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Original article

Vaginal Honey as an Adjuvant Therapy for Standard Antibiotic Protocol of Cervicitis: a Randomized Clinical Trial

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Abstract

Background and objectives: More than half of the cervicitis cases are non-gonococcal and non-chlamydial. Therefore, the cure rate of the principal treatment protocol has reduced to less than 50%. Complementary therapy is an option for adjuvant therapy when standard medical treatment is not effective enough. Honey is used as a natural agent for wound healing and antibacterial effect. This study aimed to compare the effect of honey adjuvant therapy with the standard antibiotic therapy in improving the cure rate of cervicitis. **Methods:** In this double-blind randomized clinical trial, we enrolled 102 women diagnosed with cervicitis with standard criteria who referred to the gynecological clinic of Mousavi Hospital, Zanjan, Iran. They were randomly divided into two groups. The control group received the oral standard antibiotic treatment plus lubricant gel as placebo, and the intervention group received the oral standard treatment plus vaginal *Ziziphus* honey as adjuvant therapy. Both groups received the treatment once a day for two weeks. The symptoms and clinical findings of the patients were evaluated for three weeks following the initiation of the treatments. **Results:** All clinical symptoms of cervicitis significantly decreased after the treatment in both groups ($p \leq 0.05$), but the vaginal discharge of the intervention group reduced more ($p \leq 0.05$). In addition, the intervention group showed better results for the restoration of cervical erosion in comparison with the control group ($p < 0.05$). **Conclusion:** Vaginal honey adjuvant therapy can improve the efficiency of standard antibiotic treatment to reduce the clinical symptoms of cervicitis.

Keywords: cervical erosion; cervicitis; complementary therapies; honey; vaginal discharge

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Introduction

Cervicitis is defined as lower genital tract infection during reproductive age with an estimated prevalence of 30-45% in females [1,2]. Cervicitis is diagnosed with discharge or bleeding upon swabbing the cervix with a cotton swab. The treatment of cervicitis is recommended, because untreated cervicitis may lead to some complications such as ectopic pregnancy, mucosal adhesion, salpingitis, pelvic inflammatory disease, mucosal damage, and infertility [3]. *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are known as the main causes of cervicitis. Also, *Mycoplasma genitalium*, *Trichomonas vaginalis*, and other bacterial vaginosis agents are consistently associated with cervicitis [4]. More than half of

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cervicitis cases are non-gonococcal and non-chlamydial [1].

According to the research of Keshavarz et al., the prevalence of cervicitis in the south of Iran was 71% in the urban population [5]. Even though women with purulent cervicitis are usually treated with empiric antibiotics against *N. gonorrhoeae* and *C. trachomatis*, but these two bacteria are detected in only half of the cases [6,7]. According to Taylor et al., 61% of purulent cervicitis patients showed unknown etiology with a negative bacterial test [8].

The recommended empiric therapy of cervicitis is primarily focused on the treatment of N. gonorrhoeae and *C. trachomatis*. The sexually transmitted disease treatment guideline of the Centers for Disease Control and Prevention (CDC) recommends presumptive cervicitis treatment with 1 g azithromycin orally in a single dose or 100 mg doxycycline orally twice a day for 7 days for *C. trachomatis* and 250 mg ceftriaxone intramuscular in a single dose plus 1g azithromycin orally in a single dose for *N. gonorrhoeae* [9].

Furthermore, it is reported that 18% of women with recurrent vaginal infection were positive for chlamydial infection [10]. If cervicitis is not cured by treatment procedure after 2-3 months, it would become chronic and surgical treatment is recommended. The surgical procedures are conducted as electrocautery, cryotherapy, or laser therapy. The cervical stenosis is one of the possible side effects of each one of these methods [11].

The medical communities consider the use of complementary and alternative medicine for several disorders such as genital infections, due to the effectiveness, safety, and suitability [12]. Honey is a natural agent which has been used as a traditional medicine for various medical interventions in Iran [13]. Mostly, the topical application of honey is for improvement of wounds. Honey maintains moisture of wound environment due to its high viscosity that can improve wound healing. In addition, honey produces mild acidity, and low-level of hydrogen peroxide that assists tissue repairing and contributes to the antibacterial activity [14]. The results of several studies have shown that honey is effective in treating vaginal candidiasis, cervicitis and healing wound and cesarean scar [15-18].

