Original Article

Prophylaxis Effect of Metronidazole Vaginal Gel in Decreasing the Risk of Surgical Site Infections after Elective Hysterectomy

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Abstract

Objective: Infections are an important cause of morbidity and mortality after hysterectomy. Here, we aimed to investigate and evaluate the beneficial effects of metronidazole vaginal gel on the rate of surgical site infections in women undergoing elective abdominal hysterectomy. **Methods:** This is a randomized prospective, double-blind controlled clinical trial performed in 2020 in Isfahan on 108 candidates for elective hysterectomy. At the beginning of the study, we completed a checklist of the patient's characteristics (patient age, body mass index [BMI], and history of medical conditions such as diabetes, hypertension, anemia, and immune deficiency) and the cause of hysterectomy. All patients were randomized into two groups. The first group received a lubricant vaginal gel single dosage, and the second group received a 0.75% metronidazole vaginal gel single dosage the night before surgery. Patients were visited up to 6 weeks after surgery, and the frequency of infection at the surgical site was determined. **Findings:** The rates of infection were lower in patients who received metronidazole vaginal gel (5.8%) compared to the control group (11.6%) (P = 0.03). Patients with an estimated blood loss volume of more than 500 mL had higher rates of infection (13.46%) compared to patients with a bleeding volume of fewer than 500 mL (1.9%) (P = 0.001). We also found that patients with diabetes (13.5%) and patients with BMI more than 30 kg/m^2 (13.5%) had higher rates of infection compared to patients without diabetes (5.8%) and patients with BMI <30 kg/m^2 (11.5%) (P = 0.001 for both). Patients with higher hospitalization duration had higher infection rates (P = 0.009). **Conclusion:** Administration of a single dosage of metronidazole vaginal gel before abdominal hysterectomy may reduce surgical site infection and have clinical values.

Keywords: *Hysterectomy, infection, Metronidazole, prophylaxis*

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Introduction

Hysterectomy removes the uterus with or without the cervix and with or without removal of the ovaries.[1] This operation is one of the most common surgeries in nonpregnant women and the second most common operation in women after cesarean section.[2] Every year, 6000 women in the United States undergo hysterectomy.[3,4] Based on epidemiologic data, 37% of women in the United States and 20% of women in the United Kingdom undergo hysterectomy by age 60. The hysterectomy rate varies from region to region.[3,5]

Among developed countries, most hysterectomy cases are performed in the United States, and according to reports, the number of issues per year was 510 per 100,000 women.[6,7] On the other hand, the lowest number of cases is seen in Denmark, which according to the reports of the year 2011 was at the rate of 173 per 100,000 women.[8] This operation is a heavy and invasive surgical procedure. The mortality rate was 1 in 1000,

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and various complications such as bleeding, infection, long-term hospitalization, and reduced physical function have been observed.[9] On the other hand, hysterectomy seriously affects female sexual characteristics. Women often see the uterus as a sexual organ that controls and regulates important physiological functions in the body and a source of youth, energy, activity, and a symbol of fertility.[10]

Infections are an important cause of morbidity and mortality after surgery, and surgical wound infection is one of the most important types of these infections. Hysterectomy is one of the most common surgeries in women. Infections of various sites, including wound infection, vaginal cuff infection, and urinary tract infection, are complications after hysterectomy.[11] This complication can lead to prolonged hospitalization, reoperation, and multiple manipulations in the patient. The infection rate after abdominal hysterectomy was reported to be approximately 15%–24%, which is reduced to 10%–11% using prophylactic antibiotics.[12] Based on the study by Brummer *et al*.,[13] the infection complications range after hysterectomy was lower than Andiman *et al*.[12]

Various factors are associated with postoperative infection rates, and mortality rates are associated with postoperative infection host factors. Metronidazole is an antibiotic and antiprotozoal medication used alone or with other antibiotics to treat pelvic inflammatory disease, endocarditis, and bacterial vaginosis.[14]

Different forms of metronidazole are available, including tablets, creams, gels, or ampules. Metronidazole vaginal gel once daily for 5 days is prescribed by gynecologists to treat bacterial vaginosis in nonpregnant women.[15,16]

To date, various prophylactic agents have been used to prevent surgical site infection in women undergoing hysterectomy. However, very few studies have evaluated the effects of metronidazole vaginal gel. For the first time, we aimed to investigate and assess the beneficial effects of metronidazole vaginal gel on reducing surgical site infections in women undergoing elective abdominal hysterectomy.

