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N-acetylcysteine versus Chlorhexidine in Treatment of Aphthous Ulcers: A

Preliminary Clinical Trial

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Abstract:

Introduction: This study sought to assess the efficacy of N-acetyl cysteine (NAC) in treatment of recurrent aphthous stomatitis (RAS).

Methods: Fifty eight patients, aged 28 ± 9.7 years, presented with clinically diagnosed RAS to two oral medicine centres. They were assigned randomly to a single application of either NAC (200 mg dissolved in water, $n=38$) or 0.12% chlorhexidine digluconate (CHX, $n=20$) mouthwashes for 30 seconds. Pain was measured using a Visual Analogue Scale (VAS). The size of the ulcer was measured through its greatest dimension using a periodontal probe. These two measurements were taken pre-application (day 1) and 2nd, 4th, and 6th day post-application. Average time (in days) until complete healing was assessed.

Results: Of all participants, 33 (57%) were females; 34 (59%) married; 29 (50%) reported a family history of aphthae; and 51 (88%) were affected with minor RAS. There were greater improvement in pain from day 1 with NAC on the second day (-3.0 ± 2.0 versus -1.8 ± 1.9 ; $P = 0.028$) and on the fourth day (-5.0 ± 2.6 versus -3.4 ± 2.7 ; $P = 0.041$). The differences with regard to the change in ulcer size and average healing time were not significant between NAC and CHX.

Conclusion: Single-application of NAC results in a clinically significant reduction of RAS-associated pain within one day of application and is more effective than CHX.

Key words: Recurrent aphthous stomatitis; N-acetyl cysteine; chlorhexidine; mouthwash; Single application.

Introduction:

Aphthous ulcers, or recurrent aphthous stomatitis (RAS), is a benign oral ulcerative disease and the most common ulcerative disorder of the oral mucosa. The point prevalence is 1.5%, but the annual and lifelong prevalence rates in general population are 20% and 40%, respectively, with higher figures reported for specific population segments.[1-3] A RAS episode is characterized by one or more round shallow ulcers with a well-demarcated erythematous margin and a yellowish to greyish pseudomembranous central area. The associated pain ranges from very mild to very severe.[4] On the basis of their size and number, RAS can be classified as minor, major, and herpetiform. Minor recurrent aphthous stomatitis (usually less than 10 mm) is the most common form accounting for 80% RAS patients.[2]

The etiopathogenesis of RAS is still not fully understood, with many proposed implicating factors including: genetic predisposition,[5] local trauma,[6] medications, hormones imbalance,[7] physical and psychological stress,[8] nutritional deficiencies,[9] and immunological status.[10] Recently, mounting evidence has supported a strong role for oxidative stress in the etiology of RAS. In RAS patients, compared to the healthy controls, the levels of plasma and salivary oxidative stress markers superoxide dismutase and uric acid are increased, in contrast to the decrease in the activity of antioxidants like glutathione peroxidase.[11, 12]

N-acetyl cysteine (NAC), the derivative of a thiol-containing amino acid, is a precursor for the intracellular antioxidant glutathione. Owing to its potent antioxidant, anti-inflammatory, immune-modulatory, and antimicrobial properties, NAC has received considerable attention in dentistry.[13, 14] More specifically, NAC may be a strong

candidate anti-RAS medication, being supported with many hypothesized mechanisms of pharmacological actions in this regard.[15] NAC, and similar antioxidants, are worthy to be evaluated as therapeutics for RAS at least due to their lower risk of adverse effects.

There is no cure for RAS. Many symptomatic treatments are used with variable effects, including chlorhexidine (CHX). A sucralfate suspension was compared with CHX as oral rinse in patients with RAS; it reduced pain more than sucralfate alone [16]. CHX reduced pain comparable to triamcinolone [17]. This study therefore sought to assess the efficacy of NAC as a novel therapeutic candidate for treatment of RAS in comparison to CHX.

