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Topical honey application vs. acyclovir for the treatment of recurrent herpes simplex lesions

Noori S. Al-Waili

Private Clinic and Dubai Specialized Medical Center and Medical Research Laboratories, Islamic Establishment for Education, Dubai, United Arab Emirates

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Summary

Background: The objective of this research was to investigate the effect of the topical application of honey on recurrent attacks of herpes lesions, labial and genital, as compared to acyclovir cream.

Material/Methods: Sixteen adult patients with a history of recurrent attacks of herpetic lesions, 8 labial and 8 genital, were treated by topical application of honey for one attack and acyclovir cream for another attack.

Results: For labial herpes, the mean duration of attacks and pain, occurrence of crusting, and mean healing time with honey treatment were 35%, 39%, 28% and 43% better, respectively, than with acyclovir treatment. For genital herpes, the mean duration of attacks and pain, occurrence of crusting, and mean healing time with honey treatment were 53%, 50%, 49% and 59% better, respectively, than with acyclovir. Two cases of labial herpes and one case of genital herpes remitted completely with the use of honey. The lesions crusted in 3 patients with labial herpes and in 4 patients with genital herpes. With acyclovir treatment, none of the attacks remitted, and all the lesions, labial and genital, developed crust. No side effects were observed with repeated applications of honey, whereas 3 patients developed local itching with acyclovir.

Conclusions: Topical honey application is safe and effective in the management of the signs and symptoms of recurrent lesions from labial and genital herpes.

key words: **HSV • labial herpes • genital herpes • crusting**

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Author's address: Noori S. Al-Waili, Dubai Specialized Medical Center, Department of Nephrology and Urology, and Alternative Medicine, P.O. Box 19099, Dubai, United Arab Emirates, e-mail: noori786@yahoo.com

BACKGROUND

Honey, a thick sweet liquid made by bees from the nectar of flowers, is one of the oldest known medicines. Honey has always been highly valued in the Middle East. It was mentioned in the Quran 1400 years ago: "And thy LORD taught the bee to build its cells in hills, on tree and in men's habitations, then to eat of all the produce of the earth and find with skill the spacious paths of its LORD, there issues from within their bodies a drink of varying colors, wherein is healing for men, verily in this is a sign for those who give thought [1]. In recent times, however, the medicinal use of honey has reappeared in modern medicine. Wounds treated with honey show less edema, less granular and mononuclear cell infiltration, less necrosis, better wound contraction, and lower glycosaminoglycan and proteoglucan concentrations [2]. In postoperative wound infections following cesarean section or hysterectomy, topical honey application hastens the eradication of bacterial infections, reduces antibiotic use and hospital stay, accelerates wound healing, and produces minimal scar formation [3]. In skin diseases, we have used honey to treat seborrheic dermatitis and dandruff [4]. A mixture that includes olive oil, beeswax, and natural honey accelerates healing of skin lesions and relieves the signs and symptoms of eczema, psoriasis, and fungal skin infections [5,6].

Honey has a wide range of antibacterial activities. In earlier studies, we found that conjunctival application of honey can eradicate acute bacterial conjunctivitis due to *Staphylococcus aureus* and *Psedomonas aeruginosa* [7,8]. In vitro studies have shown that a 30–50% dilution of honey in liquid broth inhibits the growth of various human pathogenic bacteria, as well as *Candida albicans* [9]. Two important classes of inhibitors found naturally in honey are flavonoids and phenolic acid (caffeic acid and ferulic acid) [10]. Honey has also been reported to have anti-leishmanial effects, as well as anti-rubella virus activity [11,12].

Labial and genital herpes are common viral diseases. Satisfactory curative agents are still unavailable. Therefore, the present study examined the possible therapeutic effect of the topical application of honey on recurrent lesions of labial and genital herpes lesions, compared with treatment by topical application of acyclovir cream.

MATERIAL AND METHODS

Otherwise healthy men and women with recurrent labial herpes (8 patients) and genital herpes (8 patients) were recruited. The subjects ranged in age from 35 to 45 years (mean 42 years). The mean number of outbreak in the preceding year was 6 episodes for genital herpes and 5 for labial herpes. A full medical history was recorded, and a physical examination was performed. The medical documentation revealed that the duration of episodes had ranged from 7 to 12 days without any antiviral interventions before admission to the experiment.

Patients who had previously received suppressive acyclovir therapy were excluded. A blood sample was obtained to assay HSV antibody, which was positive for all the patients.

After giving informed consent, the patients were examined during the course of two consecutive attacks. Honey was applied for one attack, and 5% acyclovir cream for the other attack. The patients were asked at random to use one or the other treatment in the first attack, so that half of them used honey during their first attack, and half used acyclovir. The patients were instructed to initiate treatment within one hour of the appearance of first sign or symptom of recurrence, and to report to the clinic within 24 hrs of starting treatment. The lesions were firmly pressed with gauze soaked with honey for 15 min, four times a day, until complete healing. Acylcovir cream was applied six times a day during the treated attacks. The honey was gathered from April to June in the United Arab Emirates; it was dark yellow in color and multifloral in origin.

