USE OF INTRA-VAGINAL MANUKA HONEY FORMULATION FOR CERVICAL HEALING: AN OPEN-LABEL RANDOMIZED-CONTROLLED TRIAL

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ABSTRACT

Background: Honey is commonly used for wound dressing due to its antimicrobial, anti-inflammatory, and healing properties. Manuka honey is reported to have healing activity in patients with upper-eyelid scars, neuropathic diabetic foot ulcers, atopic dermatitis, and venous leg ulcers. However, its healing potential has not been previously assessed for cervical lesions or complications.

Objectives: To report outcomes of a randomized controlled trial on the role of intra-vaginal Manuka honey formulation on cervical healing in patients with ectropion cervix and postoperative cautery or loop electrosurgical excisional procedure LEEP.

Method: Single-center, prospective, randomized, open-label study for patients with persistent vaginal discharge, those who have ectropion cervix, and those who were treated with cervical cautery or LEEP. Patients were followed up for two other visits at two and four weeks by the same healthcare providers (qualified gynecologists), which are qualified gynecology specialists. The main symptoms assessed were pain, bleeding, discharge, size, and presence of infection.

Results: A total of 179 patients completed the study (95.2%) and 9 patients were excluded because they were lost to follow-up (4.8%). Improvement of symptoms was significantly noted in the treatment group compared to the control group (p-value <0.05). After four weeks, the overall treatment group expressed a marked reduction in assessed symptoms severity (Treatment Vs. Control): pain score (66.7% Vs. 9.5%), bleeding (89.9% Vs. 25.5%), vaginal discharge (67.3% Vs. 9.4%), and size of ectropion (46.2% Vs. 10.5%).

Conclusion: This study provides evidence of the effects of intra-vaginal Manuka honey formulation on boosting cervical healing and symptomatic relief in patients with abnormalities of cervical epithelium, especially patients with a cervical ectropion and those who had cervical interventions.

Keywords: Manuka honey, cervical healing, ectropion, erosion.

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INTRODUCTION

Manuka honey is a monofloral dark honey produced from Manuka tree flowers, which is rich in phenolic content. Apis mellifera honey bees produce Manuka honey Since the beginning of time, honey has been used for its nutritional and therapeutic values.

Wound dressing is one of the most common therapeutic uses of honey, mainly due to its established antimicrobial, anti-inflammatory, and healing properties by keeping wounds moist, and establishing a protective barrier due to honey's viscosity (1).

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By the 1960s, due to the introduction of efficient antibiotics, honey was termed a "worthless but harmless substance" (2).

variety, using New Zealand Manuka trees yielding a unique floral variety termed Leptospermum scoparium (1). A classification system regulates Manuka honey, known as the Unique Manuka Factor (UMF), which reflects the equivalent phenol concentration needed to express a similar antibacterial effect as honey. Other than the usual honey content of carbohydrates, minerals, proteins, fatty acids, phenolic, and flavonoid compounds, Manuka honey expresses unusually high levels of methylglyoxal (MGO) that correlates to its antibacterial properties (3). The medicinal value of honey originates from the floral source utilized by bees. Studies have found that honey is effective against a wide range of pathogens including S. aureus, S. pyogenes, P. aeruginosa, and E. coli. (4, 5). The benefits of honey as alternative medicine extend to its unique antioxidant, anticancer, and healing properties (6, 7). Easy administration and the absence of antibiotic resistance are crucial characteristics of the use of honey for the treatment of clinical wounds (8-10). Recent literature reveals novel approaches to utilize honey-based pharmaceuticals like nanoparticles, gels, and vaginal creams for their anti-fungal potential, especially against various Candida species (11-15).

Cervical ectropion, also known as cervical erosion or ectopy, occurs when the normal stratified squamous epithelium of the vaginal portion of the cervix, found below the external os, is replaced by the columnar epithelium zone. Due to blood vessels underneath the surface, the exposed columnar epithelium appears red (16, 17).