The initial treatment of cervicitis in Iran is currently carried out as empiric antibiotic therapy against *N. gonorrhoeae* and C. *trachomatis*, and their definitive diagnostic tests are unfortunately expensive or not available. According to previous studies, more than half of the cases are not caused by *N. gonorrhoeae* and C. *trachomatis*. So, we decided to use adjuvant therapy of honey due to its antibacterial and anti-inflammatory properties and compare the results with the standard antibiotic therapy.

Materials and Methods

Ethical considerations

Ethical approval for the study was obtained from Ethic Committee of Zanjan University of Medical Sciences, Iran (approval number: IR.ZUMS.REC.1396.270). The study was performed according to Helsinki declaration. This clinical trial was registered at the Iranian Registry of Clinical Trials (IRCT) on 2018/10/12 with the IRCT code of IRCT20180707040370N3. All participants completed the written consent.

Material

Organic Ziziphus "Konar" honey was bought from Meysam Honey, Qom, Iran. It was used for the intervention group (quality control analysis by Soren Tech Toos Laboratory in Mashhad, autumn 2017). The percentage of sucrose in the honey was 0.83% and the ratio of fructose to glucose was 1.78. According to the international standards, honey has to consist of less than 5% sucrose and the ratio of the two kinds of monosaccharide could be at least 0.9 [17]. The microbial quality control of honey was in acceptable range.

Study design

This study was a double-blind randomized clinical trial that was performed on 102 women who referred to the gynecology clinic of Mousavi Hospital, Zanjan, Iran, with cervicitis diagnostic criteria, from January till April 2018. Patients were randomly divided into two groups. The control group received standard antibiotic therapy plus lubricant as placebo and the intervention group received standard antibiotic therapy plus vaginal honey once a day for two weeks. Patients were evaluated for symptoms and clinical findings after three weeks following the initiation of the treatment. Balanced block randomization was used to allocate subjects into two groups and 51 patients were finally assigned to each group.

Eligibility criteria

We included patients with the following criteria: (1) non-pregnant women aged 15-45 years, and (2) clinical symptoms and signs of cervicitis according gynecologist judgement. The patients were excluded by these criteria: pregnancy, allergy to honey or antibiotics, abnormal Pap smear, any antibiotics consumption in the last two weeks, corticosteroids use, any underlying diseases and sexual intercourse during two weeks of intervention.

Cervicitis diagnosis criteria

Three main criteria were considered for cervicitis:

1. A purulent or mucopurulent endocervical exudate visible in the endocervical canal or on an endocervical swab specimen
2. Sustained endocervical bleeding easily induced by gentle passage of a cotton swab through the cervix
3. Vaginal discharge

The patients with at least two criteria were included in the clinical trial.

Study procedure

Organic "Konar" honey was used in the study. The placebo was an ordinary lubricant gel purchased from (Piccol®) purchased from Robina Bazaar Company, Isfahan, Iran in summer 2017. Tubes were prepared with intact honey or commercial lubricant gel by a pharmacist at the Faculty of Pharmacy, Zanjan, Iran. They were coded by the pharmacist to control and intervention groups. The control and intervention group vaginally applied 5 mL of lubricant gel or honey with applicator every night for two weeks. Both groups used 1 g azithromycin plus 400 mg cefixime as a single dose orally; expedited partner therapy was done too. Also, 500 mg metronidazole twice a day was used orally for 7 days to treat bacterial vaginosis. During 2 weeks of the treatment period, the patients were asked to avoid sexual intercourse. Signs, symptoms, and complaints of patients including vaginal itching; burning; discharge, abdominal pain, dyspareunia, postcoital bleeding were recorded according to the visual analog scale (VAS) before and after the treatment. Each of the symptoms was given a score of 0 to 6 according to its severity (six indicating the highest severity). Also, the clinical findings of the speculum exam were recorded including cervical mucopurulent discharges of cervix, contact bleeding, and erosion of cervix. A Pap smear was prepared at the first examination, and the photograph of the erosion was taken with colposcopy from the cervix in case of existance. Both groups were reevaluated after 21 days in terms of clinical symptoms, signs, and erosion of the cervix and a photo of the cervix was taken by colposcopy on the 21st day to compare with the first photo (initial day of the treatment). As the vaginal medications remain in vagina for a few days after usage, for best view in examination and colposcopy, the follow up visit was planned one week after termination of the treatment. The primary outcome was evaluation of the additive effect of honey on antibiotic treatment for reducing the clinical symptoms and signs of cervicitis, and the secondary outcome was the comparison of the healing rate of cervical erosion after the treatment in the control and intervention groups.

