Clinical efficacy of nicotine replacement therapy in the treatment of minor recurrent aphthous stomatitis

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Background/aim
Recurrent aphthous stomatitis (RAS) is a common and widely recognized disease involving the oral mucous membrane. Nicotine replacement therapy (NRT) is a dose-dependent safe method for encountering useful effects of nicotine. This study aimed to evaluate the clinical efficacy of NRT in the treatment of minor RAS.
Materials and methods
A total of 50 patients from Oral Medicine and Periodontology Department, Faculty of Dentistry, Cairo University, with active minor RAS lasting for less than 48 h were randomly allocated into two groups (25 each): placebo and nicotine groups. They were treated with placebo and 2-mg nicotine chewing gum, correspondingly, twice daily for 2 weeks. All participants were assessed for pain, erythema, and ulcer size sores at 4 and 6 days from baseline. Frequency of recurrence was evaluated at 1-month, 2-month, and 3-month intervals.
Results
Regarding pain and erythema scores, the nicotine group showed lower mean with significant difference after 6 days in comparison with the placebo group. A lower mean of ulcer size was recorded in the nicotine group, with a significant difference after 4 and 6 days. A lower mean of recurrence score was recorded in nicotine group, with nonsignificant difference compared with the placebo group.
Conclusion
Low-dosage NRT in the form of chewing gum may be considered as an innovative and safe alternate treatment modality for minor RAS.

Keywords:
chewing gum, erythema, nicotine, pain, recurrence, recurrent aphthous stomatitis

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Introduction

Recurrent aphthous stomatitis (RAS) is a common and widely recognized disorder involving the oral mucosa. It occurs typically as a single or multiple well-defined painful self-limiting ulcerative lesions influencing the nonkeratinized oral mucous membrane surrounded by red halo [1]. The prevalence of RAS is up to 25% in the world population, with recurrence rate of 50% every 3 mouths. The exact cause of RAS is uncertain, and accordingly numerous components are as yet being implicated such as genetic, hormonal, traumatic, nutritional, allergic, immunological, and psychological factors [2,3].

Clinically RAS is divided into minor, major, and herpetiform types. Moreover, 85% of patients with RAS display the minor form, where ulcers are not more than 1 cm in diameter and healing is not associated with scarring. Major type of ulcers are more than 1 cm in diameter, continue for a longer time, reaching months, and characterized by scar formation. Herpetiform ulcers show up as groups of multiple tiny ulcers scattered all through the nonkeratinized oral mucous membrane [4]. RAS induces difficulty in eating, talking, swallowing, and movement of the tongue, which diminishes the patient's quality of life and adversely influences the somatic and psychological parts of personal satisfaction [5].

Because no distinct etiology of RAS has been recognized, RAS treatment is not particular and is aimed merely at reducing symptoms [6]. The commonly available medication comprise of topical anesthetic, antimicrobial mouthwashes, and topical and systemic immunosuppressive or anti-inflammatory drugs with well-known adverse effects [2]. At the present time, there is an expanding propensity to utilize medicines of herbal origin to treat RAS, and numerous ones have already been assessed as therapeutic agents for its treatment [7,8].

Nicotine is an alkaloid present in the Solanaceae group of plants, and it is a powerful stimulant of

parasympathomimetic. Nicotine derived its name from its origin *Nicotiana tabacum*. They may be transparent or yellow fluid usually found in tobacco. They are synthetized in the roots and are gathered in the leaves. Nicotine comprises nearly 3% of waterless mass of tobacco, and it is present in 2–7 μg/kg in the eatable plants [9].

Nicotine is a stimulant in lesser dosages, yet at high ones, it hinders the activity of autonomic nerves and skeletal muscle cells. It exerts its effects through action on receptors namely nicotine acetylcholine receptors that are found in autonomic ganglia, adrenal medulla, and furthermore on the central nervous system. They encourage cholinergic receptors and circuitously on the discharge of dopamine. Nicotine replacement therapy (NRT) is considered as medicinal formulas of nicotine, which can be used to deliver nicotine into the circulatory system with its useful effects without smoking and its adverse effects [10].