Herpetic lesions were evaluated daily by the physician until the lesions disappeared. They were classified as macula, papule, vesicle, pustule, ulcer, crust or healed lesions. Pain was defined as none, mild, moderate or severe. The parameters measured in both groups of patients and used for comparison were;

1. healing time (time elapsed between the appearance of signs and symptoms and return to normal skin);
2. pain resolution (time elapsed between the first pain experience and complete pain relief);
3. pain severity (none=0, mild=1, moderate=2, and severe=3),
4. duration of episodes (time elapsed between the first appearance of signs and symptoms and complete disappearance of all complaints);
5. number of patients who did not develop vesicle/ulceration/crust lesions (aborted cases);
6. daily presence of erythema, indurations, papule, vesicle, and scab;
7. occurrence of crust (time until lesions crusted).

A viral culture was not feasible in our center, so swab specimens for determination of viral shedding were not obtained.

Statistical analysis

Student's *t* test was used to compare between honey and acyclovir treatment. $P<0.05$ was deemed to be significant.

RESULTS

All the patients completed two trials, one trial with honey application and one with acyclovir ointment. With acyclovir treatment, the mean duration of labial herpes attacks was 5.28±1.2 days, while with honey the duration was 35% shorter ($p<0.05$, cf. Table 1). For labial herpes, the mean duration of pain, occurrence of crust, and mean healing time with honey treatment were 39%, 28% and 43% better, respectively, than with acyclovir treatment. For genital herpes, the mean duration of attacks and pain, occurrence of crust, and mean healing time with honey treatment were 53%, 50%, 49%, and 59% better, respectively, than with acyclovir. Honey application resulted in two cases of aborted attacks in labial herpes, and one case in genital herpes. No case of aborted attack was seen with use of acyclovir. The herpetic lesions in three patients with labial herpes and in four patients with genital herpes developed crust with the

Table 1. Parameters measured in patients with labial herpes and genital herpes with the use of acyclovir or honey.

Variables	Acyclovir		Honey	
	Labial herpes	Genital herpes	Labial herpes	Genital herpes
Duration of attacks (days)	5.28±1.2	5.71±0.95	1.85±1.46*	3.1±1.5 *
Occurrence of crust (days)	3±1	3.5±0.97	0.85±1.2*	1.71±1.7
Healing time (days)	5.85±1.57	6.28±1.38	2.57±0.95*	3.71±1.89*
Pain duration (days)	2.57±0.97	2.28±0.75	1±0.8*	1.14±0.89
Number of aborted attacks	0	0	2	1

* p<0.05 in comparison with acyclovir treatment in the same herpetic lesions

use of honey. With acyclovir treatment, the lesions in all the patients with labial or genital herpes developed crust. Five patients with labial herpes and five patients with genital herpes developed mild to moderate pain within the first 24 hrs of honey application. Symptoms of pain, tingling and burning were abated and stopped completely within 24 hrs after honey therapy in three patients with labial herpes and in two patients with genital herpes. With the use of acyclovir, none of the patients with labial herpes or genitals showed pain relief within the first 24 hrs. All the patients with labial herpes treated by acyclovir experienced mild to moderate pain within first 24 hrs. Three patients experience pain relief within 48 hrs, while the remainders were relieved of pain within 72 hrs. Regarding genital herpes, all the patients experienced mild to severe pain within the first 24 hrs. Three patients experience complete pain relief within 48 hrs, and five patients within 72 hrs.

No side effects were encountered with repeated application of honey, and the patients reported greater satisfaction with honey application than with acyclovir treatment. One patient with labial herpes and two patients with genital herpes developed itching with the use of acyclovir.

Discussion

Thsee results demonstrate for the first time that topical honey application is effective in healing labial and genital herpes lesions. The healing time is faster with the use of honey than with acyclovir. The comparison was made directly between acyclovir and honey, without the use of a placebo, since it was thought unethical to use a placebo. Nevertheless, an analysis of the medical history of these patients revealed that the duration of attacks ranged from 7 to 12 days without any intervention; the patients had experienced tingling and pain, and the lesions had developed the classical signs and symptoms, including prodromal stage. It is known that without treatment herpetic lesions may heal spontaneously within about 10 days. However, the pain and discomfort most of the patients experience usually necessitate management. Recurrence usually occurs 2 to 3 times a year. The vesicles heal completely in 8 to 10 days. Pain diminishes in 4 to 5 days. The primary goal of treatment at this time is to reduce discomfort and pain, the duration of symptoms, and viral shedding. With the use of natural honey, all the signs and symptoms of attacks were reduced, and some attacks were abated.

Honey is cheap and readily available as compared to acyclovir. It would be interesting to proceed with studies that would include the effects of horny on viral shedding.

