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The Efficacy of Hyaluronic Acid Spray in Treatment of Recurrent Aphthus Ulcer

Running title: Treatment of Aphthus Ulcer by Hyaluronic Acid

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ABSTRACT

Aims: To evaluate the clinical effectiveness of hyaluronic acid0.01% compared with the effect of kenalog in orabase in patients with recurrent aphthus ulcer.

Materials and Methods: twenty fife patients with active lesions were included in this clinical trial. Fifteen patients were treated with hyaluronic acid while the other ten patients were treated with kenalog in orabase.

Results: Complete disappearance of signs symptoms (ulcer and pain) after one week in tow groups .There is no significant difference between hyaluronic acid and kenalog in orobase.

Conclusions: hyaluronic acid appeared to be more safe in treatment of aphthus ulcer than kenalog in orobase.

Keywords: Recurrent aphthus ulcer, hyaluronic acid 0.01%, kenalog in orabase.

Introduction

Recurrent aphthus ulcer is a common disease characterised by development of painful , recurrent, solitary or multiple ulceration of the oral mucosa , with no other signs of any other disease[(1)]. Recurrent aphthus ulcer is classified according to clinical characteristics: Minor ulcers , Major ulcers (Sutton disease, periadenitis mucosa necrotica recurrence), and Herpetiform ulcers . Minor ulcers , which comprise over 80% off RAS cases, are less than (1cm) in diameter and heal without scars . Major ulcers are over 1(cm) in diameter and take longer time to heal and often scar. Herpetiform ulcers are considered a distinct clinical entity that manifests as recurrent crops of dozens of small ulcers throughout the oral mucosa [(2)]. The main factors thought to contribute are genetic predisposing , exaggerated response to trauma , infection , immunological abnormalities , gastrointestinal disorders ,haematological deficiencies , hormonal disturbances and stress[(3)].Specific tests are unavailable , so the diagnosis must be made on history and clinical feature alone[(4)] . However ,to exclude the systemic disorders it is often useful to undertake the investigations .

* full blood count
* haematinics (ferrtin , folate,vitamin B_{12})
* screen for coelic disease [(4)].

Management of Recurrent aphthus ulcer :

1. elimination of predisposing factors (stress ,eggplant, spicy food . ect)
2. topical therapy(analgesics ,anti inflammatory agent, antimicrobials)
3. systemic therapy immunomodulators and immunosupressants (prednisolone ,levamisole , pentoxyphylline , azelastine , colchicines , dapsone , azathioprine ,thalidomide)[(5)]
4. other topical (amlexanox ,sliver nitrate , KNO_3 , prostaglandins , hyaluronic acid , bioadhesive patches)
5. other systemic (ascorbic acid ,zinc sulphate ,honey)
6. physical therapies(laser ,ultrasound ,ozone ,cryotherapy)[(6)] .

Hyaluronan:

Is an endogenous polysaccharide that is present in the basement membrane of a wide variety of mammalian epithelial tissues, including oral mucosa .In the presence of inflammation, hyaluronan levels increase [(7)]. hyaluronic acid(HA) is a

linear polymer of glucuronic acid N-acetyl glucosamine disaccharide . Most cells have the capacity to synthesis HA during some point of their cell cycle . The main function of HA appears to be in tissue healing . In this process , HA is implicated in a range of activities including activation and moderation of the inflammatory response , promoting cell proliferation , migration and angiogenesis , promoting re-epithelisation via proliferation of basal keratinocytes and reducing collagen deposition and scarring [8].In sites of inflammation or tissue injury ,high molecular weight(HMW) -HA may be depolymerised in low molecular weight (LMW) fragment through the activity of oxygen radicals or via enzymatic activity by hyaluronidase , β-glucuronidase and LMW fragments are able to activate the innate immune defence , promoting the production of different cytokines [9] .

Materials Methods

1-Hyaluronic acid 0,01% (Gengigel gingival spray Ricerfarma, EU)
2-kenalog in orabase (unipharm ,Damascus, syria)Patients groups:

Total of (25) patients with recurrent minor aphthus ulcer of recent onset less than (72) hours were included in this study and have been divided into two groups. The first group was the patient group which consisted of 15 patients 6 males and 9 females .Their age ranged between (23-35)years. The mean size of the lesion before treatment was(2.93=3)mm which is measured by ruler when the ulcer in the anterior part of the oral cavity ,if the ulcer in the posterior part of oral cavity the size of lesion measured by making comparison with adjacent structure . The mean for pain analogue scale was (5.73=6). The pain VAS is comlines scale comprised of horizontal (HVAS) or vertical(VVAS) line , usually 10 centimeters (100mm) in length , anchored by tow verbal descriptors , one for each symptom extreme [10,11] .

