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REVIEW

Efficacy of low-level laser therapy compared to steroid therapy in the treatment of oral lichen planus: A systematic review

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Zohaib Akram, Department of Periodontology, Faculty of Dentistry, Ziauddin University, Karachi, Pakistan. Email: drzohaibakram@gmail.com **Background:** Low-level laser therapy (LLLT) has been proposed as a potential treatment strategy for the treatment of oral lichen planus (OLP). The aim of this systematic review was to assess the efficacy of LLLT, in comparison with corticosteroid therapy, in the treatment of OLP.

Materials and Methods: This systematic review aimed to address the following focused question: "Does LLLT yield better clinical outcomes than corticosteroid therapy in the treatment of OLP?" Indexed databases were searched up to and including April 2017. Clinical trials in humans diagnosed clinically and/or histologically with OLP allocated to test (LLLT) versus control (steroid therapy) groups were included.

Results: Five clinical studies were included. The risk of bias was considered high in four studies and moderate in one study. Laser wavelengths, power, spot size, and duration of laser exposure ranged between 630 and 970 nm, 10-3000 mW, 0.2-1.0 cm², and 6–480 seconds, respectively. The follow-up period ranged from 4 to 48 weeks. All included studies reporting clinical scores showed that LLLT was effective in the treatment of OLP in adult patients at follow-up. Three studies showed significantly higher improvements with topical use of corticosteroids compared to LLLT, while one study showed significant improvement with LLLT. One study showed comparable outcomes between LLLT and corticosteroid application.

Conclusion: It remains debatable whether LLLT is more effective as compared to corticosteroids in the treatment of OLP, given that the scientific evidence is weak. These findings are preliminary and further randomized clinical trials are recommended.

KEYWORDS

corticosteroids, low-level lasers, oral lichen planus, systematic review

1 | INTRODUCTION

Lichen planus is a common chronic mucocutaneous inflammatory disorder, which generally affects middle-aged adults. On the basis of different clinical patterns, oral lichen planus (OLP) is mainly classified into three main forms: reticular, erosive, and atrophic.¹ Reticular lesions are asymptomatic and require no treatment; however, patients with erosive-atrophic forms of OLP often seek treatment as these lesions are associated with pain and discomfort.^{2,3} Erosive-

atrophic patterns manifests as diffuse, erythematous patches surrounded by fine white lines (Wickham striae) where some lesions may undergo malignant transformation.⁴

Therapeutic methods including topical and systemic corticosteroids for the treatment of OLP are suggested. Unlike cutaneous lesions, which generally improve spontaneously, OLP requires longterm treatment and follow-up.⁵ However, long-term use of corticosteroids for chronic OLP has certain local and systemic complications, which includes opportunistic candidiasis, mucosal atrophy, adrenal

-WILEY-Oral Pathology & Medicine (

insufficiency, gastrointestinal disorders, hypertension, and diabetes.⁶ However, long-term use of corticosteroids may be associated with local and systemic complications, and moreover, some patients may not be responsive. To surmount these problems, low-level laser therapy (LLLT) has been proposed as a potential alternative treatment strategy for the treatment of OLP.⁷ The principle of LLLT application is based on its biostimulatory, anti-infective, and anti-ablation effects.⁸ LLLT includes wavelengths between 500 and 1100 nm and typically involves the intensification of electromagnetic fields excited by external source of energy such as light that emits coherent, well-collimated, and monochromatic laser beam. This mechanism implies redox regulation that explains the clinical effects in chronic inflammatory response (OLP) characterized by acidosis and tissue hypoxia that has the potential of tissue healing and tissue regeneration without systemic disturbances and undesirable effects on the healthy tissue.^{9, 10}

A number of studies have compared the outcomes of LLLT with corticosteroid therapy in the management of OLP and showed conflicting results.¹¹⁻¹³ In a clinical trial by El Shenawy et al,¹¹ OLP patients treated with local corticosteroid showed significant improvement in signs and symptoms as compared to those patients treated with LLLT. Similar results were reported by Othman et al¹² However, Jajarm et al¹³ concluded that patients with OLP treated with LLLT showed comparable improvement in clinical outcomes over the use of corticosteroids at follow-up. Moreover, in a recent study by Dillenburg et al,¹⁴ LLLT showed statistically significant improvement than topical steroid therapy in the treatment for OLP.