Herpes simplex virus affects more than one-third of the world's population [13]. Therefore, herpes simplex virus infections are among the most common human viral infections. Herpes simplex virus is a double-stranded DNA virus that may enter the host through abraded skin or intact mucus membranes [13]. Reactivation of the virus is triggered by local or systemic stimuli, such as immunodeficiency, trauma, fever, menstruation, ultraviolet radiation, and sexual intercourse [13–15]. Many medications are available for the treatment of herpes simplex virus lesions, including foscavir, famciclovir, valacyclovir and acyclovir. Various topical preparations are being used for treatment of herpes, including 1% viroptic, 1% penciclovir, and 5%. acyclovir. Acyclovir comes in topical, oral and intravenous forms. Though topical acyclovir ointment has poor penetration, the intravenous and oral forms decrease both healing time and viral shedding [16]. Topical acyclovir reduces the duration of viral shedding [13]. Oral acyclovir for the treatment of primary and recurrent genital herpes is administered five times daily for 10 days. In addition, acyclovir has been used to suppress recurrence of genital herpes [17]. It has been known that acyclovir inhibits viral enzyme DNA polymerase. Acyclovir-resistant herpes simplex virus infections are emerging, especially in immunocompromised patients [18]. Though acyclovir is a safe drug, it may induce nephrotoxicity and neurotoxicity [19]. Cases of allergic dermatitis have been encountered with the use of acyclovir [20].

In the present study, honey was used as an alternative treatment to manage recurrent episodes of herpetic lesions. The antibacterial activities of honey have been ascribed to its acidity, osmolality, and hydrogen peroxide production [21]. However, its possible effects on viral infections need further investigations. Honey contains various ingredients, such as flavonoids, vitamin E, vitamin C, zinc, copper, amino acids, and B-vitamin complex. All these ingredients have been found effective in the management of herpetic lesions [22–26]. Copper causes inactivation of herpes simplex virus, enhanced by ascorbic acid and hydrogen peroxide [27], which are likewise constituents of honey [28]. Flavonoids are more effective than acyclovir and placebo in healing genital herpes [29]. Propolis, another apiary product, reduces the viral titer of herpes simplex virus, and its content of flavonoids shows activity against herpes simplex virus -1 [30,31].

Recently we identified nitric oxide (NO) metabolites, nitrite and nitrate, in various honeys [32]. Honey contains secretion from the pharyngeal and salivary glands of the honeybee's head. Along with other researchers, we have identified nitric oxide metabolites in salivary gland section [33,34]. It is known that NO is an important active mole-

cule that plays a role in host defense against bacteria, protozoa and tumor cells. NO has antiviral effects against the DNA and RNA of several viruses [35]. There is some evidence of NO activity directly or indirectly blocking HIV-1 replication [35]. NO may inhibit herpes simplex virus ocular lesion [36]. We have found that instillation of honey on the ocular surface did not initiate any side effects, and can eradicate conjunctival infections [7,8]. Therefore, honey may also be useful in the management of ocular herpes virus infections. The presence of NO metabolites in honey and the ability of honey to increase NO production in various biological fluids may explain its potent biological effects [32,33,37].

It has been suggested that prostaglandin may be a final common pathway for stimulating recurrence of herpes simplex keratitis [38]. Prostaglandins are involved in herpes simplex 1 and 2 infections by suppressing T cell function, allowing for clinical recurrence [39]. Prostaglandins increase adhesion between cells infected with herpes simplex virus and uninfected cells [40]. Inhibition of prostaglandin by indomethacin may modify ultraviolet radiation-induced herpes simplex virus recurrence by decreasing viral reactivation and prostaglandin-induced immunosuppression [41]. Indomethacin decreases herpes simplex virus replication in cell culture [42]. We found that prostaglandins are potent immunosuppressive agents, lowering antibody titer against thymus-dependent and thymus-independent antigens during primary and secondary immune response [43]. In addition, prostaglandins are well known mediators of pain and inflammation. Recently, we have demonstrated that natural honey lowers prostaglandin concentrations in various biological fluids, such as plasma and urine [44]. Therefore, amelioration of the signs and symptoms of herpetic lesions by honey application may be due to inhibition of prostaglandins at the lesion site.

We have found that honey can enhance antibody production against thymus-dependent and thymus-independent antigens during primary and secondary immune responses [45]. The immunostimulatory effects can be explained by the ability of honey to inhibit prostaglandin synthesis and elevated nitric oxide production. However, these effects may warrant further study to explore the possible prophylactic effects of regular intake of honey against recurrent herpes attacks through stimulation of the host immune system.

CONCLUSIONS

The present study demonstrates that honey can accelerate the healing process of labial and genital herpes lesions, and markedly improves the signs and symptoms of recurrent episodes. These effects may be attributable to the antimicrobial properties of honey, the reduction of prostaglandin concentration, and elevated NO production at the lesion site. The study was not blinded because it was thought unethical to use a placebo to compare with honey, and it was difficult to do blinding with the use of honey and acyclovir. The small number of patients recruited was another limitation of present study. However, this trial encourages further study of the effects of topical application of honey on viral shedding, as well as oral administration of honey on the frequency of recurrence.

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