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The clinical effectiveness of topical propolis in comparison with Acyclovir in patients with recurrent herpes labialis

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الخلاصة

الأهداف: لتقييم الفعالية السريرية لمستخلص العكبر الكحولي (محلول لزج بتركيز 1205%) مقارنة بالتأثير السريري للاسايكلوفير (كريم 5%) للمرضى المصابين بالحَلأ المتكرّر الشفوي. **المواد وطرائق العمل**: اشتملت هذه الدراسة على ثلاثون مريضا مصابون بالجروح النشطة (حويصلة سليمة وافه ممزقة). خمسة عشر مَريض عولجوا بمستخلص العكبر الكحولي بينما المرضى الآخرون الخمسة عشر عُولجوا بكريم الاسايكلوفير 5% . **النتائج**: اظهرت النتائج شفائا تاما للاعراض التي تسبق الجروح النشطة والاحمرار في مجموعة العكبر بعد يومين من العلاج مقارنة بمجموعة الاسايكلوفير. وجدت فروقات معنوية عالية في تقليص حجم الحلأ المتكرر الشفوي مقارنة بفروقات معنوية في مجموعة العكبر. **الاستنتاجات**: كريم الاسايكلوفير 5% بدا اكثر فعالية بشكل موضعي في وقت الشفاء مقارنة بمستخلص العكبر الكحولي(محلول لزج بتركيز 1205%). العكبر الموضعي له قابلية تسكين اعراض الحَلأ المتكرّر الشفوي والاحمرار كاملة بينما وجد ان الاسايكلوفير غير قادر على ذلك.

ABSTRACT

Aims: To evaluate the clinical effectiveness of ethanolic extract of propolis (viscous solution12.5%) compared with the effect of Acyclovir (ACV) cream 5% in patients with recurrent herpes labialis (RHL). **Materials and Methods**: Thirty patients with active lesions (intact vesicle and rupture lesions) were included in this clinical trial. Fifteen patients were treated with viscous solution of ethanolic propolis extract while the other fifteen patients were treated with Acyclovir cream 5%. **Results**: Complete resolution of prodromal symptoms (itching, tingling or burning) and erythema were noticed in propolis group after two days of treatment compared with none in ACV group. Statistically very highly significant difference in RHL lesion size in ACV group was observed (P<0.000), compared with highly significant difference in propolis group (P < 0.001). **Conclusions**: ACV cream 5% appeared to be more effective topically in healing time than ethanolic extract of 12.5 % viscous solution of propolis.Topical propolis would alleviate symptoms and erythema of RHL completely after two days whereas this action was not seen in topical ACV cream 5%.

Keywords: Recurrent herpes labialis, propolis extract, Acyclovir cream 5%

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INTRODUCTION

Herpes simplex virus (HSV) infections are one of the most common communicable diseases in human. Although infection is often subclinical, HSV can cause mild to severe diseases especially in immunocompromised patients. [1] After the primary infection, the virus is transported from mucosal or cutaneous nerve endings by neurons to gangilia. [2] The latent virus can be reactivated to cause cold sore or fever blister. [3] The most common site of recurrence for HSV1 is the vermilion border and adjacent skin of the lip; this is known as herpes labialis. [4] Recurrent herpes labialis (RHL) occurs in 20 – 40 % of the young adult populations. [5] Fewer triggering factors for recurrence of HSV infection include the common cold, febrile infection, UV light, trauma, menstruation or

occasionally emotional upset. [3] The RHL is associated with a prodromal symptoms of itching, tingling or burning followed by the appearance of erythema, papule, vesicle, ulcer, crusting and then resolution of lesion. [6] Healing usually occurs within 7 – 10 days.[4]

There are no therapeutic measures that provide, reasonably consistent results and they entirely prevent further recurrence. [7] The antiviral agents currently applied for the treatment of HSV infection include Acyclovir (ACV) and its derivatives. [8] ACV is a synthetic purine nucleoside analogue. It is active against herpes of viruses especially HSV1. Many studies demonstrated that topical agents such as 5% ACV cream and 3% penciclovir cream are efficacious if applied 3-6 times a day. [9-11] Another antiviral agent recently used was propolis. Propolis is a natural brownish-green resinous product collected by honey bees from part of trees and shrubs. [12] The most important pharmacologically active constituents in propolis are flavonoids. [13] Flavonoids are well known compound that have antibacterial, antifungal, antiviral and anti-inflammatory properties .[14] The antiviral effect of ethanolic extract of propolis and seleced cnstituents, e.g. caffeic acid, galangin, acacetin, kaempferol, chrysin and quercetin against HSV was analyzed in cell culture. [15,16]

The aim of this clinical trial was to evaluate the clinical effectiveness of ethanolic extract of Iraqi propolis(12.5% viscous solution) compared with ACV 5% cream on healing ability and capacity to alleviate prodromal symptoms and signs.