Methods

This is a randomized prospective, double-blind controlled clinical trial performed in 2020 in Al-Zahra Hospital, affiliated with Isfahan University of Medical Sciences. The present study was conducted on patients who were candidates for elective abdominal hysterectomy in our medical center. The research committee approved the study protocol of Isfahan University of Medical Sciences, and the ethics committee has confirmed it (ethics code: IR.MUI.MED.REC.1398.498 and Iranian Registry of Clinical Trials code: IRCT20200217046523N9).

The inclusion criteria were 18 years, candidates for elective abdominal hysterectomy, and signed written informed consent to participate in this study. The exclusion criteria were hysterectomy followed by cesarean section, hysterectomy following normal delivery or postpartum period, emergent hysterectomy, broad-spectrum antibiotics before surgery, vaginitis or cervicitis, in particular, the preoperative period, and patient's will to exit the study.

A total of 108 patients entered the study based on inclusion and exclusion criteria. At the beginning of the study, we completed a checklist of the patient's characteristics (patient age, body mass index (BMI), and history of medical conditions such as diabetes, hypertension, anemia, and immune deficiency), cause of hysterectomy (resistant abnormal vaginal bleeding due to uterine myoma, adenomyosis, hormonal pattern, and oncological causes), history of medications such as corticosteroids, menopausal status, and history of previous surgery. All patients were randomized into two groups using Random Allocation software.

The first group (control) received lubricant vaginal gel single dosage, and the second group (case) received 0.75% metronidazole vaginal gel single dosage the night before surgeries. All patients received a dose of cefazolin 2 g 30 min before surgeries and 900 mg of clindamycin if they were allergic to cefazolin. All patients underwent vaginal lavage with betadine-impregnated gas after general anesthesia or spinal anesthesia induction. A nurse administered the drug based on the randomization of numbers, the outcome assessed by the researcher, and the operation done by gynecological oncology. The drug administrator, the patients, and the researcher were unaware of the study groups.

We considered the type of abdominal wall incisions, duration of operations, volume of intraoperative bleeding loss, a repeated dose of intraoperative antibiotic if indicated (bleeding volume >500 mL and duration of operation more than 3 h), and type of suture used during surgery (Vicryl, chromic).

After surgeries, all patients received up to three doses of the antibiotic cefazolin or clindamycin and were discharged without oral antibiotics. Patients were visited up to 6 weeks after surgery (whenever they had a problem every week and if they did not have a problem 2–6 weeks later). Symptoms of infection such as fever, purulent discharge from the vagina or incision site, and abnormal abdominal and pelvic pain were explained to the patients. They were advised to refer to our medical center if such symptoms existed.

We collected data regarding the prevalence of vaginal infections among patients. The obtained data were entered into the Statistical Package for the Social Sciences (SPSS) version 16 (Chicago, spss Inc 2007). Independent *t*-test, one-way ANOVA, Chi-square test, and Spearman's and Pearson's correlation test examine the relationship between disease severity and signs and symptoms. A multivariate linear regression test is used to investigate and eliminate the effect of confounding factors on the disease's severity. $P < 0.05$ was considered a significance threshold.

Results

A total of 108 patients entered the study based on our criteria and, according to the random number table, were divided into two groups, each containing 54 patients. In each group, two patients were excluded due to improper follow-ups. Data of 104 patients were analyzed. The consort flow diagram of the patients is indicated in Figure 1.

Initial analysis of demographic data showed that the mean age of the patients was 50.9 ± 9.3 years. The mean duration of hospitalization among patients was 6.53 ± 5.6 days. We observed 16 cases of postoperative infection (15.4%) among patients, and 16 patients (15.4%) had more than 500 mL of bleeding. We used Vicryl sutures for 50% of the patients, and chromic sutures were used for the other 50%. Seventy-eight patients (75%) also reported at least one past medical history. Other data are summarized in Table 1.

A Chi-square test was used to compare the data. Values of $P < 0.05$ indicate the significance of the test.

