Effect of a single preoperative dose of sublingual misoprostol on intraoperative blood loss during total abdominal hysterectomy

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A B S T R A C T

Objective: To investigate whether use of preoperative misoprostol can reduce blood loss during total abdominal hysterectomy (TAH). Methods: In a randomized double-blind placebo-controlled trial at a tertiary care hospital in Kolkata, India, between March 2011 and April 2012, women (n = 132) undergoing TAH with or without bilateral salpingo-oophorectomy for symptomatic myomas were randomly allocated to receive either 400 μg of misoprostol or placebo 30 minutes before surgery. The primary outcome measure was intraoperative blood loss. The secondary outcomes were postoperative drop in hemoglobin, need for blood transfusion, and incidence of adverse effects. Results: The 2 groups were similar with regard to demographic and clinical characteristics. There was a significant reduction of blood loss during TAH after sublingual administration of misoprostol compared with placebo before surgery (356 mL vs 435 mL; P = 0.049). The mean postoperative hemoglobin concentration was higher (10.5 g/dL vs 9.5 g/dL; P < 0.001) and the postoperative drop in hemoglobin was smaller (1.1 g/dL vs 1.9 g/dL; P = 0.004) in the misoprostol group than in the placebo group. No significant adverse effects occurred in either group. Conclusion: The results showed that a single dose of misoprostol administered before abdominal hysterectomy resulted in a significant reduction of blood loss with minimal adverse effects. Clinical Trial Registry India (www.ctri.nic.in): CTRI/2011/091/000216

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1. Introduction

Total abdominal hysterectomy (TAH) continues to be the most common surgical procedure worldwide for large symptomatic leiomyoma of the uterus [1]. Hemorrhage requiring blood transfusion is one of the most frequently cited complications of this procedure, occurring in 2%–12% of cases [2]. Various methods had been adopted by researchers to lessen blood loss during TAH. Preoperative administration of gonadotropin-releasing hormone (GnRH) analogs has been found to be effective in reducing the size and vascularity of large myomas; however, significant adverse effects—namely, hot flushes and osteoporosis—have been reported after its use [3–4]. The high cost of therapy is also a problem, particularly in resource-poor countries. Low-dose mifepristone had also been used for the same purpose with favorable results [5]. Although injection of vasopressin in the lower uterine segment was found to be beneficial in reducing blood loss during abdominal hysterectomy [6], serious complications such as hypotension, myocardial infarction, and cuff cellullitis have been reported after use of this drug [7–9]. Misoprostol, a synthetic analog of prostaglandin E1, has been extensively evaluated as a uterotonic agent in obstetrics mainly for prevention and management of postpartum hemorrhage and reduction of bleeding during cesarean delivery [10]. Among non-pregnant women, misoprostol has been used for cervical priming before transcervical procedures [11], and for reducing blood loss in myomectomy [12–13] and laparoscopy-assisted vaginal hysterectomy [14] with promising results. To our knowledge, only 1 pilot study has evaluated the effects of preoperative misoprostol on blood loss during TAH [15]. Intramyometrial vasopressin has been found to be effective in reducing intraoperative blood loss during TAH primarily by inducing vasospasm and also by increasing myometrial contractions [6]. Similarly, misoprostol can cause direct vasoconstriction in uterine arteries [16], and this property of misoprostol is most likely to be beneficial in reducing blood loss during TAH. Strong myometrial contractions induced by misoprostol indirectly cause relative avascularity in the myoma and may also contribute to a reduction in bleeding, particularly among women requiring concurrent myomectomy for cervical and broad ligament myoma. In addition, a decrease in uterine artery blood flow in myoma has been observed by Doppler velocimetry after misoprostol administration [17].

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Given the above findings, the aim of the present study was to investigate whether preoperative administration of misoprostol by a sublingual route might be beneficial in reducing intraoperative blood loss among women undergoing TAH.

2. Materials and methods

In a double-blind, randomized, placebo-controlled trial conducted at the Institute of Postgraduate Medical Education & Research, Kolkata, India, women undergoing TAH with or without bilateral salpingo-oophorectomy (BSO) between March 1, 2011, and April 30, 2012, were enrolled. Written informed consent was obtained from each eligible participant. The study was approved by the institutional ethics committee.

On the basis of a previous random chart review of women undergoing TAH with or without BSO for leiomyoma, the average blood loss during TAH is 510 ± 214 mL [6]. It was therefore calculated that 120 women (60 per group) would be required to have a 90% chance of detecting, at the 5% significance level, a 25% decrease in blood loss from 510 mL in the placebo group to 383 mL in the misoprostol group.