There appears to be a controversy with regard to the role of LLLT in the management of OLP, and considering the diversity of these results, a systematic review seems desirable. Therefore, the aim of this study was to systematically review the efficacy of LLLT in comparison with corticosteroid therapy in the treatment of OLP.

2 | METHODS

2.1 | Protocol registration and focused question

This review was registered at the National Institute for Health Research PROSPERO, International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO, registration number: CRD42017062401).¹⁵ The present study was carried out using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.¹⁶ The aim of this review was to compare the efficacy of LLLT and steroid therapy in the treatment of OLP.

2.2 | Search strategy

Electronic and manual literature searches were conducted in the following databases: MEDLINE, PubMed, EMBASE, ISI Web of Knowledge, Science direct, SCOPUS, Cochrane Central Register of Controlled Trials, and Cochrane Oral Health Group Trials Register, up to and including April 2017 for articles addressing the focused question. For the PubMed library, combinations of following MeSH (Medical Subject Headings) and free text words were used: ((diode lasers [MeSH Terms]) OR (low level laser therapy [MeSH Terms]) OR (lasers [MeSH Terms]) AND ((lichen planus [MeSH Terms]) OR (oral lichen planus [MeSH Terms]) OR (oral mucosal disease [MeSH Terms]) OR (oral mucosal lesions [MeSH Terms]) OR (erosive [MeSH Terms]) OR (atrophic [MeSH Terms]) AND (buccal mucosa [MeSH Terms]) OR (gingivae [MeSH Terms] OR (floor of the mouth [MeSH Terms] OR (palate [MeSH Terms] OR (tongue [MeSH Terms])).

2.3 Selection criteria

Screening and assessment of articles were conducted independently by two reviewers (ZA and FV). Any disagreement among the authors regarding study selection or exclusion was resolved through discussion and/or by consulting a third reviewer (TA). The following eligibility criteria were entailed:

- Study design: Randomized control trials (RCTs), non-RCTs, controlled or comparative clinical trials (CCTs), split-mouth clinical trials, double-blinded or blinded studies in humans of at least 4week duration.
- Participants: Adult patients (aged ≥18 years) diagnosed clinically and/or histologically with unilateral or bilateral OLP based on the criteria proposed by the World Health Organization.¹¹⁻¹³
- Intervention: Subjects allocated to test (LLLT) versus control groups (local and/or systemic corticosteroid) with at least 10 patients per group. None of the studies included systemic use of corticosteroids.
- Outcome: Changes in (i) pain symptoms in response to test and control procedures and (ii) clinical resolution of OLP signs at post-therapy. Patients' response had to be registered by means of visual analogue scale (VAS), clinical scores (CS), functional scores (FS), Thongprasm sign scoring (TSS), efficacy indices of the treatment (EI), and reticular-atrophic-erosive scores (RAE).
- Language: articles published only in English language.

In vitro studies; treatment with photodynamic therapy, patients without corticosteroid therapy, case series; case reports; animal studies; letters to the editor, opinion articles; abstract; review papers and unpublished articles were excluded.

2.4 | Screening and selection

Two reviewers (ZA and TA) independently screened titles and abstracts for eligible papers. Interobserver's agreement was assessed by means of kappa scores. If information relevant to the eligibility criteria was not available in the abstract, or if the title was relevant, but the abstract was not available, the paper was selected for full reading of the text. Next, full-text papers that fulfilled the eligibility criteria were identified and included in the review. Reference lists of original studies were hand-searched to identify articles that could have been missed during the electronic search. Manual searching of the following journals was performed: *Lasers Med Sci, Ann Dermatol*, Int J Oral Maxillofac Surg, Lasers Surg Med, Photomed Laser Surg, J Craniomaxillofac Surg. J Clin Laser Med Surg. J Clin Exp Dent. J Biomed Opt, and Photodermatol Photoimmunol Photomed. Cross-references were also considered. Studies that fulfilled the selection criteria were processed for data extraction. Figure 1 describes the screening process according to PRISMA guidelines.¹⁶

2.5 Data extraction

Two reviewers (ZA and SSA) performed the data extraction independently. The information from the accepted studies was tabulated according to the study designs, subject demographics, types and site of OLP assessed, corticosteroid therapy with number of applications, the name of outcome variables, follow-up period, main study outcomes, quality of the studies, and laser parameters. Data collected were based on the focused question outlined for the present systematic review. The reviewers cross-checked all extracted data. Any disagreement was resolved by discussion until consensus was reached.