MATERIALS AND METHODS

Patient selection and groups:

Thirty selected patients attending Oral Medicine clinic, College of Dentistry at Mosul University with RHL lesion and those patients were divided into two groups, each group include fifteen patients. Patients in group 1 were treated with ethanolic extract of Iraqi propolis (12.5% viscous solution), whereas group 2 patients were treated with ACV 5% cream, three times daily for each one according to many studies.[9-11] Treated patients were re-examined on the first, second, fifth, seventh and tenth days of treatment by two Oral Medicine Specialists, concentrating on symptoms and lesion size at each examination.

Diagnostic Criteria:

This trial conducted in patients whom showed active lesions (intact vesicle and ruptured lesion on erythematous base), and considered having RHL according to the following criteria:

1. Presence of active lesions on lips.
2. All patients had prodromal symptoms (itching, tingling or burning).
3. All patients had previous history of RHL.

Propolis preparation and Acyclovir:

Ethanolic extract of Iraqi propolis was prepared according to (Sorkun et al. , 2001) by cutting each sample into small pieces and extracted with 70% - 96% ethanol (250 grams of propolis in 2000 ml of ethanol) at 37^{o}C, then the mixture was filtered through a Whatman No.1 filter paper and evaporated to become dry. The filtrate was distilled by simple distillation apparatus resulting in 12.5% viscous solution of propolis.[17]

Acyclovir 5% cream (ViraMed) from MEPICO LABs. HOMS- SYRIA was readily available.

Case Sheet Record:

The data including age, sex, prodromal symptoms (tingling, itching and burning), erythema, redness and lesion size were recorded for each patient before and after receiving the medications.

Data analysis:

Data obtained was expressed as mean, standard deviation and statistically analyzed by using student`s t-test.

RESULTS

total of thirty patients enrolled in this clinical trial. The characteristic of the patients with RHL is shown in Table (1)

Table (1). Characteristics of the thirty patients with RHL.

Patient characteristics	Propolis group 15 patients	ACV group 15 patients
Age -- year **Mean** **Range**	 24.5 20 - 40	 29 21 - 53
Sex **Male** **Female**	 2 13	 9 6
Prodromal symptoms	15	15
Erythema and redness	15	15
Lesion size (mm) **Mean** **Range**	 6.5 1 -15	 5.6 2 -10

RHL = Recurrent herpes labialis**.**

Clinical evaluation of patients in propolis group demonstrated that all prodromal symptoms (itching, tingling or burning) were completely disappeared in about one day, followed by disappearance of erythema and redness in the 2nd day and the lesions were completely healed in 5 – 10 days. Both propolis and ACV treated groups showed percentage of reduction in a lesion size (46.7% and 73.4 %) respectively at the fifth day of treatment Table (2).

Table (2). Percentage of reduction in lesions size of RHL after 5 days of treatment in both patients groups.

Treatment groups	Size reduction (mm)After 5 days	Frequency	Percentage
Propolis	0	7	46.7
	1	1	6.7
	3	3	20
	4	1	6.7
	5	2	13.2
		1	6.7
ACV	0	11	73.4
	1	2	13.3
	2	2	13.3

RHL= Recurrent herpes labialis. ACV= Acyclovir.

At the seventh day, ACV group had 100 % reduction in lesion size, whereas propolis group had 53.2 % reduction. Both groups showed 100 % reduction in lesions size at the tenth day as shown in Table (3).

Table (3). Percentage of reduction in lesions size of RHL after 7 days of treatment in both patient groups.

Treatment groups	Size reduction (mm)After 7 days	Frequency	Percentage
Propolis	0	8	53.2
	1	3	20
	2	1	6.7
	4	1	6.7
	5	1	6.7
	6	1	6.7
ACV	0	15	100

RHL= Recurrent herpes labialis. ACV= Acyclovir.

Descriptive statistic for percentage of reduction in lesion size of both groups were shown in Table (4).

Table (4). Descriptive statistic for percentage of reduction in lesion size of both groups in RHL patients.

Patient group	Size of lesion before and after treatment	Patient number	Mean	Standard deviation
Propolis	Size B* --- Size A1**	15	25.5556	24.14225
ACV		15	26.4339	18.14570
Propolis	Size A1** --- Size A5***	15	69.1772	34.6519
ACV		15	94.4048	10.43136
Propolis	Size B* --- Size A5***	15	71.6296	32.43190
ACV		15	95.1852	8.79769

Size B*= Size of the lesion before treatment, Size A1**= Size of the lesion after 1 day of treatment, Size, A5***= Size of the lesion after 5 day of treatment, RHL= Recurrent herpes labialis, ACV= Acyclovir.