According to the previous study of Meyer [11], the lethal dose of nicotine is ~500 mg where it may produce death by general obstruction of respiratory system. Nicotine in the form of NRT has been reported valuable in several neurological illnesses such as Parkinson's disorder [12] and depression [13]. In addition, it could be an excellent combining modality in the treatment of ulcerative colitis [14].

Nicotine may be a treatment for the ulcers of RAS as previously observed, where it has been discovered that people who use different profitable formulas of nicotine are believed to be not influenced by these sorts of ulcerative lesions. Furthermore, curiously that these sores are observed less frequently in smokers in comparison with non-smokers and between clients of smokeless tobacco than nonclients [15,16].

Previous case reports discovered the use of various forms of NRT such as nicotine tablets 8 mg nicotine/day for 4 weeks [15] and nicotine patches 14 mg nicotine/day [17]. Nicotine lozenges 15 mg nicotine/day over a time of 12 weeks [16] and nicotine lozenges 4.5 mg nicotine/day for 2 weeks [18] in the treatment of RAS prompted fast healing of the ulceration associated with significant improvement of the symptoms, and increased ulcer-free periods for 1 year without unwanted effects were reported.

Considering the aforementioned finding, the current study was conducted to evaluate the clinical efficacy of NRT in the treatment of minor RAS.

Materials and methods

Materials

(1) Nicotine chewing gum is commercially available in Egypt as Nicorette 2 mg nicotine chewing gum (McNeil AB, Helsingborg, Sweden).
(2) Placebo chewing gum was pharmaceutically prepared in Pharmaceutics and Industrial Pharmacy Department, Faculty of Pharmacy, Cairo University.

Preparation and standardization of placebo chewing gum

The gum base (Pharmagum M; Spi Pharma, Wilmington, Delaware, USA) and the sweetener (mannitol; HiMedia Labs, Mumbai, India) were first mixed in a bench-scale cube mixer for 10 min. An accurately weighed amount of the powder mixture (250 mg) was fed manually and compressed at a constant compression force by single-punch press machine (Royal Artist, Bombay, India) equipped with 10-mm flat-faced punches and die set. To prevent the gum from sticking to the die and punches, 100 mg of maltodextrin (dextrose equivalent 13–17; Sigma Aldrich, St Louis, Missouri, USA) was incorporated below and above the gum acting as antiadherent agent. Before patient administration, the prepared placebo chewing gums were standardized in terms of weight and thickness variations, hardness, and friability. The average weight and thickness were 348±5 mg and 3.16±0.05 mm, respectively. Gum hardness and friability were 2.5 ±0.2 kg and 0.2%, respectively. Thus, the gums were acceptable according to the BP [19].

Sample size calculation

As no former studies concerning the effect of pure nicotine on RAS were existent in the literature, the sample size of each group was gained from the existing cases statistics. After recording the results of the present trail, the power was calculated based on pain, erythema, and ulcer size scores, stated in mean and SD values. The power fulfilled the criteria to be greater than 0.8, demonstrating that the sample size of 25 for each study group was satisfactory. The used formula for sample size calculation was as follows:

$$1-\beta=\Phi\left(z-z_{1-\alpha/2}\right)+\Phi\left(-z-z_{1-\alpha/2}\right),$$

$$z=\frac{\mu A-\mu B}{\sigma\sqrt{\frac{1}{nA}+\frac{1}{nB}}}$$

where $k=n_A/n_B$ is the matching ratio; σ is SD; Φ is the standard normal distribution function; Φ^{-1} is the standard normal quantile function; α is type I error; and β is type II error, meaning $1-\beta$ is power.

Ethical approval

This randomized single-blinded placebo-controlled clinical research protocol was approved by Ethical Committee of the Faculty of Dentistry, Cairo University, and registered in Code no 17 12 19. This study was conducted following the ethical guidelines of the World Medical Association (Declaration of Helsinki) for studies involving human participants. All the participants signed an informed consent after explanation of the study procedures.

Inclusion and exclusion criteria

The inclusion criteria were as follows: age 18–30 years and a minimum of 2 years of RAS history, with at least one episode per month history of RAS.