Evaluation of past medical history of patients showed that 12 patients (11.5%) had hypertension, nine patients (8.65) had anemia, 26 patients (25%) had BMI of more than 30 kg/m^2, 20 patients (19.2%) had diabetes, and 1 patient (0.96) were immunocompromised due to consumption of corticosteroids or immunosuppressant drugs.

A comparison of case and control groups showed that the infection rates were lower in patients who received metronidazole vaginal gel than in the control group ($P = 0.03$). However, no other differences were observed between the case and control groups regarding bleeding volume ($P = 0.9$), types of sutures ($P = 0.60$), having oncologic procedures ($P = 0.08$), and past medical history ($P = 0.12$). These data are indicated in Table 2.

We also evaluated the frequency of infection among patients with past medical histories. Based on our data, we found that patients with a bleeding volume of more than 500 mL had higher rates of infection (13.5%) compared to patients with a bleeding volume of fewer than 500 mL (1.9%) ($P = 0.001$). We also found that patients with diabetes (13.5%) and patients with BMI more than 30 kg/m^2 (13.5%) had higher rates of infection compared to patients without diabetes (1.9%) and patients with BMI <30 kg/m^2 (1.9%) ($P = 0.001$ for both). Other data are shown in Table 2.

Based on our data, no significant differences were observed between the infection rate of patients with types of sutures having an oncologic surgical procedure

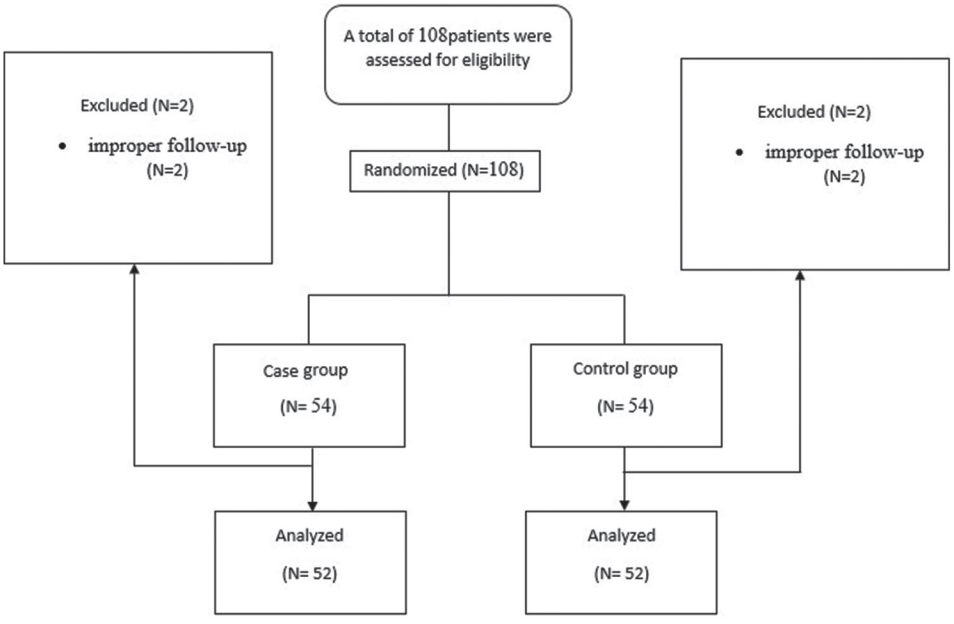

Figure 1: Consort flow diagram of the patients

Table 1: Demographic data of the study population and comparison of clinical data between case and control groups