Material and Methods:

This preliminary randomized clinical trial was conducted in two centres: College of Dentistry, Jazan University, KSA and Faculty of Dentistry, Ibb University, Yemen. The relevant ethical approvals were obtained from the relevant Scientific Research Ethics Committee: Jazan University (REC39/8-FS002) and Ibb University (SEC15-13/05/2018). In addition to being strictly adhered to CONSORT guidelines (Figure 1), the study has been conducted with a full adherence to the World Medical Association Declaration of Helsinki. A written informed consent was obtained from each of the participants knowing that they were informed in advance about the study procedures.

The sample size was calculated to detect a mean difference in pain reduction (based on the Visual Analogue scale [VAS]) of not less than 1.5 with a standard deviation of this difference of 1.75. The power and the statistical significance of this two-tailed analysis were set at 0.8 and < 0.05 , respectively. The total sample size was 54 (27 each group). We tried to exceed this number to compensate for the potential dropout.

The potential participants were recruited from amongst the dental clinics' attendants of both centres. The participant was recruited provided he/she fulfilled the following criteria: had an episode of oral ulcer(s) within at most the last 72 hours on condition of presence of some degree of pain owing to this/these ulcer(s). Those who had already taken any therapeutic preparation(s) to treat those ulcers, and those who had disease processes that compromise their immunity were excluded. Based on the demographic and family data and on the history and the clinical signs and symptoms, these ulcerative episodes were diagnosed as: RAS. Pain was subjectively measured using 0-10 VAS where 0 means no pain at all and 10 means severe unbearable pain; score 5

means moderate level of pain that is not mild not sever. Personal, demographic and habit data, if any, were recorded. Data on clinical presentation of the ulcers, such as onset, number, size, duration, side, site and associated family history, if any, were recorded. The ulcer size was measured along the greatest dimension using periodontal probe; if there were multiple ulcers, only the largest one was considered.

Once eligible, the participant was randomly assigned into either NAC or CHX groups based on a draw from two envelopes: one for NAC and the other for CHX. Those who assigned to NAC were given a sachet of NAC 200 mg (ACC[®], HEXAL AG, Holzkrichen, Germany) to be dissolved in 20 ml water and used as a mouthwash for 30 sec., while those who assigned to CHX were given 0.12% CHX digluconate (KINGINGIVAL, Enjoague Bucal, Kin, Spain) to use 20 ml as a mouthwash for 30 sec. The patients were instructed to use the assigned intervention once only under supervision of one of the co-investigators.

The above mentioned measurements were taken on the day of presentation (the first day before application of the intervention which is considered as baseline measurements) and on the second, fourth and sixth days. The participants were emphasized not to miss recall visits. It was not necessary to attend the last visits in case a complete healing occurred before that. The main outcome was pain based on VAS. The secondary outcomes were ulcer size (in mm), and the time elapsed till complete healing (in days). The independent variables include the age, gender, centre (Jazan versus Ibb), marital status, habits, and systemic health, and the family history, onset, frequency, number, size, side, and site of the ulcers, and the intervention (NAC versus CHX). Descriptive statistics were presented as frequencies with corresponding proportions for

the qualitative variables, and as means with corresponding standard deviations for the quantitative variables. Analytic statistics included paired t-test to compare pre and post interventional measurements for each individual intervention. Independent t-test was used to compare the measurements for both groups (NAC versus CHX) in any given measurement day. A significant value (P) of less than 0.05 was considered significant.

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Results:

The total sample included 59 subjects. A participant in the NAC group missed the follow-up visits and thus was excluded. Of the remaining 58 participants (aged 28 ± 9.7 years), 38 were included in NAC group; 25 (43%) were males; 34 (59%) were married; 22 (38%) reported to have either GIT/malabsorption, anaemia, malnutrition, allergy or menstrual cycle disturbances; and 5 (8.6%) reported a history of trauma (Table 1).

Up to 45% (29 participants) reported a presence of family history of aphthae (Table 2). Most of the ulcers were of minor form (51 [88%]), and attacked the participants within 48 hours (50 [86%]). Up to 67% (39 participants) reported frequent episodes within more than a month but less than 6 months. The most affected oral sites were the labial mucosa (21 [36%]) and the buccal mucosa (18 [31%]). Most of the attacks were of one ulcer (42 [72%]) followed by two ulcers (12 [21%]).