The exclusion criteria were as follows: (a) known history of hypersensitivities to tobacco or NRT; (b) use of any medication as a treatment for the present active ulcer; (c) smoking and presence of systemic diseases such as Behçet disease, anemia, Crohn's disease, ulcerative colitis, acquired immune deficiency syndrome, and liver or kidney disease; (d) pregnant or breast-feeding women; (e) hyperthyroidism, pheochromocytoma, or heart disease, including heart attack, disorders of heart rate or rhythm, angina, high blood pressure or stroke; (f) stomach ulcer, duodenal ulcer, and inflammation of the stomach or the esophagus; and (g) treatment with systemic nonsteroidal anti-inflammatory drugs, systemic steroids or other immune modulatory agents, oral antihistamines, or systemic antibiotics in the previous 3 months or taking other medicines such as theophylline or clozapine.

Study design

The present study was carried out on 50 patients with active minor RAS lasting for a duration less than 48 h from its occurrence who were referred to Oral Medicine and Periodontology Department, Faculty of Dentistry, Cairo University. Using balanced randomization method, the patients were randomly allocated into two groups:

(1) Group 1 (placebo group): 25 patients using placebo chewing gum.
(2) Group 2 (nicotine group): 25 patients using nicotine chewing gum (Nicorette).

The patients were instructed to use the chewing gum, that is, placebo in group 1 and nicotine in group 2, twice daily for 2 weeks. They were instructed on the method of chewing, which is not the same as that for the ordinary chewing gum. They were instructed to chew it slowly until the taste became strong, then rested it between the gingiva and the buccal mucosa. When the taste faded, they chewed the gum again. This chewing technique was kept for half an hour. After this time, the gum had lost its strength and the patients should dispose it carefully. This way confirms that nicotine is properly released from the gum. Food and drinks intake was prohibited for 30 min after chewing the gum. No other medications were allowed to be used during the period of the study. The patients were advised not to use any hard tooth brushes or foods nor acidic foods or drinks as these may intensify pain. The records of the first visit were taken as baseline data. The patients were followed up after 4 and 6 days, and then after 1, 2, and 3 months from the first visit. All the patients who contributed in the study were blinded to the therapeutic agents used.

The diagnosis of RAS was based on the patient's history and clinical examination according to Tarakji *et al.* [2]. The medical history of the patients was done using Modified Cornel Medical Index questionnaire [20].

Clinical assessment

All the patients in both the study groups were assessed for pain intensity, erythema grade, ulcer size, and frequency of recurrence. The ulcer that happened lastly was taken for assessment in case of the presence of multiple ulcers. They were all evaluated at the first visit (baseline) before starting treatment and at each following evaluation (days 4 and 6) except for frequency of recurrence which was evaluated at 1-month, 2-month, and 3-month intervals. Pain score was recorded after irritation of the ulcer with the periodontal probe, using a visual analog scale comprising of a 10-cm straight line among ends, with 0 representing no pain and 10 for intolerable pain [21]. The erythema score was evaluated according to Greer *et al.* [22] as follows: grade 0 (no erythema), grade 1 (light red/pink), grade 2 (red but not dark in color), and grade 3 (very red, dark in color). The ulcer size was evaluated by determining the distance between two opposed boundaries of the ulcer edge, using a periodontal probe in millimeters. The surface area of the ulcer is the product of extreme ulcer width and the length vertical to it [23]. Frequency of recurrence was evaluated as number of RAS episodes occurred during 1-month, 2-month, and 3-month periods.

Each participant was interviewed at each visit regarding the appearance of any adverse effects, if any, in relation to used chewing gum. Participants were asked to attend the clinic the next day for the occurrence of any signs or symptoms of RAS episodes.

Statistical analysis

Statistical analysis was performed using a commercially available software program (SPSS 19; SPSS Inc., Chicago, Illinois, USA). The *t*-Test was used for comparison of age and sex. Pain, erythema scores, and ulcer size revealed a nonparametric distribution and were compared between groups using Mann–Whitney *U*-test. Friedman test for dependent samples was used to study the effect of time on pain, erythema, and ulcer size within the same group. The level of significance was set at *P* less than 0.05.

Results

Clinical results

The current contemplate was carried out on 50 patients who continued and fulfilled the duration of the study without any dropout.

In the placebo group, age ranged from 19 to 30 years, whereas in the nicotine group, it ranged from 20 to 30 years. No statistically significant difference was shown between mean age values (P=0.387) and sex distribution (P=1) in the two groups as shown in Table 1.