Cervical ectropion is as common as 17% to 50% among women (17, 18). Cervical ectropion is one of the most common reasons for hospital attendance of women aged 15–44 years (17). Many etiologic factors have been associated with the development of cervical ectropion including, but not limited to pregnancy, using combined oral contraceptives, inflammation, trauma, and Chlamydia trachomatis infection (19-21). Pelvic routine examination commonly uncovers cervical ectropion during fertile years (22, 23) The most common symptom of cervical ectropion is vaginal discharge (24). Moreover, postcoital bleeding may be observed, especially in pregnant women (25). Treatment for cervical ectropion is only indicated when patients are symptomatic. In patients with cervical ectropion who frequently bleed or spot benefit from intervention such as diathermy (cervical cautery) and cryotherapy (cryocautery) to relieve their symptoms (26, 27).

Our study aims to assess the potential healing effects of intra-vaginal Manuka honey ointment formulation among patients with cervical ectropion and post cervical interventions like cauterization and loop electrosurgical excisional procedure (LEEP), including an assessment of the overall improvement of pain, bleeding, discharge, size, and infection status. To the best of our knowledge, this is the first study to assess cervical healing potentials for Manuka honey.

METHODS

The study design adopted by the authors is a single-center, prospective, randomized, open-label study for patients with persistent vaginal discharge, those who have ectropion cervix, and those who were treated with cervical cautery or LEEP. The study was conducted at the colposcopy clinic at King Hussein Medical Centre, Royal Medical Services (RMS), Amman, Jordan. Institutional research and review board approval was obtained before conducting the study (approval number 6/2016). **Figure 1** includes a flow chart of this study protocol.

Inclusion criteria included patients with persistent vaginal discharge and cervical ectropion or patients who had treatment with cervical cautery or excision via LEEP. All cases had a vaginal examination, high vaginal swab culture, and cervical pap smears. **Exclusion criteria** included patients with abnormal high vaginal swab, abnormal cervical pap smear, except for patients undergoing cervical cautery or excision via LEEP. and those who failed to attend the follow-up visits.

Participant recruitment and allocation. Patients attending our colposcopy clinic at King Hussein Medical Centre, Royal Medical Services (RMS) who fit the inclusion criteria and were able to provide informed consent were asked to be involved in the study. Explanation of the study protocol was carried out to all participants, and participation was completely voluntary with all patients conserving the right to withdraw from the study anytime with no obligations or influence on the level of care provided. The study was conducted from June 2016 to January 2017.

All cases were randomized by simple randomization using computer generated sequence into two groups: the first group of patients (treatment group) were instructed to apply intra-vaginal Manuka honey ointment formulation into the cervix once daily and the second group had a standard care (control group). Each study group was divided into three arms: symptomatic without ectropion, symptomatic with ectropion, post cautery or LEEP. A simple randomization process was adopted for each related arm of the study to reach the target sample size.

Intervention. Manuka honey 35% vaginal ointment formulation (Ectros® ointment; registration code MD204/2015, RAZA for Medical Supplies – RAZA International, Jordan), which is supplied as a 30-gm tube with five disposable vaginal applicators, to be used for 10 days. All patients in the treatment group received two packs for the whole period. The first dose was given at the clinic and patients were instructed to continue its use once daily at home. Patients were evaluated after two weeks and four weeks of treatment use. The control group for all subgroups received no further management, as the standard care is watchful waiting and symptomatic management when necessary. Same professional gynecology specialists who are well qualified in their respective field performed all clinical evaluations and followed up the patients across all stages in this study.

Outcomes. The study's primary outcomes were: (1) A comparison of mean symptoms score change between each comparable arm of the study groups (treatment vs. control), and (2) The mean score changes of symptoms in each arm of the study.