During the study period, women with symptomatic myomas were initially counseled about the available treatment options and those who opted for TAH with or without BSO were screened for eligibility. Women with heart disease, severe hypertension, hematologic disorders, glaucoma, bronchial asthma, liver disease, or pelvic endometriosis and adnexal mass, and those who had undergone previous myomectomy were excluded from the study. Women who received GnRH analogs and who were allergic to prostaglandins were also excluded.

A few hours before the expected time of surgery, enrolled women were randomized to the study or control group via a computer-generated random number sequence. Those randomized to the study group received a pre-prepared sealed opaque packet containing 400 μg of misoprostol (Zitotec, Sun Pharmaceutical Industries, Mumbai, India; 2 tablets of 200 μg), whereas those allocated to the control group received a similar packet containing 2 placebo tablets. The placebo tablets were similar to the misoprostol tablets in size, shape, and color, and the investigators and surgeons were blind to the allocation. The hospital pharmacy prepared the packets and theater nurses opened the allotted packets and administered the tablets (misoprostol or placebo) sublingually 30 minutes before the operation. Baseline demographic data comprising age, parity, body mass index (calculated as weight in kilograms divided by the square of height in meters), and size of uterus were recorded.

Preoperative hemoglobin levels were measured. All operations were conducted under general anesthesia. To avoid bias related to surgical skill, 4 consultant gynecologists, each with more than 5 years of experience, performed all of the operations.

A gravimetric method was used to measure blood loss. The total volume of blood loss (M) during operation was measured by adding the volume of contents of the suction container (a) to the difference in weight (where 1.06 g is equivalent to 1 mL) between the dry (b) and wet (c) mops used during operation: M = a + (c − b) [11]. The mops used for skin and surface bleeding was discarded on opening the peritoneal cavity and excluded from this calculation. The total duration of surgery from skin incision to skin closure was noted.

Postoperative hemoglobin levels were measured 24 hours after the operation. An automated cyanmethemoglobin method was used for hemoglobin measurement. Records were kept regarding blood transfusions and complications during the postoperative period. Patients were discharged on postoperative day 5 if permissible and asked to attend an outpatient department for follow-up 6 weeks after the operation or earlier if required. The primary outcome measure was the hysterectomy-related blood loss during operation. Secondary outcome measures were the drop in hemoglobin level 24 hours after the operation, requirement for blood transfusion, duration of hospital stay, and incidence of complications.

Microsoft Excel version 7 (Microsoft, Redmond, WA, USA) and Medcalc version 11 (Medcalc Software, Mariakerke, Belgium) were used for statistical analysis. Student t, Mann–Whitney U, χ², and Fisher exact tests were used to compare variables as appropriate. Results were reported as mean ± SD or number (percentage). The relative risk with 95% confidence interval was calculated for outcome parameters. A P value of less than 0.05 was considered statistically significant.

3. Results

The study was reported in accordance with the CONSORT scheme (Fig. 1). During the study period, 170 women with symptomatic myoma who opted for TAH with or without BSO were screened for eligibility. Twenty-seven women were ineligible owing to the presence of severe hypertension (7 women), cardiovascular disease (3 women), bronchial asthma (4 women), or adnexal mass (13 women). Two women received preoperative GnRH analog and 1 woman had undergone previous myomectomy and were also excluded. Eight women declined to participate.

As a result, 132 women were recruited and randomly allocated to the study and control groups before surgery. Subsequently, 1 woman had an anesthetic complication (intubation failure) leading to cancellation of the operation, and was not included in the analysis. Ovarian malignancy was suspected for 2 women, leading to a change of surgical plan and subsequent withdrawal from the study. In addition, because women diagnosed with endometriosis were excluded prior to randomization, data were excluded from 5 women for whom severe endometriosis was detected during the operation. Injury of the ureter occurred for 1 participant, leading to additional surgical interventions; this participant was also withdrawn from the study. Blinding was maintained during the withdrawal of these 9 participants. During data analysis, however, it was revealed that 4 women were from the study group and 5 women were from the control group.

Both groups were similar in terms of baseline variables as age, BMI, preoperative hemoglobin concentrations, size and weight of uterus, incidence of previous operative scars, and duration of surgery (Table 1).