Data analysis

The qualitative data were presented in frequency and percentage through frequency tables and quantitative variables were presented as mean±standard deviation (SD). The normality of data was assessed with the Kolmogorov-Smirnov test. The continuous variables of the two groups were compared by Student's t-test or U Mann-Whitney. The VAS scores of baseline and endpoint in both groups were compared using the Kruskal-Wallis test. On the other hand, the categorical variables were compared using the chi-squared test. Data were analyzed using SPSS, version 23.0 (SPSS Inc., USA) and a p-value less than 0.05 was statistically considered as significant.

Results and Discussion

In the present study, 106 patients with cervicitis who referred to Mousavi Hospital in Zanjan were screened. Two patients did not have inclusion criteria, and two did not want to attend the study. Therefore, 102 patients were evaluated and assessed in two groups (Figure 1).

Table 1 presents the demographic baselines and history of individuals. About 75% of patients in the two groups lived in urban aeries in both groups. The majority of patients in the intervention and control groups had under diploma education. Most of the patients in both groups have experienced cervicitis at least once in their lifetime. As shown, there was no statistically significant difference between groups with respect to age, location, education, and previous history of cervicitis (p-value >0.05).

As shown in Table 2, the VAS score variable means of both groups including irritation, abdominal pain, vaginal itching, vaginal discharge, postcoital bleeding, and dyspareunia significantly decreased after 21 days in comparison to the first day (p-value<0.001). Also, Table 2 presents the clinical symptoms of the control and intervention groups in the first and 21st day. According to the findings, there were not any statistically significant differences in the level of irritation, abdominal pain, vaginal itching, dyspareunia, and postcoital bleeding between the control and intervention group (p-value>0.05). But there was an extremely significant difference in regard to the vaginal discharge between the two groups (p-value <0.001).