Baseline data

At the first visit (baseline), comparison of both groups regarding pain, erythema, and ulcer size scores revealed a nonsignificant difference (P=0.657, 0.513, and 0.866, respectively) (Tables 2–4).

Pain score

Pain score gradually decreased by time, recording the least mean value after 6 days. Friedman test revealed that within each group, the difference in pain score by time was statistically significant in the placebo group (group 1) (P=0.000) and in the nicotine group (group 2) (P<0.05) (Table 2).

Comparing both study groups showed a lower mean score recorded in the nicotine group after 4 and 6 days, with a significant difference after 6 days (P=0.000) (Table 2).

Table 1 Demographic distribution of both study groups

Age (mean±SD)		Sex [*n* (%)]			
		Placebo group		Nicotine group	
Placebo group	Nicotine group	Male	Female	Male	Female
22.9±3.6	23.89±3.3	8 (40)	12 (60)	8 (40)	12 (60)
t-test=0.875 align="center"			χ^2=0		
P (*t*-test)=0.387 (NS) align="center"			$P_{(\chi 2)}$=1 (NS)		

NS, insignificant difference.

Table 2 Comparison of pain score in both study groups with different observational times

Groups	Baseline	After 4 days	After 6 days	*P* value (time) (Friedman test)
Placebo group (mean±SD)	6.1±1.17	3.4±1.23	2.3±0.92	0.000**
Nicotine group (mean±SD)	6.3±1.59	2.7±0.80	0.9±0.32	0.000**
P value (both groups)	0.657	0.059	0.000*	–

*Significant difference than placebo using *U*-test at P<0.05. **Significant difference than baseline at P<0.05.

Table 3 Comparison of erythema score in both study groups with different observational times

Groups	Baseline	After 4 days	After 6 days	*P* value (time) (Friedman test)
Placebo group (mean±SD)	2.6±0.5	1.6±0.5	1.2±0.77	0.000**
Nicotine group (mean±SD)	2.7±0.47	1.3±0.66	0.7±0.36	0.000**
P (both groups)	0.513	0.143	0.036*	–

*Significant difference than Placebo using *U*-test at P<0.05. **Significant difference than baseline at P<0.05.

Table 4 Comparison of ulcer size in both study groups with different observational times

Groups	Baseline	After 4 days	After 6 days	*P* value (time) (Friedman test)
Placebo group (mean±SD)	6.1±1.17	4.8±1.01	3.6±0.94	0.000**
Nicotine group (mean±SD)	6.2±1.01	3.6±1.14	2.7±0.8	0.000**
P (both groups)	0.866	0.001*	0.004*	–

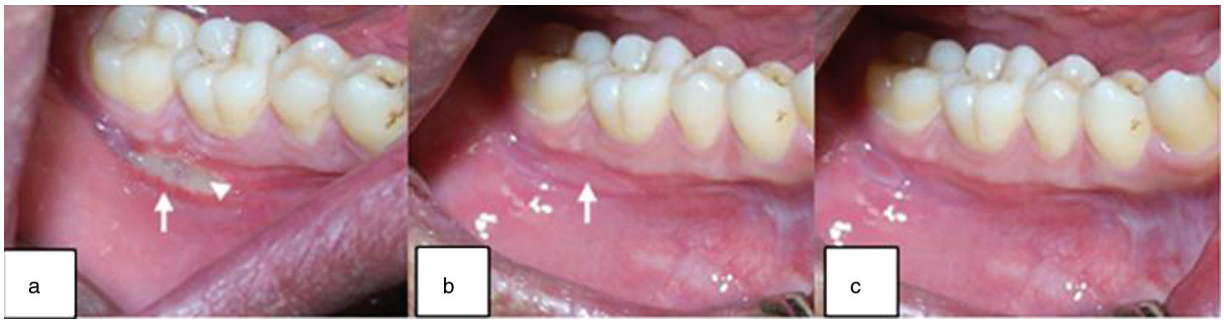
*Significant difference than Placebo using *U*-test at P<0.05. **Significant difference than baseline at P<0.05.

