, a study carried out by Soleimani et al. demonstrated that sublingual misoprostol was effective in preventing bleeding during cesarean sections such that the decline in the hemoglobin and hematocrit levels of the misoprostol group were significantly lower than those of the placebo group. Moreover, there was no significant difference between the two groups regarding the need for a blood transfusion and the incidence of medication-attributed adverse effects (19). These results are in line with the results of the current study, which yielded the effect of misoprostol on reducing intraoperative bleeding. Similar to our study, the mentioned study showed that this reduction in bleeding did not lessen the need for a blood transfusion (19). In another study, the positive effect of misoprostol on the reduction of bleeding during myomectomies was confirmed. Moreover, the results of this study showed that the hemoglobin levels were significantly higher in the misoprostol group 6 hours after the surgery. However, this difference was not significant after 24 hours. Additionally, there was no difference in the need for a postoperative blood transfusion between the groups (20).

In another study, the effects of sublingual misoprostol and intravenous oxytocin in controlling postpartum hemorrhage were compared, and the results showed that postpartum hemorrhage was significantly lower in patients treated with misoprostol than in the oxytocin group. Comparing hemoglobin differences before and after deliveries between the two groups indicated that hemorrhage was lower in the misoprostol group and this group experienced lower levels of hemoglobin decline compared to the other group (21).

Strengths and Limitations

One of the main strengths of this study was the design of the study. The current study was conducted as a single-blind RTC. Moreover, the online randomization was used to randomize and create random sequences.

The following can be mentioned as the main limitations of the study: not considering the patients’ underlying diseases, and not considering the weight of the patients’ uterus as an intervening factor for bleeding. Examining other complications which were not investigated in this study, such as nausea and vomiting, can be useful in obtaining more accurate results.

Conclusion

Taking a single preoperative dose of sublingual misoprostol is effective in reducing intraoperative blood loss. Additionally, this intervention led to a decline in hemoglobin.

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Conflict of Interest

Authors declared no conflict of interests.

References

1. Banu NS, Manyonda IT. Alternative medical and surgical options to hysterectomy. Best Practice & Research Clinical Obstetrics & Gynaecology. 2005; 19(3): 431-49. [DOI:10.1016/j.bpobgyn.2005.01.006] [PMID]
2. A A. World Health report 2002. Report. 2002 2002. Report No.
3. Harris WJ. Early complications of abdominal and vaginal hysterectomy. Obstetrical & gynecological survey. 1995; 50(11): 795-805. [DOI:10.1097/00006254-199511000-00019]

4. Hakimeh Alereza NB, Iman Akhlaghi, Parviz Amri, Mahtab Zinalzadeh, Shahnaz Barat. Effect of Different Anesthetic Techniques on Post-operative Hemoglobin and Hematocrit Levels Following Abdominal Hysterectomy; a Randomized Clinical Trial. Iranian Journal of Obstetrics, Gynecology and Infertility; 2012; 10(2): 9-16.

5. Berkowitz R, Barbiere R, Ryan K. Kistner's gynecology: principles and practice. 6th Sub ed. St Louis: Mosby. 1995.

6. Chai J, Hon E, Li C-F, Pan T-C, Yeung S-B, Ho P-C. A pilot study of pre-operative misoprostol in reducing operative blood loss during hysterectomy. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2011; 158(1): 72-5. [DOI:10.1016/j.ejogrb.2011.03.023] [PMID]

7. Lethaby A, Vollenhoven B, Sowter M. Efficacy of pre-operative gonadotrophin hormone releasing analogues for women with uterine fibroids undergoing hysterectomy or myomectomy; a systematic review. BJOG: A International Journal of Obstetrics & Gynaecology. 2002; 109(10): 1097-108. [DOI:10.1111/j.1471-0528.2002.01225.x] [PMID]

8. Lethaby A, Vollenhoven B, Sowter MC. Pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids. The Cochrane Library. 2001. [DOI:10.1002/14651858.CD0000547]