2.6 Assessment of the risk of bias (Quality assessment)

The assessment of methodological quality of the included studies was done by two assessors (SSA and MSB) based on the revised recommendations of the Consolidated Standards of Reporting Trials statement (CONSORT).¹⁷ The risk of bias was estimated for each selected RCT based on the Cochrane Handbook for Systematic Reviews of Interventions¹⁸: (i) low risk of bias (when all criteria were met); (ii) high risk of bias (when ≥ 1 criterion was not met); and (iii) unclear (when ≥ 1 criterion was partially met). The risk of bias of non-RCTs was assessed with a modified version of the Downs and Black checklist.19

2.7 | Statistical analysis

Due to the lack of methodological uniformity of the included studies, a meta-analysis could not be performed. Therefore, the pattern of the present systematic review was customized to summarize the pertinent data.

3 | RESULTS

3.1 Study selection

A total of 807 study titles and abstracts were initially identified. After removal of the duplicates, 602 articles were identified. Five hundred and eighty-five records were excluded as irrelevant to the focus question (k score for interassessor agreement at initial screening kappa = 0.91). A total of 17 papers were selected for full-text reading. Of these 17 studies, 12 studies were further excluded. After the final stage of selection, five studies^{11-14,20} were included and processed for data extraction (k score for interassessor agreement at full-text eligibility kappa = 1 [100% agreement]). Figure 1 shows the study identification flowchart according to PRISMA¹⁶ with the reasons for exclusion of articles.

3.2 General characteristics of included studies

Five studies^{11-14,20} were included in this review out of which three were RCTs^{13,14,20} and two were non-RCTs.^{11,12} The studies were carried out in Brazil,¹⁴ Egypt,^{11,12} Iran,¹³ and Turkey.²⁰ In all studies,^{11-14,20} number of subjects ranged between 120 and 24 individuals with mean age ranging between 42.6 and 61.3 years. All studies^{11-14,20} reported the percentage of female participants, which ranged between 53% and 83%. All the studies^{11-14,20} included

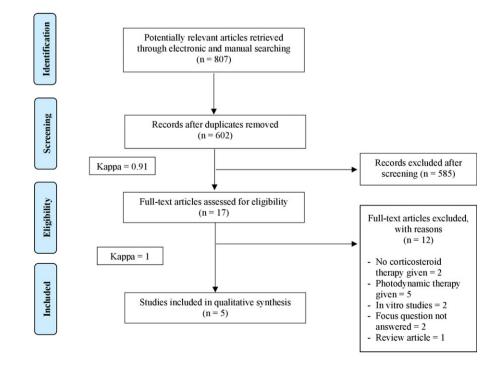


FIGURE 1 PRISMA flow diagram for studies retrieved through the searching and selection process

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erosive-atrophic type of OLP. One study¹⁴ included OLP on tongue, buccal mucosa, lips, floor of the mouth, gingiva, palate, and alveolar mucosa, while two studies^{13,20} included OLP only on tongue and buccal mucosa. Two studies^{11,12} did not report anything with regard to the site of OLP studied. In all studies,^{11-14,20} the follow-up period ranged from 4 to 48 weeks (Table 1).

Various scales and measurement were used to assess post-therapy outcomes. Four studies asked their participants to score their response with a VAS from 0 to 10.^{11,13,14,20} Reduction in sign scores was assessed by TSS in three studies.^{12,13,20} EI of the treatment were determined in two studies.^{13,20} For patients with more than one lesion, a sign score was derived by summation of the scores of all areas (RAE score) was assessed in two studies.^{12,20} CR was determined in two studies,^{12,14} whereas CS, FS, RR, and BAI were assessed in one study only.¹⁴

3.3 | Treatment modalities

3.3.1 | Corticosteroid therapy

Three studies^{11,12,14} used topical application of corticosteroid, whereas two studies^{13,20} used corticosteroid mouth rinse. Two studies^{11,12} used topical 0.1% triamcinolone acetonide with 16 number of applications. Only one study¹⁴ used 0.05% topical clobetasol

TABLE 1 General description of included studies

propionate with 90 applications. Two studies 13,20 used dexamethasone mouth rinse with 120 times rinsing throughout the study period.