Pain and ulcer size were reduced between any successive measurements. However, the absolute mean scores of pain and ulcer size for any given recording days were not different between NAC and CHX groups. NAC reduced pain from baseline more than CHX on the second day (-3.0 ± 2.0 versus -1.8 ± 1.9 ; $P = 0.028$) and on the fourth day (-5.0 ± 2.6 versus -3.4 ± 2.7 ; $P = 0.041$). The differences with regard to the change in ulcer size were not different between both groups (Table 3).

Discussion:

Acute oral ulcers, like RAS, are bothersome due to the associated pain that is in most instances so severe, interfering with the patient daily essential functions like eating and talking, and extremely affecting the patient's quality of life.[18] There is no cure for RAS, but there are many symptomatic treatments that aim to reduce the pain, increase the time between episodes, and/or accelerate the healing time.[19]

Owing to the mounting evidence pointing oxidative stress as a predisposing factor in development of RAS,[11, 12, 20, 21] we designed this preliminary clinical trial to assess the effect of washing the mouth using NAC (a very strong antioxidant) in reducing the RAS-associated pain, and ulcer size, and in promoting healing (time needed for complete cure). NAC also has antiinflammatory, immune-modulator, antimicrobial and nutritional supplement effects that may also be relevant.[15]

NAC appears promising as a symptomatic treatment of RAS. The single use of NAC mouthwash resulted in an immediate relief of pain (results not shown), and in more pain reduction in the second and fourth days than with CHX mouthwash use.

A reduction in pain severity of at least 23% may be considered significant clinically [22]. The reduction of pain severity of 47% and 31% in the second day for NAC and CHX, respectively, appears clinically meaningful.

In our preliminary clinical trial, we used a single application of either medications (NAC or CHX). Such a study design had been conducted using topical 1% lidocaine[23] and using 3% diclofenac in 2.5% hyaluronan [24] In anticipation of unpredictable side effects due to keeping NAC mouthwash in contact with oral mucosa for long time (30

sec), we proposed a single-application (not repeated) regimen. And in order to keep the same for the comparator, we applied the same for CHX. It is expected, however, that the treatment effect would have been greater with repeated applications. However, the single-application regimen may be advantageous as: 1) the reported pain reduction is clinically significant; 2) no adverse effects were reported; and 3) the patient's compliance is guaranteed unlike the case with the repeated applications.

A limitation of this study is the limited sample size. The study compared two treatments, but no placebo. The study was not blinded. Pain was subjectively measured using VAS, although it is the only available tool that can be considered reliable in this context.

Conclusions

Single-application of NAC results in a clinically significant reduction of RAS-associated pain within one day of application, and is more effective than.

Disclosure statement: no potential conflict of interest was reported by the authors.

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Figure Legend:

Figure 1 CONSORT flowchart diagram.

Table 1. Demographic, medical, and habits data of the study sample

Variable		NAC (n = 38)	CHX (n = 20)	Total
Gender	Males	16 (42.1)	9 (45)	25 (43.1)
	Females	22 (57.9)	11 (55)	33 (56.9)
Center	Saudi Arabia	22 (57.9)	13 (65)	35 (60.3)
	Yemen	16 (42.1)	7 (35)	23 (39.7)
Marital status	Single	19 (50)	15 (75)	34 (58.6)
	Married	19 (50)	5 (25)	24 (41.4)
Systemic problems ("Yes" responses)	GIT/malabsorption	3 (7.9)	1 (5)	4 (6.9)
	Malnutrition	1 (2.6)	0 (0)	1 (1.7)
	Anemia	2 (5.3)	0 (0)	2 (3.4)
	Allergy	3 (7.9)	1 (5)	4 (6.9)
	Menstrual cycle disturbance	3 (7.9)	3 (15)	6 (10.3)
	History of trauma	3 (7.9)	2 (10)	5 (8.6)
	Others	4 (10.5)	1 (5)	5 (8.5)
Habits	Smoking	3 (7.9)	0 (0)	3 (5.2)
	Khat chewing	8 (21.1)	5 (25)	13 (22.4)
	More than one habit	0 (0)	1 (5)	1 (1.7)
	None	27 (71.1)	14 (70)	41 (70.7)
Age; mean (SD)		30.13 (16.62)	25.5 (6.86)	28.53 (9.69)

NAC: N-Acetyl Cysteine; CHX: Chlorhexidine.