Table 5 Comparison of frequency of recurrence in both study groups with different observational times

Groups	First month	Second month	Third month	*P* value (time) (Friedman test)
Placebo group (mean±SD)	0.8±0.31	0.8±0.27	1.1±0.34	0.301 (ns)
Nicotine group (mean±SD)	0.5±0.12	0.6±0.26	0.8±0.26	0.549 (ns)
P (both groups)	0.123 (ns)	0.173 (ns)	0.201 (ns)	–

NS, insignificant difference.

Figure 1



Showing a case of minor RAS before and after treatment in nicotine group. (a) Minor RAS showed as a single oval ulcer (arrow head) covered by necrotic yellowish exudate and surrounded by erythematous halo (arrow) (baseline). (b) After 4-day visit, minor RAS in the same case with significant clinical improvement regarding erythema and ulcer size (arrow). (c) Complete resolution of minor RAS was noted after 6-day visit. RAS, recurrent aphthous stomatitis.

Erythema score

Erythema score gradually decreased by time, recording the least mean value after 6 days. Friedman test revealed that within each group, the difference in erythema score by time was statistically significant in the placebo group (group 1) (*P*=0.000) and in the nicotine group (group 2) (*P*=0.000) (Table 3). Comparing both study groups showed a lower mean score was recorded in the nicotine group after 4 and 6 days with a significant difference after 6 days (*P*=0.036) (Table 3).

Ulcer size

Ulcer size gradually decreased by time where recording the least mean value after 6 days. Friedman test revealed that within each group, the difference in ulcer size by time was statistically significant in the placebo group (group 1) (*P*=0.000) and in the nicotine group (group 2) (*P*=0.000) (Table 4). Comparing both study groups showed a lower mean score was recorded in the nicotine group after 4 and 6 days, with a significant difference (*P*=0.001 and 0.004, respectively) (Table 4). A case is showed in Fig. 1.

Frequency of recurrence

Within each group, Friedman test revealed that the difference in frequency of recurrence by time was statistically not significant in the placebo group (group 1) (*P*=0.301) and in the nicotine group (group 2) (*P*=0.549), as in Table 5. Comparing both study groups showed a lower mean score in the nicotine group, with nonsignificant difference in the first month (*P*=0.123), second month (*P*=0.173), and third month (*P*=0.201) (Table 5).

Safety assessment

There were not any adverse or unwanted effects reported by the study participants, except one patient in the nicotine group experienced temporary disturbance in taste sensation after 2 weeks of nicotine chewing gum use.

Discussion

Recurrent aphthous ulcers is a periodic ulcerative disorder, which is self-limiting with frequently of 7–10 days duration; however, it reasons significant pain and soreness thus unfavorably disturbing the patient's satisfaction toward his/her life [3]. Accordingly, the basic goal of the treatment is to decrease the associated pain and soreness, reduction of the incidence of relapses, and the induction of healing process [24]. Medications of natural origin are well known to be harmless and efficient substitute treatment for numerous disorders [25].

For these reasons, the present research was carried out to assess the efficacy of NRT in the form of commercially available chewing gum in terms of pain intensity, erythema score, ulcer size, and frequency of recurrence as a treatment of minor RAS in comparison with pharmaceutically prepared placebo chewing gum.

In recent times, the chewing gum bases are broadly utilized in organized drug distribution methods. The chewing gum as a method of medicine release offers numerous new reasonable benefits above the ordinary methods used. These comprise lesser unwanted effects owing to evading of increased plasma greatest absorptions and the increase of the organized medication release, rapid beginning of the act as the active ingredients pass through the jugular veins directly to the circulatory system, increased bioavailability, both local and systemic effects, pleasing taste, and stress-free intake without water need encourages advanced compliance of the patient [26].

In accordance with a recent study found that nicotine in the pure form (not further constitutes of tobacco) is a nontoxic constitute, in spite of the fact that it relies upon the dosage [11]. Nicotine in the form of transdermal patches did not produce a major rise in cardiovascular occasions in heart disease patients even in high-risk ones [27]. A survey of unwanted effects did not discover proof of abundance of unwanted cardiovascular occasions identified with patches of nicotine [28]. Nicotine gum utilized in another trail [29] seemed, by all accounts, to be nontoxic and not associated with any cardiovascular disease or additional severe adverse events.