The second group was the control group which consisted of 10 patients (4) males and (6) females . Their age ranged between (23-29) years .The mean size of the lesion before treatment with kenalog was (3.2=3)mm and the mean for pain analogue scale was (4.8=5) . This study was conducted in patients attended to College of dentistry in Mosel university with no signs or symptoms of systemic diseases and the patients were none smokers. These drugs gave to patients for home use four times daily after drying the area of ulcer. There is no additional drugs like mouth wash used with these drugs. Those patients re examined after 24 hours ,48hours, 72hours and one week respectively. Statistical computations were calculated using SPSS 11.5 for windows software Statistical significance assessed by using t test and one way a nova test at the $P \leq 0.05$ level.

Results

The results of the present study were divided into two main groups according to the type of treatment (Hyaluronic acid, Kenalog in orabase) , and response of the lesion to these treatment in relation to the size of ulcer and pain . There were no significant differences in the size of lesions treated by Hyaluronic acid during the first(24hours). While there were significant differences in the size of lesions treated by Hyaluronic spray during (48hours, 72hours and one week) when it compared with the size of the lesions before treatment $p \leq 0.05$.Also there were no significant difference in the size of lesions treated by and Hyaluronic acid and those treated by Kenalog in orobase during the first (24 hours, 48 hours, 72 hours and one week) at $P \geq 0.05$ and $P \geq 0.01$ Tables (1,2,3and4).

There were significant differences in the pain analogue scales of lesions treated by hyaluronic acid during the first (24hours , 48 hours ,72 hours and one week) when it compared with pain analogue scales before treatment $p \leq 0.05$. There were no significant difference in the pain scales (VAS) of lesion treated by hyaluronic acid and those treated by Kenalog in orabase during the(first 24 hours , 72 hours and one week) $p \geq 0.05$.Also there is significant difference in the pain analogue scales of lesion treated by hyaluronic acid and those treated by Kenalog in orobase during the (48hous) Tables (5, 6,7and8)

Discussion

HA is a vital component of cellular structure and offers a multitude of benefits including anti-inflammatory and antioxidant effects, pain-relief , joint lubrication and cartilage –protection ,collagen regeneration ,and enhancement of cell viability. Most of these actions are mediated via the HA –specific CD44 receptor present on endothelial , epithelial , and smooth muscle cell membranes [12] . HA is a hygroscopic macromolecule and solutions are highly osmotic. In the skin and perhaps 0n the oral mucosa , this property is likely to be relevant in controlling tissue hydration during periods of change such as the inflammatory process or response to tissue injury .This is also particular relevance for cell proliferation and migration ,when HA synthesis contributes to local foci of tissue hydration .This result in the weakening of cell anchorage to the extra cellular matrix , allowing temporary detachment to facilitate cell migration and division [13] . The highly viscous native of HA also contributes to retardation of viral and bacterial passage through the HA –rich pericellular zone [14] .HA may also have antioxidant effect [15].Due to its tissue-healing properties ,HA

may be a useful adjunct in diseases of oral cavity[16,17]. All of these properties are likely to contribute to the healing process and may account for the reduction in the ulcers . Topical steroids are the standard regimen used to evade immunologic and inflammatory-mediated attacks resulting in ulceration [6] . Only one crossover ,randomized controlled trial demonstrated a significant reduction in pain compared with placebo, but showed no effect on reducing the frequency of RAU occurrence [18] .Our result showed no significant difference between hyaluronic acid and kenalog inorobase in the reduction of the size of lesion and pain . HA offers advantages over steroids in that it is safe in all patients including infants and pregnant women ,in whom there may be reluctance to use steroid . There is no risk of overdose and can be safely recommended to individuals who may not follow instructions easily, it is widely available as an over the counter preparation and does not cause any discomfort ,making it acceptable to children[19] .

Conclusion

HA is preferable to use for treatment of recurrent aphthuos ulcer due to its tissue-healing properties, overcome the side effect of the steroid and safe in all patients.

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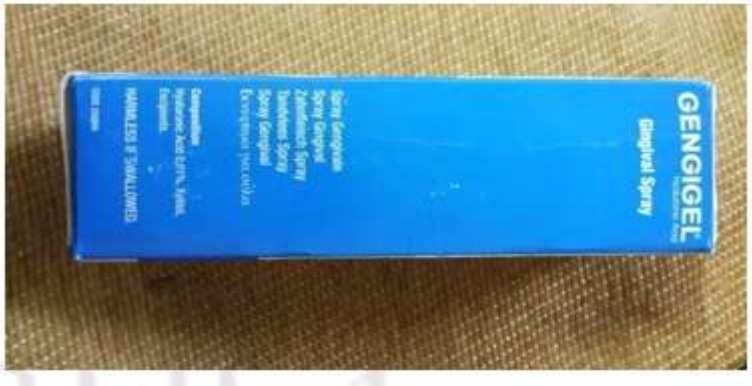
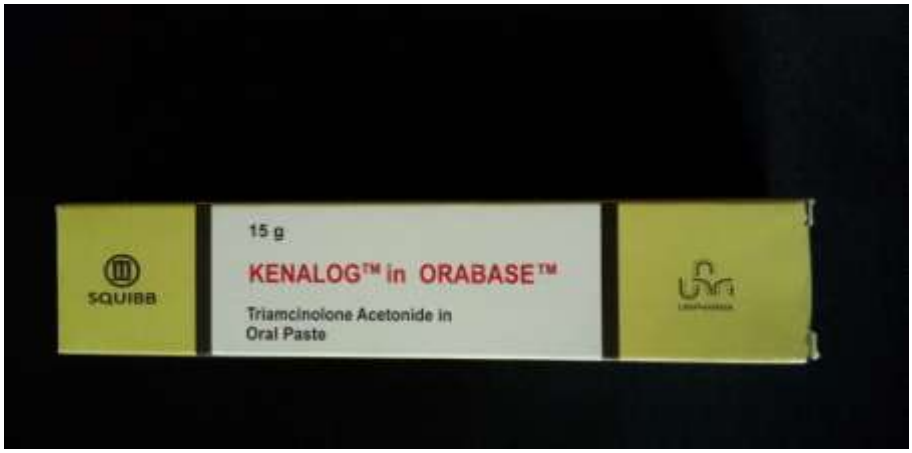