3.4 | Laser parameters of the included studies

Three studies^{11,13,20} used diode lasers, whereas two studies^{12,14} used In:Ga:AI:P (indium-gallium-aluminum-phosphate) laser. The wavelengths of different lasers used in the included studies^{11-14,20} ranged between 630 and 970 nm. Power output, energy fluence, and exposure time were 3000 milliwatts (mW), 120 joules per square centimeters (J/cm²), and 6 seconds (s)-480 seconds, respectively. The power density ranged from 10 to 1000 mW/cm². The optic fiber diameter used was 320 μ m. Four studies^{11-13,20} reported ten applications of LLLT throughout the study period (Table 2).

3.5 | Quality of the clinical studies

Two^{13,20} of three^{13,14,20} RCTs did not estimate the sample size. The masking of assessor(s)^{13,20} and methods of allocation concealment¹³ was inadequate in the included studies. All studies^{11-14,20} presented appropriate statistical analysis and description of randomization. The two non-RCTs^{11,12} were associated with selection bias and did not present appropriate blinding. The risk of bias was considered high in four studies^{11-13,20} and moderate in one RCT assessed.¹⁴

Investigators; Country	Study design	Sample size; Mean age in years (range); M/F ratio	Type(s) of OLP	Site of OLP	Corticosteroid therapy; number of applications	Outcomes studied	Follow- up (weeks)	Study outcome	Risk of bias
El-Shenawy et al ¹¹ ; Egypt	Non- RCT	Corticosteroids n=12; 52.2 y; 2/10 LT n=12; 53.6 y; 3/9	Erosive- atrophic	NA	0.1% triamcinolone acetonide; 16 applications	VAS	Up to 8	Topical corticosteroid showed significant improvement than LLLT at follow-up	High
Othman et al ¹² ; Egypt	Non- RCT	Corticosteroids n=12; 45- 62 y; 2/10 LT n=12; 35- 70 y; 4/12	Erosive- atrophic	NA	0.1% triamcinolone acetonide; 16 applications	TSS, RAE, CR	Up to 8	Topical corticosteroid showed significant improvement than LLLT at follow-up	High
Jajarm et al ¹³ ; Iran	RCT	30; NA; NA	Erosive- atrophic	T, BM	0.5 mg in 5 ml water dexamethasone mouthwash; 120 × rinses	VAS, TSS, El	Up to 48	Both LLLT and corticosteroids showed comparable results at follow-up	High
Dillenburg et al ¹⁴ ; Brazil	RCT	Corticosteroid n = 21; 61.3 y; 3/18 LT n = 21; 55.1 y; 4/17	Reticular, erosive, atrophic	T, BM, LM, FM, G, P, AR	0.05% topical clobetasol propionate; 90 applications	CS, VAS, FS, CR, RR, BAI	Up to 12	LLLT showed significant improvement than topical corticosteroid at follow-up	Moderate
Kazancioglu et al ²⁰ ; Turkey	RCT	120; 42.6 y; 56/64	Erosive- atrophic	T, BM	Dexamethasone mouthwash; 120 × rinses	VAS, RAE, TSS, EI	Up to 4	Corticosteroid showed significant improvement than LLLT at follow-up	High

LLLT, low-level laser therapy; T, tongue; BM, buccal mucosa; LM, labial mucosa/lip; FM, floor of the mouth; G, gingiva; P, palate; AR, alveolar ridge; CS, clinical scores; VAS, visual analogue scale; FS, functional scores; CR, clinical resolution; RR, recurrence rate; BAI, beck anxiety inventory; TSS, Thong-prasm sign scoring; EI, efficacy indices of the treatment; RAE, reticular-atrophic-erosive score; NA, not available.

All included studies^{11-14,20} reporting clinical scores showed that LLLT was effective in the treatment of OLP in adult patients at follow-up. Three studies^{11,12,20} showed significantly higher improvements with topical use of corticosteroids compared to LLLT, while one study¹⁴ showed significant improvement with LLLT. One study¹³ showed comparable outcomes between LLLT and corticosteroid application.