Statistically there were no significant difference in percentage of reduction before and after one day of treatment in both groups($P < 0.911$), whereas statistically significant differences were recorded in percentage of reduction before and after five days of treatment ($P < 0.011$) in both groups with better clinical effect of ACV as revealed in Table (5).

Table (5). Student`s t-test for percentage of reduction in lesion size for both groups in RHL patients.

Percentage of reduction	t	df	*P* - value	
Size B* --- Size A1**	0.113	28	0.911	NS
Size A1 --- Size A5*****	2.742	28	0.011	S
Size B* --- Size A5***	2.715	28	0.011	S

Size B*= Size of the lesion before treatment, Size A1**= Size of the lesion after 1 day of treatment, SizeA 5***= Size of the lesion after 5 day of treatment, RHL= Recurrent herpes labialis, ACV= Acyclovir**,** NS= no significant, S= significant.

There was very highly significant difference in the size of lesion in ACV group after five days of treatment ($P < 0.000$) compared with highly significant difference in propolis group ($P < 0.001$) as demonstrated in Table (6).

Table (6). Comparison of RHL lesion size in propolis and ACV groups before and after treatment.

Patient group	Lesion size	Mean	Standard deviation	t	df	*P* - value	
Propolis	**Size B* --- Size A1****	6.500 – 5.267	3.9143 – 3.4271	4.970	14	0.000	VHS
15 patients	**Size B* --- Size A5*****	6.500 – 2.000	3.9143 – 2.2361	4.432	14	0.001	HS
ACV	**Size B* --- Size A1****	5.600 – 4.467	2.5857 – 2.6957	8.500	14	0.000	VHS
15 patients	**Size B* --- Size A5*****	5.600 – 0.400	2.5857 – 0.7368	9.111	14	0.000	VHS

Size B*= Size of the lesion before treatment, Size A1**= Size of the lesion after 1 day of treatment, Size A5***= Size of the lesion after 5 day of treatment, RHL= Recurrent herpes labialis, ACV= Acyclovir, VHS= very highly significant, HS= highly significant.

DISCUSSION

One of the most common oral and extra-oral lesions caused by viruses is RHL. Although RHL is self-limiting, the use of topical antiviral medications can reduce shedding, infectivity, pain, size and duration of lesion. [2] In this trial, two different topical agents used (propolis and ACV) to assess the capacity for relief of associated prodromal symptoms and erythema in addition to healing ability. Clinical evaluation after 5 day was selected due to the fact that most of RHL lesions heal within 7 – 10 days without treatment.[4]

ACV is primarily active in viral infected cells and has high selectivity and minimal toxicity in other tissues. The antiviral drug require virus specific enzyme for conversion to active metabolites that inhibit DNA synthesis and viral replication. ACV in presence of herpes virus specific thymidine kinase is converted to ACV monophosphate which in presence of cellular kinase, converted to ACV di and triphosphate. This metabolite gets incorporated in viral DNA and stops lengthening of DNA strand and inhibit herpes virus DNA polymerase competitively.[18] Our results showed significant reduction on percentage of lesion size at 5th (73.4%) and (100%) at 7th day of cases treated with ACV 5% cream three times daily application, mostly attributed to above mentioned specific action of ACV. This result is in agreement with other studies.[9,10]

For many years, significant efforts have been made to identify the antiviral agent with different mechanism of action. Propolis possesses different mechanism of action and it might be a good agent against HSV. [19] This trial reported that propolis completely relief prodromal symptoms and erythema in about 1-2 days. This result mostly due to anti-inflammatory properties of propolis through inhibition of prostaglandin synthesis. [13] Healing time in propolis group occurred at 7-10 days of treatment. This result due to stimulation of cellular immunity, promotion of phagocytic activity and augment healing effects on epithelial tissues.[14] The antiviral effect of flavonoids and selected constituants were induced by cytotoxicity on HSV1 infected cells. Chrysine and kaempferol caused a concentration-dependent reduction on cell growth and viability, whereas quercetin reduced infectivity and intracellular replication.[16] In this trial, the potent anti-inflammatory action of propolis may be related to retard healing process and elongate the healing time for 7-10 days.

Deterioration occurred in one case of propolis group manifested by increased in prodromal symptoms and lesion size which disappeared after discontinuation of application. Another disadvantage of propolis was unacceptable color of viscous solution. Similar study showed no side effects and irritation for topical uses of propolis. [20]

CONCLUSION

ACV cream 5% appeared to be more effective topically in reducing healing time than ethanolic extract of 12.5 % viscous solution of propolis. Topical propolis would alleviate prodromal symptoms and erythema of RHL completely in two days whereas this action was not seen in topical ACV cream 5% .

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