Table 2. History and Clinical findings of the study sample

Variable		NAC (n = 38)	CHX (n = 20)	Total
Family history	Yes	15 (39.5)	14 (70)	29 (50)
	No	23 (60.5)	6 (30)	29 (50)
Onset	Within 42 hours	18 (47.4)	6 (30)	24 (41.4)
	> 24 but ≤ 48 hours	16 (42.1)	10 (50)	26 (46.6)
	After 48 hours	4 (10.5)	4 (20)	8 (13.8)
Frequency	< a month	5 (13.2)	3 (15)	8 (13.8)
	A month to 3 months	14 (36.8)	7 (35)	21 (36.2)
	> 3 months to 6 months	13 (34.2)	5 (25)	18 (31)
	> 6 months	4 (10.5)	3 (15)	7 (12.1)
	First time attack	2 (5.3)	2 (10)	4 (6.9)
Type	Minor	32 (84.2)	19 (95)	51 (87.9)
	Major	6 (15.8)	1 (5)	7 (12.1)
Side	Right	15 (39.5)	9 (45)	24 (41.4)
	Left	18 (47.4)	9 (45)	27 (46.6)
	Midline	5 (13.2)	2 (10)	7 (12.1)
Site	Buccal mucosa	12 (31.6)	6 (30)	18 (31)
	Labial mucosa	12 (31.6)	9 (45)	21 (36.2)
	Lateral border of the tongue	6 (15.8)	4 (20)	10 (17.2)
	Ventral surface of the tongue	3 (7.9)	0 (0)	3 (5.2)
	Tip of the tongue	2 (5.3)	1 (5)	3 (5.2)
	Floor of the mouth	3 (7.9)	0 (0)	3 (5.2)
Number of the ulcers	One	28 (73.7)	14 (70)	42 (72.4)
	Two	7 (18.4)	5 (25)	12 (20.7)
	Three	2 (5.3)	1 (5)	3 (5.2)
	Six	1 (2.6)	0 (0)	1 (1.7)

NAC: N-Acetyl Cysteine; CHX: Chlorhexidine.

Table 3. Measurements of pain, ulcer size and average healing time

Variables	NAC (n = 38)	CHX (n = 20)	P value
Pain upon the first presentation	6.32 ± 2.15	5.5 ± 1.82	0.153
Pain second day of treatment	3.32 ± 2.3	3.75 ± 2.22	0.493
Pain fourth day of treatment	1.34 ± 2.1	2.05 ± 2.58	0.265
Pain sixth day of treatment	0.63 ± 1.62	1.05 ± 1.7	0.362
Change in pain from baseline (Second day)	-3 ± 2.04	-1.75 ± 1.94	0.028
Change in pain from baseline (Fourth day)	-4.97 ± 2.57	-3.45 ± 2.74	0.041
Change in pain from baseline (Sixth day)	-5.68 ± 2.36	-4.45 ± 2.16	0.057
Size of the lesion on the first presentation (greatest dimension in mm)*	4.9 ± 2.96	4.73 ± 2.51	0.882
Size of the lesion second day	3.99 ± 2.86	4.23 ± 2.61	0.758
Size of the lesion fourth day	2.83 ± 2.2	2.59 ± 2.56	0.753
Size of the lesion sixth day	1.07 ± 1.64	1.48 ± 2.12	0.458
Change in size from baseline (Second day)	-0.86 ± 1.55	-0.5 ± 1.24	0.378
Change in size from baseline (Fourth day)	-2.46 ± 2.16	-2.14 ± 1.84	0.592
Change in size from baseline (Sixth day)	-3.78 ± 3.15	-3.25 ± 2.32	0.514
Duration of the lesion till complete healing (Days)	4.87 ± 2.46	5.4 ± 2.82	0.46

*: The largest ulcer was considered if multiple. NAC: N-Acetyl Cysteine; CHX: Chlorhexidine.