The mean operative blood loss was significantly less in the misoprostol group than in the placebo group (356.9 ± 303.7 mL vs 435.2 ± 277.8 mL; P = 0.049). The mean postoperative hemoglobin concentration was higher in the misoprostol group than in the placebo group (10.5 ± 1.2 g/dL vs 9.5 ± 1.3 g/dL; P = 0.001); similarly, women in the misoprostol group had a smaller drop in hemoglobin levels after surgery compared with women in the placebo group (1.1 ± 1.0 g/dL vs 1.9 ± 1.2 g/dL; P = 0.004). No significant difference was observed in the requirement for blood transfusions or duration of hospital stay between the 2 groups. The incidence of adverse effects was similar between the 2 groups (Table 2). No major complication or morbidity occurred in either group.

4. Discussion

Total abdominal hysterectomy is the widely practiced definitive management for symptomatic myoma of the uterus among parous women, particularly in low-resource countries such as India, where costly modalities of treatment such as GnRH analogs, uterine artery embolization, and endometrial ablation are not universally available. TAH is associated with considerable operative blood loss, resulting in the need for transfusions and related hazards in 2%–12% of cases [2]. Reducing this blood loss might not only lessen the requirement for transfusion but also prevent postoperative anemia and the need for hematinic drugs.

Misoprostol is a synthetic prostaglandin analog with strong uterotonie action. It is cheap, is stable at room temperature, and has a long shelf life. It has been found to reduce blood flow in the uterine arteries among women with myoma [16]. Effective myometrial contractions along with increased uterine artery resistance induced by misoprostol may help to reduce blood supply to the diseased uterus.
and thus may be an effective alternative to preoperative GnRH or intraoperative vasopressin in reducing blood loss during TAH. Except for a pilot study by Chai et al. [15], misoprostol is yet to be evaluated for reduction of intraoperative blood loss in TAH.

In the present study, there was a significant reduction of blood loss during TAH after sublingual administration of 400 μg of misoprostol 30 minutes before surgery compared with placebo (356 mL vs 435 mL; P = 0.049). The mean postoperative hemoglobin concentration was higher (10.5 g/dL vs 9.5 g/dL; P < 0.001) and the postoperative drop of hemoglobin was smaller (1.1 g/dL vs 1.9 g/dL; P = 0.004) in the misoprostol group. These results are in agreement with those of Chang et al. [14], who investigated the efficacy of misoprostol and oxytocin on reducing blood loss during laparoscopy-assisted vaginal hysterectomy in a placebo-controlled trial. They observed a significant reduction of blood loss (198.1 g vs 396 g; P < 0.0001) and a smaller drop in postoperative hemoglobin (1.5 g/dL vs 1.9 g/dL; P = 0.02) and hematocrit levels (4.8 % vs 5.8%; P = 0.04) among women receiving uterotonic drugs compared with placebo. The blood losses were much lower in both the study group and the control group of Chang et al. [14] than in the present study, possibly due to the use of oxytocin along with misoprostol and the laparoscopic approach of operation.

Table 1
Demographic and clinical characteristics of patients.a

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Misoprostol group (n = 62)</th>
<th>Placebo group (n = 61)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>44.3 ± 7.5</td>
<td>46.9 ± 9.5</td>
<td>0.10b</td>
</tr>
<tr>
<td>BMI</td>
<td>23.9 ± 4.8</td>
<td>24.9 ± 4.1</td>
<td>0.22b</td>
</tr>
<tr>
<td>Previous operation scars</td>
<td>4 (6.5)</td>
<td>6 (9.8)</td>
<td>0.49</td>
</tr>
<tr>
<td>Size of uterus, wk of pregnancy</td>
<td>14.4 ± 5.0</td>
<td>15.3 ± 6.1</td>
<td>0.37b</td>
</tr>
<tr>
<td>Weight of uterus, g</td>
<td>262.8 ± 299.8</td>
<td>250.9 ± 221.3</td>
<td>0.81c</td>
</tr>
<tr>
<td>Preoperative hemoglobin, g/dL</td>
<td>116 ± 7.4</td>
<td>114 ± 1.1</td>
<td>0.37b</td>
</tr>
<tr>
<td>Duration of operation, min</td>
<td>87.5 ± 27.2</td>
<td>80.5 ± 25.6</td>
<td>0.14d</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).

Values are given as mean ± SD or number (percentage) unless stated otherwise.

a By t test.
b By χ² test.
c By Mann–Whitney U test.
d By Fisher exact test.

