

Comparison of New Topical Treatment (Curcumine viscous solution 30%) For Recurrent Herpes Labialis (RHL)

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ABSTRACT

Aims: To determine the therapeutic effect of viscous solution of curcumine 30% , as a topical treatment of RHL in comparison with the traditional antiviral agent " acyclovir ". **Materials and methods:** A total of 120 patients (100 female, 20 male) with RHL divided into four groups: Group I: Fifty patients used viscous solution of curcumine 30% topically. Group II: Thirty patients used viramed "acyclovir" cream topically. Group III: Twenty five patients used glycerol topically "control positive group". Group IV: Fifteen patients without treatment "control negative group". **Results:** Female were more affected than male with RHL (83.3% female, 16.3% male) with high percentage of association between highly stressed events and RHL. The results also showed significant differences between size of lesion, duration of healing and pain in patients using viscous curcumine solution topically and patients received viramed cream and patient received no treatment. The patients group which received glycerol "control positive" showed a significant differences in duration of healing compared with group I and group II. While, patients group which received viramed topically showed no significant differences compared with group III and IV in relation to duration of pain and show significant difference with group I, III and IV in relation to duration of healing. **Conclusions:** Topical application of viscous curcumine solution 30% showed a good effective response on RHL compared with other antiviral agent with the lower percentage of adverse effect, and further study for its effect on other oral lesion may be recommended.

Key Words: RHL, antiviral effect of curcumine, anti inflammatory effect of curcumine.

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INTRODUCTION

Recurrent Herpes labialis (RHL) lesion is a mild self limiting infections with Herpes simplex virus type 1(HSV-1). It causes pain and blistering on the lips and perioral area (cold sores),⁽¹⁾ approximately (20%–40%) of HSV-1 infected individual will experience recurrent outbreaks after the primary oral infections⁽²⁾.

The mechanism by which the virus is reactivated is not known⁽³⁾. However, it is likely that cellular and host signals, (in response to stress) reactivate the virus⁽⁴⁾.

The stages of cold sore out breaks are⁽⁵⁾:

Stage (0) prodrome: It is characterized by tingling, burning, itching sensation. The duration from 1–24 hrs.

Stage (1) erythema: It appears as redness of skin due to dilation and congestion of the capillaries. The duration from 1–2 days

Stage (2) papule oedema: It appears as solid, raised lesion with inflammation. Duration from 1–2 days .

Stage (3) vesicle / pustule : It appears as blister – like skin elevation in which fluid is vesible through the outer layer of skin. Duration from 1–3 days .

Stage (4) ulcer / soft crust blister or has collapsed or burst duration 1–3 days .

Stage (5) hard crust: drying of ulcer ,amber colored crust develops duration 4–14 days .

Stage (6) Re-epithelialization: crust is lost, residual redness inflammation duration 4–14 days .

Stage (Normal skin, complete disappearance of all signs of disease.

Systemic therapy with acyclovir, valaciclovir or famciclovir can suppress or shorten the duration of attack although the cost of these agent restrict their availability⁽⁶⁾.

Topical therapy with acyclovir is popular, although studies assessing the effects of treatment have yielded inconsistent results⁽⁷⁾. Acyclovir is the prototypic anti-herpetic therapeutic agent, it incorporates into replicating viral DNA causing chain termination, its the main adverse effect is local irritation⁽⁸⁾. The efficacy of many preparations for topical use in herpes infection have remained rather disappointing. The development of new antiviral drugs, especially herbal preparation, thus remain desirable⁽⁹⁾.

Curcumin is the main yellow phenolic material present in the rhizomes of turmeric (*Curcuma longa* L.) and is widely used as a food coloring agent⁽¹⁰⁾.

The structure of curcumin ($C_{21}H_{20}O_6$) was first described in 1910 by Lamp and Milobedaska and it is shown to be diferuloyl methane⁽¹¹⁾.

Curcumin exhibits anti-inflammatory and antiviral effects, and it is also considered as a potent scavenger of reactive oxygen and nitrogen species⁽¹²⁾. In addition, the wound healing and detoxifying properties of curcumin have also received considerable attention.

This study aimed to compare between the efficacy of curcumin viscous solution "herbal extract", and acyclovir cream in the treatment of recurrent herpes labialis "RHL".

MATERIALS AND METHODS

Study Population: A pool of eligible subjects was identified, the study was explained, subjects were required to have a history of perioral HSV occurring 6 or more times per year and to be 18 years of age or older.

Exclusion criteria included antiviral therapy in the previous month, long-term steroid therapy, immune compromised status, pregnancy or known allergy to drugs used.⁽⁶⁾

This study was carried out over a period of 8 months at a private dental clinic in Mosul City from September 2007 to May 2008. It included a total of 120 patients (100 females, 20 males) who participated, the patients were divided into four groups:

Group I: It included 50 patients, with RHL and treated by viscous curcumin solution 30%

Group II: It included 30 patients with RHL and treated by viramed (acyclovir) cream.