The collected data included: cervix pictures using speculum, patient's age, parity, menopausal status, an indication of surgery performed, presenting symptoms (discharge and bleeding), presence of infection, and healing of the cervix. Table 1 lists the severity scales used in this study for each outcome of interest. For pain, bleeding, and discharge reporting was subjective by the patient according to the usual perceived norm. For ectropion size, sequential assessment using colposcopy were compared at each visit and scored based on size change by the same physician as 0: >40% reduction, 1: 20-40% reduction, 2: <20% reduction, and 3: Original size. The change in infection status was only assessed for post-cautery or LEEP patients and subjectively scored by the same physician.

Sample size. Based on previously published data, we estimated using G-power software (Version 3.1) (28) that the sample size necessary to detect a 1-point difference between any 2 treatment groups with 80% power and a significance level (alpha) of 0.05 was 30 subjects per group (total of 180 patients considering arms of each group). To compensate for dropouts and abnormal data distribution, we decided size, sequential assessment using colposcopy were to recruit 33 patients per arm in each group (a total of 200 patients).

Statistical analysis. All data were entered into SPSS version 24 (IBM, Armonk, NY, USA). Continuous variables were expressed as mean ± SD and categorical variables were expressed as percentages (95% confidence interval). Baseline differences between groups were examined using the independent samples t-test for independent study groups and related arms which include socio-demographic characteristics, pain, bleeding, discharge, size, and infection status. Two-way ANOVA was used to compare mean symptoms score change between each comparable arm of the study groups (treatment vs. control). P-value <0.05 indicates statistical significance.

RESULTS

A total of 188 consenting female patients were approached to participate in the study. They were assessed for eligibility criteria and were randomized among the study arms. 179 patients completed the study (95.2%) and nine patients were excluded because they were lost to follow-up (4.8%). Therefore, they were not included in the statistical analysis. The mean age of patients completing the study for the treatment and control groups were 37.34±9.18 years and 39.79±9.11 years respectively, with no significant difference between the study groups (p-value>0.05) (Table 2). Patients who received vaginal Manuka honey ointment formulation were 94, distributed as 32 patients symptomatic without ectropion, 29 patients symptomatic with ectropion, and 33 patients with post cautery or LEEP, while 94 other patients were distributed as a control group among the same latter arms as 33, 28, and 33 patients for each arm respectively. Additionally, there were no significant differences between measures of symptom severity at baseline (p-value>0.05) . **Table 2**

As per each patient cluster, the mean score of symptoms at the last visit for the treatment versus the control group was compared. Patients symptomatic without cervical ectropion showed significant mprovement in pain, bleeding, and discharge in response to the vaginal Manuka honey iointment formulation treatment group compared to the control group as shown in **Figure 2**.

Patients symptomatic with cervical ectropion showed significant improvement in pain, bleeding, and discharge in response to vaginal Manuka honey ointment formulation in the treatment group compared to the control group, while the size was not significantly reduced, yet the change in ectropion size was noted in the treatment group as shown in **Figure 3**. Patients who underwent cauterization or LEEP showed significant improvement in bleeding, discharge, and lesion size in response to the vaginal Manuka honey ointment formulation treatment group compared to the control group.

Moreover, postoperative infection was significantly reduced in the treatment group compared to the control group, as patients treated with vaginal Manuka honey ointment formulation expressed minimal levels of infection compared to the control group, which expressed rising levels of infection postoperatively as shown in **Figure 4.**

Overall, improvement in symptoms was significantly noted in the treatment group compared to the control group (p-value<0.05) as expressed in **Figure 5**.
By the end of the 4-week follow-up, the treatment group expressed a marked reduction in symptoms severity: the mean percent reduction in pain score from baseline was 66.7% in the treatment group compared to 9.5% in the control group; the mean percent reduction in bleeding from baseline was 89.9% in the treatment group compared to 25.5% in the control group; the mean percent reduction in vaginal discharge baseline was 67.3% in the treatment group compared to 9.4% in the control group; the mean percent reduction in the size of ectropion from baseline was 46.2% in the treatment group compared to 10.5% in the control group.

Table 1 : Severity scale.