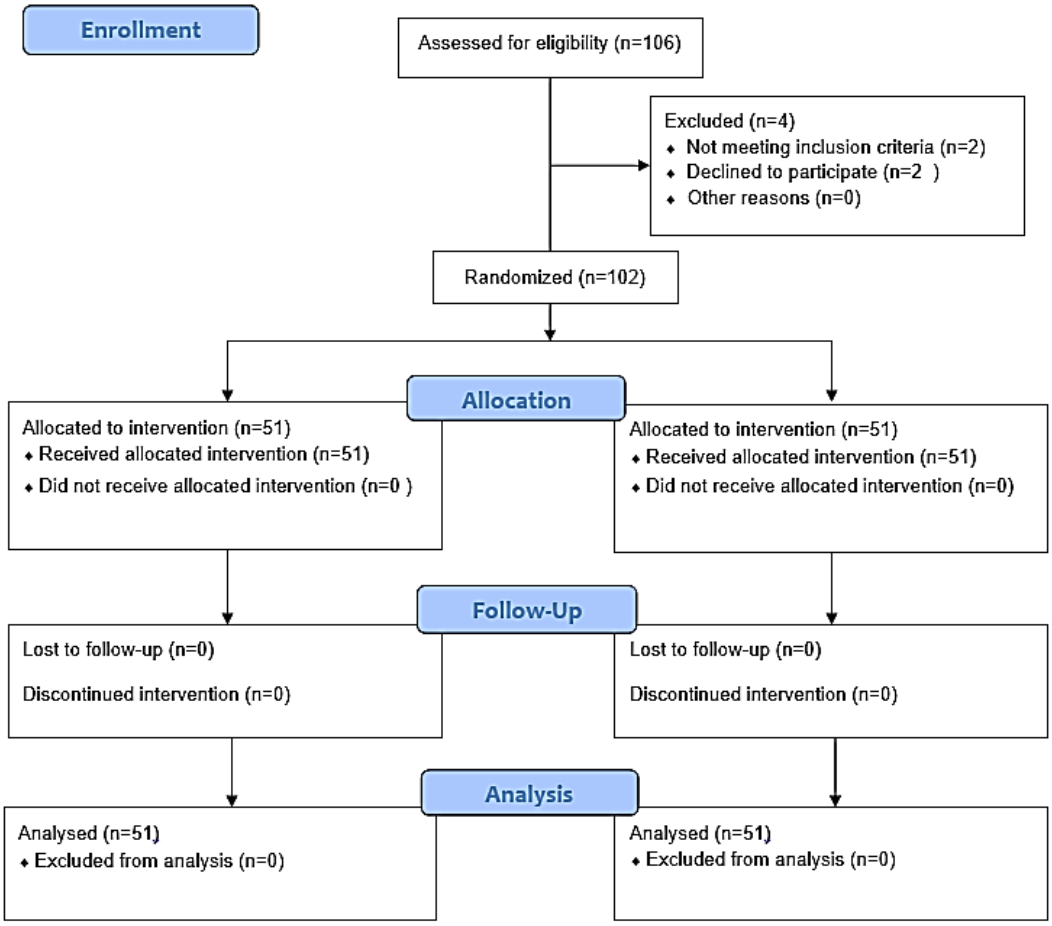

Figure 1. Flowchart on the allocation of patients to the studied groups

Table 1. Demographic baselines and past history of patients in two groups

Variables		Intervention group N (%)	Control group N(%)	p-Value
Age (year ± SD)		33.76 ± 7.9	32.08 ± 7.28	0.35
Location	Rural	13 (25.5)	15 (29.4)	0.66
	Urban	38 (74.5)	36 (70.6)	
Education	Lower diploma	28 (54.9)	26 (51)	0.66
	Diploma	12 (23.5)	16 (31.4)	
	Academic	11 (21.5)	9 (17.6)	
Previous history of cervicitis	No history	10 (19.6)	5 (9.8)	0.21
	1-2 Times	22 (43.1)	30 (58.8)	
	>2 Time	19 (37.3)	16 (31.4)	

Table 2. Comparison of differences in clinical symptoms (VAS scale) before treatment and on day 21, between control and intervention groups

Variable	Group	Baseline VAS score	VAS score 21 days after treatment	Diff*	p-Value**
Irritation	Control	3.33±1.52	1.08±1.40	2.25±2.01	**<0.001**
	Intervention	2.57±1.70	0.21±0.64	2.35±1.87	**<0.001**
	p-Value		*p* for diff comparison= 0.84		-
Abdominal pain	Control	4.92±1.05	1.70±1.66	3.21±1.73	**<0.001**
	Intervention	3.70±1.84	0.25±0.69	3.45±2.00	**<0.001**
	p-Value		*p* for diff comparison = 0.34		-
Vaginal itching	Control	2.94±1.43	1.06±1.42	1.88±1.99	**<0.001**
	Intervention	2.16±1.58	0.39±0.82	1.76±1.77	**<0.001**
	p-Value		*p* for diff comparison = 0.51		-
Vaginal discharge	Control	5.12±0.84	2.9±1.54	2.21±1.49	**<0.001**
	Intervention	5.00±1.09	0.10±0.36	4.90±1.24	**<0.001**
	p-Value		*P* for diff comparison <0.001		-
Dyspareunia	Control	3.76±1.96	0.37±1.06	3.39±2.41	**<0.001**
	Intervention	3.17±2.05	0	3.17±2.05	**<0.001**
	p-Value		*p* for diff comparison = 0.37		-
PostcoitalPost-coital bleeding	Control	2.21±1.87	0.08±0.27	0.65±0.52	**<0.001**
	Intervention	1.55±1.31	0	0.70±0.46	**<0.001**
	p-Value		*p* for diff comparison = 0.63		-

*Diff: difference between VAS score in baseline and 21 days after treatment; ***p*-value for difference in VAS score in baseline and 21 days after treatment

Table 3. Comparison of the results of clinical examinations after the treatment period

Variable		Intervention group N(%)	Control group N(%)	p-Value
Remission of erosion	Yes	11 (100)	4 (44.44)	0.02
	No	0	5 (55.56)	
Vaginal purulent discharge	Yes	2 (4)	18 (35.3)	<0.001
	No	49 (96)	33 (64.7)	
Contact bleeding	Yes	3 (5.9)	5 (9.8)	0.46
	No	48 (94.1)	46 (90.2)	