Group III: included 25 patients with RHL and treated by glycerin vehicle "control positive".

Group IV: included 15 patients with RHL without treatment "control negative".

Preparation of Solution and Procedure:
For group I viscous curcumin solution prepared by dissolving curcumin which rhizome portion of the plant used medicinally and its usually boiled, cleaned and dried "30 gm of grinded curcumin in 100 ml of glycerin"⁽¹⁴⁾.

For group II, the patients received viramed (Acyclovir) dermic cream 20 gm from Medico labs. Homs-Syria each 1 gm contains 50 mg Acyclovir.

For group I, II and III, patients were instructed to start applying the solution, cream, vehicle respectively as soon as possible after onset of first prodromal symptom of attack and to continue treatment five times per day for five days⁽¹⁵⁾. They were seen in the clinic as soon as possible after the start of the attack and subsequent attempts were made to see them daily for assessments. All patients were seen at least three times during each attack⁽¹⁶⁾.

The patients were instructed to apply topical therapy of a RHL in the prodromal or erythema stage. If lesion was in papule, vesicle or ulcer stage. Therapy was not to be applied and patients were instructed to wait and attempt early treatment of subsequent episode⁽¹⁷⁾.

Evaluation of effectiveness of treatment based on⁽¹⁸⁾:

1. Lesion area: (by measuring the diameters of lesion in square millimeter mm^2).
2. The time of healing: time from first vesicle or ulcer to loss of crust (in hours).
3. The duration of pain (days).

For each patient information was recorded by a special case sheet for this study (Figure 1).

The patient did not record any side effect of drugs.

Data Analysis:

The data obtained from this study were subjected to statistical analysis including descriptive and analytic methods.

For descriptive way the mean of variance were used, while one way Analysis of variance and Duncan's Test for (intra –

group comparison) and for the (inter – group) matching with 5% level of significance.

Name:	Age:	sex:	
Group of patient:	I II III IV		
Stressful condition:			
* lesion area :	mm ²		
* time of healing:	hrs		
* duration of pain:	day		
side effects if present:			

Figure (1): Case record.

RESULTS

A total of 120 patients participated in this study. Most of them were females (83.3% females, 16.7% males), Table (1).

The mean age of samples was 22.5 ± 6.68 years for female and 30.5 ± 3.5 years

for male (Table 2).

The association between RHL and occurrence of stressful situation had been shown in Table no.3 The effectiveness of drug used are shown in Table (4).

Table (1): distribution of study samples.

Sex	Number	Percentage
Male	20	16.7
Female	100	83.3
Total	120	100

Table(2): descriptive statistic of study samples for both sexes.

Sex	Mean of age ± SD	Minimum	Maximum
Females	22.5 ± 6.68	18	30
males	30.5 ± 3.5	20	40

SD: standard deviation.

Table (3): The occurrence of stressful situation.

Events	Number	Percentage
Common cold	20	16.6%
Emotional upset	20	16.6%
Menstruation	30	25%
Oral trauma	10	8.3%
Other illness	25	20.8%
No known events	15	12.5%
Total	120	100%

Table (4): The effectiveness of drug used among treatment group.

Treatment	Mean lesion area (mm ²)	Healing time hr	Duration of pain(days)
Group I	34.8 ± 3.89 A	91.8 ± 31.9 A	1.5 ± 0.54 A
Group II	65.5 ± 20.1 B	172.6 ± 26.3 B	3.9 ± 1.8 B
Group III	71 ± 14.7 BC	153.2 ± 24.1 C	4.2 ± 2.0 B
Group IV	75 ± 16.58 C	181.3 ± 21.9 C	4.0 ± 2.0 B
<i>p</i> =	0.001	0.001	0.001

All values are shown as mean ± standard deviation; Different letter mean significant differences.

This result showed that smaller lesion area "mean 34.8 ± 3.89" and shorter period of healing "mean 91.8 ± 31.9" and duration of pain "mean 1.5 ± 0.54" were seen in group (gp) I patients which received curcumine viscous solution followed by gp II which received viramed cream "mean lesion area 65.6 and duration of pain 3.9 day respectively". Then gp III "control positive group" "mean lesion area 71.0 ± 16.58 and duration of pain 4 days respectively followed by gp IV " control negative group", which showed larger lesion area "mean 75.0 ± 16.58" healing time "mean 181.3 ± 21.9 hr" and duration of pain "mean 4.0 ± 2.0" respectively , except that gp III which show less duration of healing "mean 153.2 ± 24.1 hr" compared with gp II and gp IV.