Scale item	Severity scale	Scale measurement
Pain	0: Free; 1: Mild; 2: Moderate; 3: Severe	Subjective by patient
Bleeding	0: Free; 1: Mild; 2: Moderate; 3: Severe	Subjective by patient
Discharge	0: Free; 1: Mild; 2: Moderate; 3: Severe	Subjective by patient
Size a	0: >40% reduction; 1: 20-40% reduction; 2: <20% reduction; 3: Original size	Objective by physician
Infection b	0: Free; 1: Mild; 2: Moderate; 3: Severe	Objective by physician

a only applicable for patients with cervical ectropion; b only applicable for patients who underwent cauterization or loop electrosurgical excisional procedure.

Table 2. Baseline data of each study group and their related arms.

	Treatment group (n=94)				**Control group (n=94)**			
	Overall Group	Arm 1: Sympto	Arm 2: Sympto	Arm 3: Post	Overall Group	Arm 1: Sympto	Arm 2: Sympto	Arm 3: Post
Age * mean(±STDEV)	**37.34 (9.18)**	38.53 (9.26)	34.45 (8.39)	38.73 (9.45)	**39.79 (9.11)**	43.42 (9.63)	35.96 (8.17)	39.40 (8.15)
Parity Number * mean(±SD)	**3.24 (1.00)**	3.28 (1.02)	3.29 (0.86)	3.16 (1.14)	**3.37 (0.97)**	3.58 (0.81)	3.00 (1.11)	3.48 (0.93)
Menopause * mean(±SD)	**0.08 (0.27)**	0.133 (0.35)	0.00 (0.00)	0.08 (0.27)	**0.15 (0.36)**	0.28 (0.46)	0.06 (0.24)	0.08 (0.28)
Pain * mean(±SD)	**2.08 (1.33)**	2.09 (1.35)	2.07 (1.34)	NA	**1.89 (1.33)**	1.67 (1.43)	2.14 (1.18)	NA
Bleeding * mean(±SD)	**0.84 (1.29)**	1.31 (1.40)	1.10 (1.40)	0.10 (0.54)	**1.17 (1.38)**	1.21 (1.39)	2.179 (1.19)	0.25 (0.80)
Discharge * mean(±SD)	**2.09 (1.36)**	2.97 (0.18)	2.97 (0.19)	0.36 (0.95)	**1.90 (1.43)**	2.76 (0.75)	2.86 (0.59)	0.188 (0.74)
Size * mean(±SD)	**2.97 (0.18)**	NA	3.00 (0.00)	2.94 (0.25)	**2.82 (0.50)**	NA	2.96 (0.19)	2.70 (0.64)
Infection * mean(±SD)	**0.00 (0.00)**	NA	NA	0.00 (0.00)	**0.06 (0.35)**	NA	NA	0.063 (0.35)

SD: Standard deviation; * mean value difference between each study group was not significantly different using an independent sample t-test with 95% confidence (p-value > 0.05); NA: Not applicable; LEEP: Loop Electrosurgical