Evidently, there is no agreement on the active dosage of nicotine replacement substances for inhibition or treatment of the RAS. According to Hill *et al.* [16] who did not observe any unwanted effects associated with lozenges of nicotine, it is worth to remark that the dose of nicotine to treat RAS is lesser than that utilized for the stopping of smoking which may reach 100 mg nicotine/day; therefore, the adverse effects could be minor if they are present [30]. Considering that in this research, nicotine chewing gum dose was 2 mg nicotine/twice daily for 2 weeks. In addition, Bittoun [15] found that the average level of cotinine, a nicotine metabolite, was 139 nmol/L after urinary assays, which is considered very low, although he used 8 mg nicotine/day for 4 weeks, hence the prescribed dose in the current trail which is 4 mg nicotine/day for 2 weeks appeared to be safe for the kidney.

Sample size calculation was problematic to achieve in advance to the start of study as no randomized controlled researches were formerly carried out using NRT in treatment of RAS, with only few case reports without any evidence-based case–control trails. The results of the present research showed that pain, erythema, and ulcer size scores gradually decreased by time in both placebo group (group 1) and nicotine group (group 2), recording the least mean value after 6 days. It was revealed that the difference in these assessment parameters was statistically significant in both the study groups. This may be attributed to the self-limiting nature of RAS [1].

The findings gained from the current contemplate revealed that after 4 and 6 days, a lower mean score was recorded in the nicotine group when compared with the placebo group, with a significant difference after 6 days regarding pain and erythema scores (P=0.000 and 0.036, respectively). In addition, after 4 and 6 days, a lower mean score of ulcer size was recorded in nicotine group in comparison with placebo group, with a significant difference revealed after 4 days (P=0.001) and after 6 days (P=0.004).

The data obtained from the present study results when comparing both study groups with respect to the frequency of recurrence revealed a lower mean score noted in nicotine group, with a nonsignificant difference in the first month (P=0.123), second month (P=0.173), and third month (P=0.201).

The results of the current study were similar to the earlier finding reported by Bittoun [15], Scheid *et al.* [17], Hill *et al.* [16], and Deen *et al.* [18]. Primarily Bittoun [15] found that three nonsmoking patients with RAS who were given nicotine tablets in a dose of 8 mg nicotine/day for four weeks were completely free from fresh ulcers for three months after the treatment associated with complete healing of their current ulcers. Next, it was suggested by Scheid *et al.* [17] that nicotine replacement patches may be used to treat ulcerative lesions of Behcet's syndrome.

It was observed by Hill *et al.* [16] that the use of nicotine lozenges with a preliminary dosage of 15 mg per day, which was progressively decreased along 3-month duration to be a single lozenge comprising 5 mg nicotine per day, made the patient had not any relapse of the RAS for 12 months. Another case was report by Deen *et al.* [18] who successfully used nicotine lozenges in a dose of 4.5 mg once daily which continued for 2 weeks to treat RAS in a lifelong nonsmoker female patient with infantile history of it. The patient was free from RAS episodes along 6 months without any adverse effects noted after use of 1.5 mg nicotine lozenges in three dosages administered above 1.5 h once per day for 2 weeks.

Nicotine has been proven to upregulate the vascular endothelial growth factor expression in basal cells and blood vessels lining cells, in addition to stimulating new blood vessels formation and healing of the wound in

experimental animal through the stimulation of nicotinic acetylcholine receptors [16]. Nicotine can modify immune reactions locally, because it prompts anergy of the T lymphocytes and hinders the synthesis of proinflammatory cytokines, comprising interleukin (IL)-2, IL-6, IL-8, IL-10, and tumor necrosis factor-α. Besides, it elicits the secretion of adrenocorticotrophic hormone and cortisol, which could furthermore decrease inflammatory response. It motivates an increase in the oral mucosa keratinization and thus hinders development of RAS and decreases trauma or diffusion of bacteria into oral mucous membrane [3].

Conclusion

Low dosage of NRT in the form of chewing gum may be considered as an innovative and safe alternate treatment modality for minor RAS. Nicotine chewing gum was effective in reducing pain, erythema, and ulcer size in RAS without any adverse side effects. Additional clinical research studies with larger sample size, more follow-up period, and different dosages of nicotine with other various available therapeutic agents are recommended.

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Conflicts of interest

There are no conflicts of interest.

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