9. O'kin CR, Guido RS, Meyn LA, Ramathan S. Vasopressin during abdominal hysterectomy: a randomized controlled trial. Obstetrics & Gynecology. 2001; 97(6): 867-72. https://doi.org/10.1097/00006250-200106000-00001 [DOI:10.1016/S0029-7844(01)01353-9]

10. Eisinger SH, Meldrum S, Fiscella K, le Roux HD, Gazzick DS. Low-dose mifepristone for uterine leiomyomata. Obstetrics & Gynecology. 2003; 101(2): 243-50. https://doi.org/10.1097/00006250-200302000-00009 [DOI:10.1016/S0029-7844(02)02511-5]

11. Tulandi T, Béique F, Kimia M. Pulmonary edema: a complication of local injection of vasopressin at laparoscopy. Fertility and sterility. 1996; 66(3): 478-80. [DOI:10.1016/S0015-0282(16)58523-9]

12. Dabbaghia Gale T, Elmizadeh K, Moradi S, Rashvand Melli E. Comparison of Intravenous Oxytocin and Oral Misoprostol in Reduction of Postpartum Hemorrhage. Journal of Zanjan University of Medical Sciences. 2012; 20(81): 1-8.

13. Harriott J, Christie L, Wynter S, DaCosta V, Fletcher H, Reid M. A randomized comparison of rectal misoprostol with syntometrine on blood loss in the third stage of labour. West Indian Medical Journal. 2009; 58(3): 201-6.

14. Baxter G, Clayton J, Coleman R, Marshall K, Sangha R. Senior J. Characterization of the prostaglandin receptors mediating constriction and relaxation of human isolated uterine artery. British journal of pharmacology. 1995; 116(1): 1692-6. [DOI:10.1111/j.1476-5381.1995.tb16393.x] [PMID] [PMCID]

15. Chong Y-S, Chua S, Shen L, Arulkumaran S. Does the route of administration of misoprostol make a difference? The uterotonic effect and side effects of misoprostol given by different routes after vaginal delivery. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2004; 113(2): 191-8. [DOI:10.1016/j.ejogrb.2003.09.011] [PMID]

16. Ng P, Chan A, Sin W, Tang L, Cheung K, Yuen P. A multicentre randomized controlled trial of oral misoprostol and im sintometrine in the management of the third stage of labour. Human Reproduction. 2001; 16(1): 31-5. [DOI:10.1093/humrep/16.1.31] [PMID]

17. Nasr A, Shahin AY, Elsamman AM, Zakherah MS, Shaaban OM. Rectal misoprostol versus intravenous oxytocin for prevention of postpartum hemorrhage. International Journal of Gynecology & Obstetrics. 2009; 105(3): 244-7. [DOI:10.1016/j.ijgo.2009.01.018] [PMID]

18. Biswas J, Chaudhuri P, Mandal A, Bandypadhyay SN, Dasgupta S, Pal A. Effect of a single preoperative dose of sublingual misoprostol on intraoperative blood loss during total abdominal hysterectomy. International Journal of Gynecology & Obstetrics. 2013; 122(3): 244-7. [DOI:10.1016/j.ijgo.2013.03.025] [PMID]

19. Aghazadeh Naini A. The effectiveness of sublingual misoprostol in prevention of bleeding during cesarean delivery. The Iranian Journal of Obstetrics, Gynecology and Infertility. 2014; 17(125): 1-7.

20. Valdat M, Kashanian M, Asadollah S, Yazdkhasti P, Nikravan N. The effect of misoprostol on intraoperative blood loss after myomectomy. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2017; 6(4): 776-9. [DOI:10.18203/2530-1770.ijro e20150090]

21. Beigi A, Tabarestani H, Moini A, Zarrinkoub F, Kazempour M, Amree AH. Sublingual misoprostol versus intravenous oxytocin in the management of postpartum hemorrhage. Tehran University Medical Journal. 2009; 67(8).