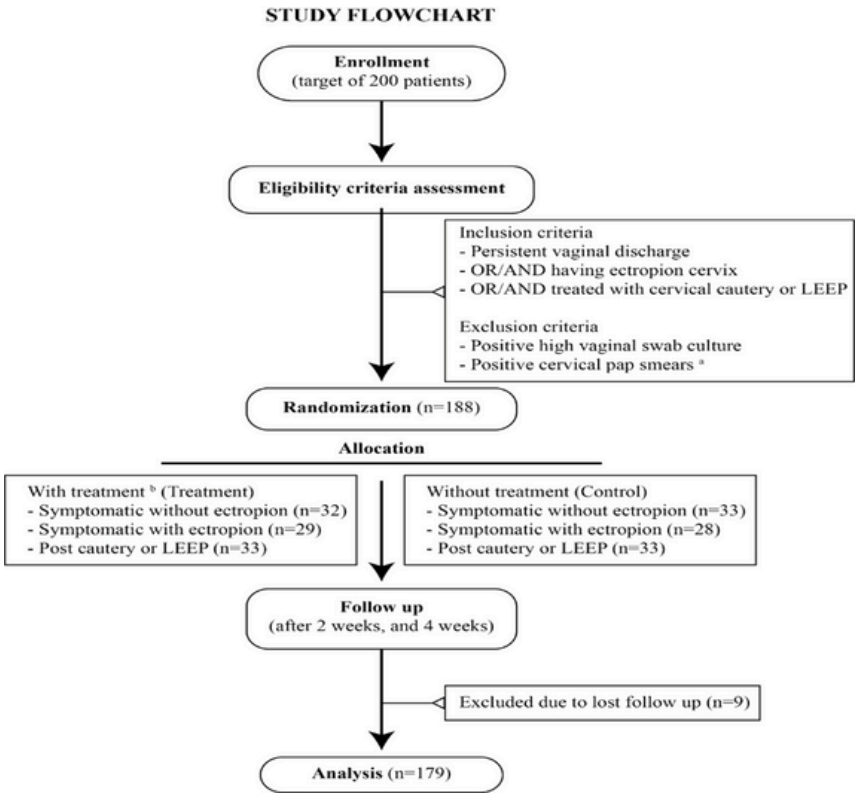

Figure 1. Study protocol flowchart

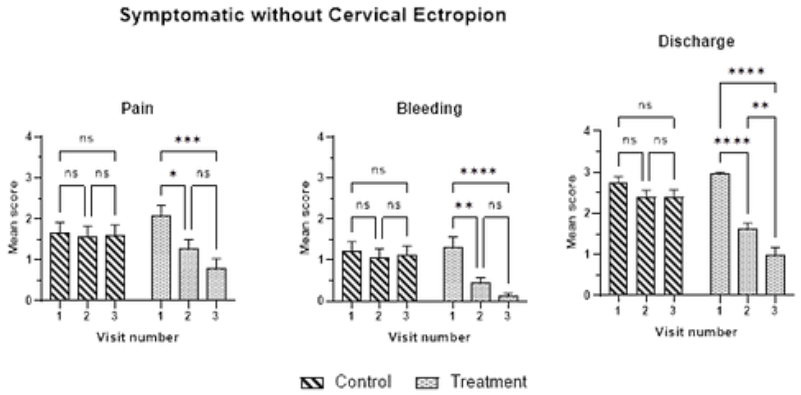

Figure 2. Comparison between Treatment and Control groups considering the mean score of symptoms for patients symptomatic without cervical ectropion per visit. Error bars represent standard deviation. Lines represent statistical comparison of the output in different study groups using two-way ANOVA accounting for multiple comparisons with 95% confidence; P-value <0.05 indicates statistical significance, while asterisk: ns (not-significant) P > 0.05; * P ≤ 0.05; ** P ≤ 0.01; *** P ≤ 0.001; **** P ≤ 0.0001 (according to GraphPad prism 9).

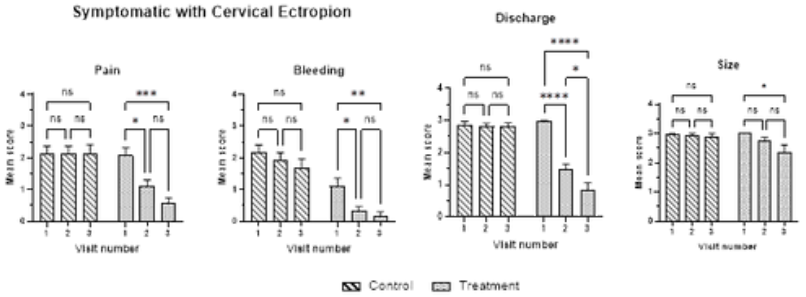

Figure 3. Comparison between Treatment and Control groups considering the mean score of signs and symptoms for patients symptomatic with cervical ectropion per visit. Error bars represent standard deviation. Lines represent statistical comparison of the output in different study groups using two-way ANOVA accounting for multiple comparisons with 95% confidence; P-value <0.05 indicates statistical significance, while asterisk: ns (not-significant) P > 0.05; * P ≤ 0.05; ** P ≤ 0.01; *** P ≤ 0.001; **** P ≤ 0.0001 (according to GraphPad prism 9).