The one way analysis of variance (ANOVA) showed a highly significant difference $p < 0.05$ " $p = 0.00$ " between and within groups.

Table (4) also showed the Duncan analysis of variance in relation to the mean lesion area which showed that gp I is high-

ly significant different than group II, III and gp IV also gp II is highly significant different than group IV also group II was highly significant different than group IV while, there was no significant difference between group II , III and group IV .

Table (4) showed Duncan analyses of variance in relation to the mean healing time and it showed that group I had significant difference in related to group II, III and IV ($p < 0.01$), also group II showed a significant difference in related to group I , III and IV

While group III showed no significant difference in related to group IV

Table(4) showed Duncan analyses of variance in relation to the duration of pain which clarify that group I significantly difference in related to group II, III and IV while there was no significant differences among other groups.

The minor adverse effect were reported and that shown in Table (5) which revealed that viscous solution of curcumin report a lower percentage of adverse effect 18.6% compared with viramed cream .

Table(5): Minor adverse effect of drug used.

Adverse effect	Number of patients	%	Drug group
Flaking of skin	5	16.6%	Viramed n=30
Stinging sensation	7	23.3%	Viramed n=30
Permenant discoloration of skin	8	26.6%	Viramed n=30
Temporarily discoloration of skin	8	18.6%	curcumine n=50

DISCUSSION

A large number of individuals suffer from RHL and seek treatment. A variety of treatment modalities have been used⁽¹⁹⁾. It includes⁽⁵⁾:

1. Non-prescriptivetreatmentlikeskin protectant "glycerin", external analgesic with possible antiviral activity "zinc-Heparin" and viral entry blocking agent "Docosanol"
2. Prescriptive treatment which include Acyclovir, penciclovir and famciclovir.

According to this study , females were more susceptible to RHL than males, this is due to factor which is triggers of recurrent infection which include internal (unpreventable) stress like menstruation, fever illness, and external (preventable) stress like sunburn, emotional stress, dental treatment are more common in female than male⁽²⁰⁾. This was in agreement with the study of Shaws *et al.*,⁽¹⁶⁾ and Bernstein *et al.*⁽¹⁸⁾.

This study showed that RHL are closely associated with different highly stressed situations which considered to be important factors known to activate the recurrent Herpes infection⁽²¹⁾ this was in agreement with the study of Spruance⁽²²⁾.

According to the results of this study viscous solution of curcumine is the most effective treatment for RHL than other treatment groups which demonstrated by smaller lesion size, less duration of healing and pain "with higher significant difference" when comparing with other groups. This was due to the fact that the sign and symptom of RHL were in part due to the inflammatory response following viral reactivation accordingly combination therapy with a drug which have anti inflammatory, and antiviral properties may have

a beneficial effects compared to the use of antiviral drug alone⁽²³⁾.

Curcumine has a potent anti inflammatory effects^(12,24,25) which may attributed to its ability to inhibit pro-inflammatory arachidonic acid as well as neutrophil function during inflammatory state⁽²⁴⁾, also it inhibit Cox activity result in decrease in the yield of infections viral progeny⁽²⁶⁾.

Curcumine has been shown to have antiviral activity by inhibiting viral replication⁽²⁷⁾.

According to this study viramed showed significant differences only in the reduction of area of inflammation compared with control negative groups and group I, this was in agreement with the study of Shaw *et al.*⁽¹⁶⁾, Mark *et al.*⁽²⁸⁾, and Spruance *et al.*⁽¹⁷⁾, Which showed that there is no clinical benefit from treatment with ac-yclovir compared with placebo cream but it was disagreement with the study of Fiddia *et al.*⁽¹⁵⁾, who showed that acyclovir modify the course of sever RHL when therapy initiated by patient during prodrome.

According to this study glycerin "control positive group" showed a significant differences only in a reduce of duration of healing compared with the group I and group II; this was because glycerin kept the cold sores moist to discourage cracking of the skin, cracks increase discomfort, and increase the chance for secondary bacterial infections and prolong healing time glycerin also forms a protective barrier over the lesion which often improve the symptoms and aid healing⁽²²⁾.

In related to minor adverse effects associated with the drug used stinging, flak-

ing of skin, and discoloration, viramed caused the main adverse effect followed by curcumine solution, that cause temporally staining of skin only which in agreement with the study of Shaw *et al*⁽¹⁶⁾.

CONCLUSIONS

The viscous solution of curcumine 30% (herbal preparation) proved to be more effective than topical acyclovir cream in reducing size of lesion area, duration of healing and reducing pain of Recurrent Herpes labialis compared with control positive "which receive glycerin only" and control negative "which receive no treatment" with minimum adverse effects which potentiat it use in the treatment of RHL due to it safety, effectiveness and low cost compared with other rotinal anti-viral

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