(Figuer 1): Gengigel gingival spray



(Figure 2): kenalog in orabase

Table (1): The means of the lesions size before and after one day treatment by two therapies.

group	Size of the lesion before treatment in m	Size of the lesion after treatment in m	t	d.f	p
	Mean+ SD	Mean+ SD			
Hyaluronic acid	2.9333 +.96115	2.8667+.99043	1.000	14	.334 NS
Kenalog in orobase	3.2000+.78881	3.2000+.78881	1.000	24	.327 NS
d.f		23			
p		.382 NS			

NS p≥0.05

Table (2): The means of the lesions size before and after tow days treatment by two therapies.

group	Size of the lesion before treatment in m	Size of the lesion after treatment in m	t	d.f	p
	Mean+ SD	Mean+ SD			
Hyaluronic acid	2.9333 +.96115	1.9333+.88372	7.246	14	0.00 *
Kenalog in orobase	3.2000+.78881	2.2000+.78881	12274	24	.000 *
d.f		23			
p		.449 NS			

***p≤0.01 NSp≥0.05**

Table (3):The means of the lesions size before and after three days treatment by two therapies.

group	Size of the lesion before treatment in m	Size of the lesion after treatment in m	t	d.f	p
	Mean+ SD	Mean+ SD			
Hyaluronic acid	2.9333 +.96115	.8667+.51640	11.374	14	0.0 *
Kenalog in orobase	3.2000+.78881	1.2000+.78881	18.941	24	.00 *
d.f		23			
p		.213 NS			

***p≤0.01 NS p≥0.05**

Table (4): The means of the lesions size before and after 0ne week treatment by two therapies.

group	Size of the lesion before treatment in m	Size of the lesion after treatment in m	t	d.f	p
	Mean+ SD	Mean+ SD			
Hyaluronic acid	2.9333 +.96115	.0000+.0000	11.820	14	.000 *
Kenalog in orobase	3.2000+.78881	.0000+.0000	17.101	24	.00 *
d.f					
p					

*p≤0.01

Table (5): Themeans of pain analogue scale before and after one day treatment by two therapies.

group	Pain analog scale before treatment	Pain analog scale after treatment	t	d.f	p
	Mean+ SD	Mean+ SD			
Hyaluronic acid	5.7333+1.09978	3.200+.77460	10.717	14	.000*
Kenalog in orobase	4.800+1.03280	3.800+1.22927	8.609	24	0.000 *
d.f		23			
p		.147 NS			

* p≤0.01 NSp≥0.05

Table (6): The means of pain analogue scale before and after tow days treatment by two therapies.

group	Pain analog scale before treatment	Pain analog scale after treatment	t	d.f	p
Hyaluronic acid	5.7333+1.09978	1.6000+.63246	19.199	14	.000 *
Kenalog in orobase	4.800+1.03280	2.4000+1.07479	14.859	24	.000 *
d.f		23			
p		.028**			

* p≤0.01 * *p≤0.05

Table (7): The means of pain analogue scale before and after three days treatment by two therapies.

group	Pain analog scale before treatment	Pain analog scale after treatment	t	d.f	p
Hyaluronic acid	5.7333+1.09978	.6000+.63246	23.844	14	.000 *
Kenalog in orobase	4.800+1.03280	1.2000+1.03280	20.134	24	.000 *
d.f		23			
p		.084 NS			

* p≤0.01 NSp≥0.05

Table (8): The means of pain analogue scale before and after 0ne week treatment by two therapies.

group	Pain analog scale before treatment	Pain analog scale after treatment	t	d.f	p
Hyaluronic acid	5.7333+1.09978	.000+.000	20.190	14	.00 *
Kenalog in orobase	4.800+1.03280	.000+.000	23.297	24	.000 *
d.f					
p					

* p≤0.01