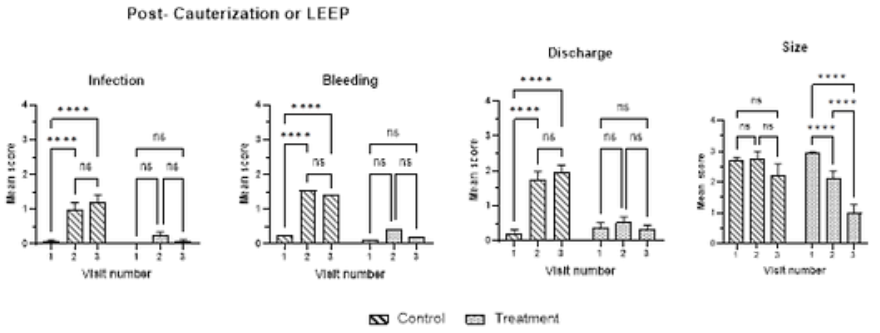

Figure 4. Comparison between Treatment and Control groups considering the mean score of symptoms for patients who underwent cauterization or LEEP per each visit. Error bars represent standard deviation; LEEP: Loop Electrosurgical Excision Procedure. Lines represent statistical comparison of the output in different study groups using two-way ANOVA accounting for multiple comparisons with 95% confidence; P-value <0.05 indicates statistical significance, while asterisk: ns (not-significant) P > 0.05; * P ≤ 0.05; ** P ≤ 0.01; *** P ≤ 0.001; **** P ≤ 0.0001 (according to GraphPad prism 9).

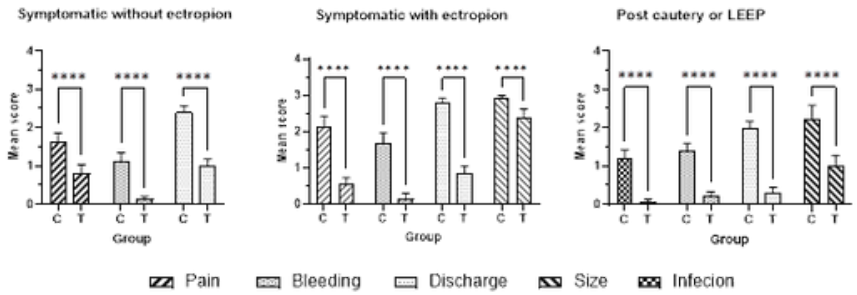

Figure 5. Comparison between Treatment (T) and Control (C) groups at last visit (visit 3) considering the mean score of symptoms relevant to each subgroup. Error bars represent standard deviation; LEEP: Loop Electrosurgical Excision Procedure. Lines represent statistical comparison of the output in different study groups using two-way ANOVA accounting for multiple comparisons with 95% confidence; P-value <0.05 indicates statistical significance, while asterisk: ns (not-significant) $P > 0.05$; * $P \leq 0.05$; ** $P \leq 0.01$; *** $P \leq 0.001$; **** $P \leq 0.0001$ (according to GraphPad prism 9)

DISCUSSION

To the best of our knowledge, this is the first randomized controlled trial assessing the effects of Manuka honey, a core constituent in a pharmaceutical vaginal ointment formulation, on cervical healing related to cervical ectropion and cervical injury due to cautery or LEEP. This study shows that cervical ectropion treated with vaginal Manuka honey ointment formulation healed very well with a significant difference in the overall symptom improvement assessed by self-validated scales for pain, bleeding, discharge, size, and infection status compared to women who had a standard care.Manuka honey can stimulate macrophages, a mechanism related to the Apalbumin-1 protein's ability to release mediators such as IL-1β, TNF-α, and IL-6, which aid tissue healing and reduce microbial infections (29-31). Rich literature is available on the successful use of Manuka honey in the resolution of non-healing wounds and the resolution of infections that failed conventional antibiotics (32, 33). Healing with Manuka honey was also noted in patients with upper eyelid scars, neuropathic diabetic foot ulcers, atopic dermatitis, and venous leg ulcers (32, 34-36).