Variable	Total	Case group	Control group	*P*
Age (years)		49.6±8.7	51.2±9.2	0.36
Hospitalization duration (days)	6.5±5.6	5.3±2.4	6.9±3.3	0.02
Duration of operation (min)	133±10	120±15	130±15	
Repeated dose of intraoperative antibiotic	28 (26.9)	13 (12.5)	15 (14.4)	
Menopause status	16 (15.4)	7 (6.75)	9 (8.65)	
Past surgical history	82 (78,8)	48 (46.1)	34 (32.7	
Estimated blood lost (mL)				
>500	16 (15.4)	8 (7.7)	8 (7.7)	0.9
<500	88 (84.6)	46 (44.2)	42 (40.4)	
Suture type				
Chromic	52 (50)	26 (25)	26 (25)	0.60
Vicryl	52 (50)	26 (25)	26 (25)	
Infection				
Yes	18 (17.4)	6 (5.8)	12 (11.6)	0.03
No	86 (82.6)	46 (44.2)	40 (38.4)	
Oncologic surgery				
Yes	48 (46.1)	26 (24.9)	22 (21.1)	0.08
No	56 (53.9)	26 (25)	30 (28.9)	
Past medical history				
Positive	78 (75)	42 (40.4)	36 (34.6)	0.12
Negative	26 (25)	10 (9.6)	16 (15.4)	
Cause of hysterectomy				
Oncology	26 (25)	14 (13.46)	12 (11.54)	
Resistant of AUB	78 (75)	40 (38.46)	38 (36.54)	
Type of abdominal wall incision				
Vertical	30 (28.84)	16 (15.4)	14 (13.46)	
Transverse	74 (71.15)	38 (36.54)	36 (34.61)	

A Chi-square test was used to compare the data. Values of $P<0.05$ indicate the significance of the test. Data are presented as mean ± SD, or number (%), as applicable; SD: Standard deviation, AUB=Abnormal uterine bleeding

or the age of patients ($P = 0.44$, $P = 0.85$, and $P = 0.25$, respectively). On the other hand, we found that patients with higher hospitalization duration had higher infection rates ($P = 0.009$). These data are indicated in Table 2.

Discussion

The present study aimed to investigate the effects of metronidazole vaginal gel on the rate of surgical site infections in women undergoing elective abdominal hysterectomy. Based on the evidence, surgical site infection is one of the important complications of hysterectomy that could cause morbidities and mortalities among women. Different strategies have been investigated in the prevention of postoperative infections.

Our results showed that patients receiving metronidazole vaginal gel had lower infection rates than the control group. Furthermore, we found that patients with a bleeding volume of more than 500 mL, patients with diabetes and a BMI of more than 30 kg/m^2, and patients with higher hospitalization duration had higher rates of infection than other patients. Our study showed the effectiveness of metronidazole vaginal gel in candidates for hysterectomy.

We should note that most of the infected cases had cellulitis 12 cases (11.5%), 3 cases had a purulent infection (2.9%), and 1 patient had necrotizing fasciitis.

In 2012, a study was conducted by Uysal *et al*. on the prevention of infectious morbidity after elective abdominal hysterectomy. They divided 192 patients into two groups receiving vaginal combination therapy, including 500 mg metronidazole and 100 mg miconazole nitrate two times a day for 7 days, and the control group. They showed that the patients who received the interventions had significantly lower infection rates than controls.[17] Another study by Soper explained that bacterial vaginosis could cause surgical site infections in patients who undergo gynecologic surgeries. It was also explained that preoperative treatments with metronidazole, clindamycin, tinidazole, and secnidazole had been approved by the Food and Drug Administration (FDA) to reduce infection chances.[18] The results of our study were in line with these findings showing the effectiveness of metronidazole vaginal

Table 2: The relationship between underlying diseases and blood loss with the incidence of infection

Variable	Infection		*P*
	Yes, *n* (%)	No, *n* (%)	
Estimated blood lost (mL)			
>500	14 (13.5)	2 (1.9)	0.001*
<500	2 (1.9)	86 (82.7)	
Diabetes			
Yes	14 (13.5)	6 (5.8)	0.001*
No	2 (1.9)	82 (78.84)	
Hypertension			
Yes	2 (1.9)	10 (9.6)	0.075*
No	14 (13.5)	78 (75)	
Anemia			
Yes	1 (0.96)	8 (7.7)	0.15*
No	15 (14.4)	80 (77)	
Immunosuppression			
Yes	2 (1.9)	1 (0.96)	0.27*
No	14 (13.5)	87 (83.65)	
BMI (kg/m^2)			
>30	14 (13.5)	12 (11.5)	0.001*
<30	2 (1.9)	76 (73)	
Risk factor			
Yes	14 (13.5)	66 (63.5)	0.31*
No	2 (1.9)	22 (21.15)	
Suture type			
Chromic	6 (5.8)	37 (35.6)	0.44*
Vicryl	10 (9.6)	51 (49)	
Oncologic surgeries			
Yes	2 (1.9)	8 (7.7)	0.85*
No	14 (13.5)	80 (77)	
Age (years), mean±SD	46.6±5.7	51.65±9.6	0.25**
Hospitalization duration (days), mean±SD	11.25±8.3	5.6±4.6	0.009**

*Chi-square test was used to compare the data, **Independent *t*-test. SD=Standard deviation, BMI=Body mass index

gel in reducing the infection rate after abdominal hysterectomy.