Table 2
Outcome measures.a

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Misoprostol group (n = 62)</th>
<th>Placebo group (n = 61)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood loss, mL</td>
<td>356.9 ± 303.7</td>
<td>425.2 ± 277.8</td>
<td>0.049</td>
</tr>
<tr>
<td>Postoperative Hb, g/dL</td>
<td>10.5 ± 1.2</td>
<td>9.5 ± 1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in Hb, g/dL</td>
<td>1.1 ± 1.0</td>
<td>1.9 ± 1.2</td>
<td>0.004c</td>
</tr>
<tr>
<td>Need for blood transfusion</td>
<td>5 (8.1)</td>
<td>6 (9.8)</td>
<td>0.72d</td>
</tr>
<tr>
<td>Hospital stay, d</td>
<td>6.2 ± 0.1</td>
<td>6.4 ± 0.1</td>
<td>0.30e</td>
</tr>
<tr>
<td>Adverse effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever (&gt;38.5 °C on day0/1)</td>
<td>4 (6.5)</td>
<td>2 (3.3)</td>
<td>0.68e</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (1.6)</td>
<td>1 (1.6)</td>
<td>1.96</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (1.6)</td>
<td>1 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (1.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Shivering</td>
<td>1 (1.6)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; Hb, hemoglobin.
a Values are given as mean ± SD or number (percentage) unless stated otherwise.
b By Mann–Whitney U test.
c By t test.
d By Mann–Whitney U test.
e By χ² test.
f By Fisher exact test.
Reduction of blood loss and higher postoperative hemoglobin levels were also reported by Celik et al. [12], who administered misoprostol before abdominal myomectomy in a small placebo-controlled study. They reported blood losses of 472 mL and 621 mL in the misoprostol and placebo groups, respectively ($P < 0.05$), and postoperative hemoglobin levels of 9.7 g/dL and 8.9 g/dL, respectively ($P < 0.05$) [12].

By contrast, a similarly designed pilot study among 64 women undergoing TAH by Chai et al. [15] failed to show any significant reduction of intraoperative blood loss during TAH (570 mL vs 521 mL; $P = 0.904$). These opposing findings of Chai et al. [15] may be due to the following factors: recruitment of women with larger myoma (17 weeks and 16 weeks in their respective control and placebo groups vs 14 weeks and 15 weeks, respectively, in the present study); use of a more accurate (alkaline hematin) method for blood loss assessment; non-exclusion of women with major adhesions; and a smaller sample size.

As mentioned above, the uterine action of misoprostol may be beneficial to facilitate hysterectomy among women requiring myomectomy for cervical or broad ligament myoma. In the present study, only 1 woman (1.6%) in the misoprostol group and 2 women (3.2%) in the control group required myomectomy. The pilot study by Chai et al. [15] reported a high incidence of concurrent myomectomy in both cohorts (21% and 25%); however, subgroup analysis to compare blood loss among these women was not done.

The route and timing of administration of misoprostol varies between reported studies. Vaginal and rectal administration 1 hour before surgery was used by Celik et al. [12] and Chang et al. [14], respectively. Similar to the study of Chai et al. [15], a sublingual route of misoprostol administration 30 minutes before surgery was used in the present study. The sublingual route offers unique pharmacokinetic advantages in terms of rapid onset of action and greater bioavailability, leading to a longer duration of action compared with other administrative routes [18].

Neither group in the present study had major adverse effects or complications, which is in accordance with other studies [12,14,15]. The incidence of gastrointestinal adverse effects such as diarrhea and vomiting were very low in the misoprostol group (1.6% each), which is possibly attributable to the sublingual route of drug administration.

The present study has some limitations. The alkalii-hematin method, which is the gold standard for blood loss assessment, was not available in the study setting. In addition, the exclusion of 9 women (4 in the misoprostol group and 5 in the placebo group) after randomization might lead to a study bias. In an “intention to treat” analysis, the data from these women should have been included; however, it was not possible to include them because the database did not contain sufficient information on these cases.

In conclusion, the present study showed that a single preoperative dose of 400 μg of misoprostol administered 30 minutes before abdominal hysterectomy resulted in a significant reduction of blood loss and the subsequent need for blood transfusion and risk of morbidity related to anemia. No major complication was associated with use of the drug. The foremost advantage of misoprostol would be its low cost compared with popular methods of reducing bleeding with GnRH analogs and vasopressin. However, large trials comparing the efficacy of misoprostol with that of GnRH and vasopressin are required to verify the beneficial effects of this drug.

Conflict of interest

The authors have no conflicts of interest.

References