Our study identified an excellent value for Manuka honey in boosting cervical healing, which is being reported for the first time. Cervical ectropion often needs treatment when accompanied by bothersome spotting or excessive discharge of mucus. Malignancy should always be excluded by cervical cytology. Nevertheless, whether cervical ectropion should be treated remains controversial (37, 38).

Theoretically, treatment of cervical ectropion could prevent the development of cervical cancer and could cut the infective process of sexually transmitted microorganisms, this can be extrapolated since pre-cancerous lesions often present at the squamous-columnar junction and Neisseria gonorrhea and Chlamydia trachomatis often infect glandular epithelium (39-41).

Patients diagnosed with ectropion cervix in our study expressed marked improvement in terms of pain, bleeding, and discharge upon using a vaginal Manuka honey ointment formulation compared to its relevant untreated arm.

Several treatment modalities have been used for cases of cervical ectropion, including use of antibiotics, electrocautery, cryosurgery, microwave tissue coagulation, laser cauterization, alpha-interferon suppository, and polydeoxyribonucleotide vaginal suppositories (37, 42-45). However, limited data is available for the efficacy of all the above treatments. Treatment is usually assumed effective if cervical appearance is altered, explained as the disappearance of red columnar epithelium and relief of symptoms at follow-up (38). Characteristic improvement of cervical mucus and restoration of B- and T-lymphocytes were also reported to guide the success of cervical ectropion treatment (43, 45). The cure rate of cervical ectropion using cryosurgery and microwave tissue coagulation was 92%, while a 79% cure rate has been reported using carbon dioxide laser with more bleeding compared to microwave tissue coagulation (37, 46). In our study, patients undergoing cautery or LEEP for their cervical condition management expressed marked improvement in terms of bleeding and discharge upon using a vaginal Manuka honey ointment formulation compared to its relevant untreated arm. Moreover, infection post-operatively was markedly prevented for treated patients compared to untreated ones. Likewise, lesion size post-operatively expressed a significant reduction over time when exposed to Manuka honey vaginal ointment formulation compared to the relevant untreated control patients.

Limitations of this study can include failure to recruit the required number of participants. However, with 188 participants, the study is still the largest study assessing the efficiency of manuka honey formulation in the treatment of cervical benign lesions. Since the numbers in each group were small, statistical interpretation of the results was constrained. We do hope, however, that the findings will contribute to the body of information about the use of Manuka honey in vaginal wounds. Despite their confirmation, wound assessment measures remain subjective and have inherent limitations when assessing light wounds. Quantitative wound healing assays could have offered a more comprehensive picture. Moreover, it is widely assumed that vaginal lesions heal without complications on their own; therefore, determining the additional advantage that Manuka honey administration may provide to vaginal surgery wounds is particularly difficult. We attempted this task in our work by establishing a randomized controlled trial, but the low number of patients in the study may have played a part in the lack of statistical significance in change of size of the lesion. Further research comparing Manuka honey with other forms of treatments would also warrant a better understanding of its significance in wound management.

CONCLUSION

In conclusion, this study provides evidence of the effects of vaginal Manuka honey ointment formulation on boosting symptomatic relief and healing of cervical ectropion and patients undergoing cervical procedures like cautery or LEEP.

Cervical ectropion and postoperative cervical lesions treated with vaginal Manuka honey ointment formulation healed very well.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Vaginal Manuka honey 35% ointment formulation (Ectros® ointment; registration code MD204/2015, Raza for Medical Supplies – RAZA International, Jordan) was supplied free of charge by the manufacturer.

Availability of Data and Materials

Data supporting this study's findings are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

informed consent was obtained from all participants in the study.

CONSENT FOR PUBLICATION

Consent to publish from the participants was also obtained.

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