The results of the clinical examinations between two groups 21 days after the treatment are shown in Table 3. The erosion of cervix was observed in 11 and 9 patients in the intervention and control groups, respectively that was statistically similar in the two groups. This sign was improved in all patients of the intervention group without recurrence, while about half of patients in the control group experienced the remission of the erosion (p-value=0.02). Also, purulent vaginal discharge of the control group was significantly higher than the intervention group (p-value<0.001). There was no statistical difference in terms of contact bleeding between the two groups (p-value = 0.46).

According to the findings of our study, all clinical symptoms, including vaginal discharge, burning; itching; abdominal pain, dyspareunia, and postcoital bleeding decreased significantly after the treatment in both groups, but the vaginal discharge of the intervention group reduced more. It has been reported that several kinds of honey have antibacterial activity against a wide range of bacteria [14,20,21]. Nabimeybodi et al. reported that a vaginal product of flixweed honey could be used for the treatment of clinical symptoms of cervicitis [15].

More than half of cervicitis cases are not gonococcal and chlamydial. Mattson et al. have reported that the treatment rate of the non-gonococcal and non-chlamydial cervicitis was 66% with antibiotic monotherapy, including azithromycin, doxycycline, or moxifloxacin. Therefore, they suggested a prospective study or controlled trial in order to identify other strategies for the treatment of the non-gonococcal and non-chlamydial cervicitis by randomized controlled treatment studies [22].

A clinical trial on Fifty-four women with recurrent vaginal infection was performed and the patients were treated at least one cycle by antibiotic treatment plus 5% aqueous propolis solution (bee glue) as a vaginal douche for seven days. The results represented that 87% of women experienced relief concerning at least one complaint. Also, 61.1% of women were satisfied with the treatment method without any need for

further treatment after 6 months. Therefore, 5% propolis solution could be used in adjuvant therapy for chronic vaginal infection [23].

In our study, the cervical secretions of the honey users reduced more than control group which can be due to the anti-inflammatory and antibacterial effects of honey [24]. Pure honey acts as a sterile substance, and no microbial agent can grow in it. Studies have shown that honey can produce hydrogen peroxide without any damage to the tissue itself and consists of phenolic acid, bioflavonoids, and other antioxidants such as vitamin C that are antibacterial agents [24,25].

Besides other improvements, we found that the cervical erosion significantly improved in the intervention group. This effect of honey on erosion is not unexpected because it is proved that honey can promote wound and erosion healing by stimulating the proliferation of lymphocytes, formation of clean healthy granulation tissue, promoting epithelization, and reducing inflammation, edema and exudation [24]. Osmotic action, angiogenic effect, regulating immune responses such as elevating fibroblast proliferation, increasing phagocytic activity, producing antibodies, and reducing prostaglandins, are the most important molecular mechanisms of honey for promotion of healing [26,27]. In our study, the use of honey as an adjuvant therapy with a standard antibiotic regimen accelerated the recovery process; however, more researches are needed with a larger sample size, different doses of honey, and long-term follow-up in order to suggest application of honey in the adjuvant therapy of bacterial cervicitis. In this study, we found that honey can be effective in reducing cervical erosion and vaginal discharge of patients with cervicitis.

The major limitation of our study was that no laboratory methods were used to identify the bacterial agents, and the number of micro-organisms was not determined before and after the treatment.

Conclusion

Application of vaginal honey with standard antibiotic regimen was more effective than standard regimen alone in improving the clinical symptoms of cervicitis and reducing the cervical erosion and discharge. So, vaginal honey application, as an adjuvant therapy, can be recommended for the treatment of cervicitis.

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Author contributions

Robabeh Hatami, Nazanin Soltani and Mahdi Tavakolizadeh developed the original idea and the protocol, and prepared the manuscript; Robabeh Hatami and Atefeh Kazemi Robati participated in the study design and analyzed the data; Nazanin Soltani and Narges Forouzideh contributed to the study design and data gathering. All authors read and approved the final manuscript.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

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Abbreviations

VAS: visual analog scale; CDC: Centers for Disease Control and Prevention