Another study was conducted by Hodges *et al*. in 2014 in the United States on the prevention and management of hysterectomy complications. Based on their study, hemorrhage, infection, thromboembolism, injury to viscera, and neuropathy were the most common complications of hysterectomy. They explained that preventive strategies such as prophylactic antibiotic therapies or topical antibiotics could have beneficial effects, but no solid strategy has been reported yet.[19] In 2016, Masoudi *et al*. showed the effectiveness of metronidazole vaginal gel for bacterial vaginosis treatments. Based on their results, using metronidazole vaginal gel is associated with decreased bacterial vaginosis in patients, and this finding could be used in similar situations.[20] Sobel and Sobel also emphasized that metronidazole could be used vastly in vaginal infections and cases of gynecologic interventions.[14]

These previous data have explained that metronidazole vaginal gel effectively reduces vaginal infections, but here in the present study, we compared the infection rate of patients after elective abdominal hysterectomy. To the best of our knowledge, this is the first randomized clinical trial in the English literature that compares the effectiveness of metronidazole vaginal gel before abdominal hysterectomy. Other findings of our study were increased frequencies of infection among patients with a bleeding volume of more than 500 mL, diabetes, BMI of more than 30 kg/m^2, and patients with higher hospitalization duration.

Another point is that we observed an infection rate of 11.6% in control patients. This issue could be due to the fact that our medical center is an educational referral center. Therefore, most admitted cases are considered high risk for possible complications. We also used vaginal gel metronidazole instead of intravenous administrations because vaginal use of the medication could be conducted the night before the surgery and by the nurse without an invasive procedure.

In 2013, a review article reported that patients with obesity or overweight are at higher risk of morbidities following hysterectomy. They also mentioned that patients with weight disorders have higher chances for postoperative infection (odds ratio [OR] = 1.7).[21] Another study showed that obesity was associated with an increased risk of heavy bleeding during surgery (OR = 3.64) and infection (OR = 1.47).[22] It has also been mentioned that obesity is associated with increased wound complications and infection in women undergoing abdominal hysterectomy and with longer operative times and hospitalization duration regardless of surgical approach.[23] A study also showed that postoperative surgical site infection rates increase in patients with higher bleeding volumes during surgeries; therefore, less-invasive treatments should be considered.[24] These data are in line with our findings.

We showed that applying a single dosage of metronidazole vaginal gel could reduce infection rates in patients undergoing elective abdominal hysterectomy. These data were consistent with previous studies, but we recommend further research on this issue, especially in larger study populations. We also suggest that gynecologists should pay attention to the beneficial roles of metronidazole vaginal gel before elective abdominal hysterectomy.

The limitations of this study were restricted study population and conducting this survey in a single center. Using only one dose of metronidazole vaginal gel was also

another limitation. We recommend multicentric studies with a larger sample size using vaginal metronidazole gel.

It is concluded that a single dosage of metronidazole vaginal gel before the elective abdominal hysterectomy was associated with reduced surgical site infection. However, patients with bleeding volumes more than 500 ml, diabetes, BMI more than 30 kg/m^2, and patients with higher hospitalization duration had higher infection rates than others. We recommend that the administration of metronidazole vaginal gel before elective abdominal hysterectomy could have clinical values.

Administration of a single dosage of metronidazole vaginal gel before the elective abdominal hysterectomy was associated with reduced surgical site infection. However, patients with a bleeding volume of more than 500 mL, diabetes, BMI more than 30 kg/m^2, and patients with higher hospitalization duration had higher infection rates than others. We recommend that the administration of metronidazole vaginal gel before elective abdominal hysterectomy could have clinical values.

Authors' contribution

All authors designed the study, supervised the data collection, and drafted and approved the manuscript for submission.

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Conflicts of interest

There are no conflicts of interest.

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