3.6.1 Visual analogue scale

Four studies^{11,13,14,20} reported VAS as continuous outcome. El-Shenawy et al¹¹ and Kazancioglu et al²⁰ reported significant improvement in pain scores for topical steroid therapy from baseline (6.8 \pm 0.9 and 5.0 \pm 0.9) to follow-up (0.9 \pm 1.0 and 0.22 \pm 1.0) as compared to LLLT at baseline (7.0 \pm 1.8 and 4.1 \pm 1.8) and followup (3.9 \pm 3.0 and 0.33 \pm 1.6), respectively. In contrast, Dillenburg et al¹⁴ showed significantly better improvement in pain scores for LLLT group as compared to steroid group. Jajarm et al¹³ showed significant but comparable outcomes in pain scores between both the groups.

3.6.2 | Thongprasm sign scoring

Three studies^{12,13,20} reported TSS outcome. Two studies^{12,20} showed significant improvement in TSS for topical steroid therapy as compared to LLLT. One study¹³ showed significant but comparable TSS outcomes.

3.6.3 Reticular-atrophic-erosive score

Two studies^{12,20} reported mean RAE scores. Othman et al¹² reported statistically significantly lower mean RAE scores for corticosteroid group from baseline (21.6 \pm 11.8) to post-treatment (6.0 \pm 7.9) than LLLT at baseline (28.5 \pm 11.7) and post-treatment (16.1 \pm 15.8). Kazancioglu et al²⁰ also showed significantly lower RAE for corticosteroid therapy as compared to LLLT group.

TABLE 2 Laser parameters of included studies

3.6.4 Clinical resolution and recurrence rate

Dillenburg et al¹⁴ reported complete CR observed in 61.9% of LLLT group versus 28.6% of steroid group while RR was significantly less in the LLLT group (4.8%) compared to steroid group (47.6%).

3.6.5 | Efficacy index

Two studies^{13,20} reported El scores as percentage. Study by Kazancioglu et al²⁰ showed El were significantly higher for steroid group as compared to LLLT group, whereas Jajarm et al¹³ concluded EI were more than 75% in 36.4% of the LLLT group and 38.5% in the steroid group indicating a comparable level of improvement between both the groups.

4 DISCUSSION

The present systematic review was based on the hypothesis that LLLT significantly improves patient-centered outcomes in OLP as compared to steroid therapy. Overall, the studies included in the present systematic review^{11-14,20} showed that LLLT showed significant clinical resolution of the lesions. This suggests that LLLT is a potential treatment strategy for the management of OLP in contrast to traditional steroid therapy. However, it is important to interpret these findings with caution due to a number of factors.

Evidence suggests that frequency of laser application also influences the overall efficacy of laser therapy.²¹ As mentioned in the clinical studies, 11-13,20 which showed significant improvement with steroid therapy, laser was applied in ten sessions as compared to 12 sessions in which LLLT showed significant improvement as compared to steroid therapy. It can therefore be hypothesized that at least 12 laser applications should be sufficient; however, it is difficult to contemplate this protocol into clinical settings. As there are limited number of studies that have addressed the focus question, it is rather difficult to determine a threshold for how many times the LLLT should be applied to achieve favorable outcomes in the treatment of OLP.

Investigators	Type of laser	Wavelength (nm)	Energy flu- ence (J/cm ²)	Power out- put (mW)	Power density (mW/cm ²)	Exposure time (sec- onds)	Optic fiber diameter (μm)	Spot size (cm ²)	Frequency of LLLT application
El-Shenawy et al ¹¹	Diode laser	970	NA	3000	NA	480	320	NA	10
Othman et al ¹²	ln:Ga: Al:P	970	NA	2000	NA	240	320	NA	10
Jajarm et al ¹³	Diode laser	630	1.5	10	10	150	NA	0.2	10
Dillenburg et al ¹⁴	In:Ga: Al:P	660	6	40	1000	6	NA	0.04	12
Kazancioglu et al ²⁰	Diode laser	808	120	100	10	150	NA	1	10

In:Ga:Al:P, indium-gallium-aluminum-phosphate; NA, not available; nm, nanometers; J/cm², joules per square centimeters; mW, milliwatts; mW/cm², milliwatts per square centimeters; mg/mL, milligram per milliliter; cm², square centimeters; LLLT, low-level laser therapy.

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It is noteworthy that the included studies^{11-14,20} had either significant heterogeneity or there was a lack of data pertinent to laser parameters. Parameters such as energy fluence, power density, power output, and exposure time (6-480s) of laser light either varied considerably or were not available in some studies. Other factors such as fiber diameter also have an overall effect on power density and energy output during laser application and can modify the actual amount of energy released during the process, potentially affecting the proliferation of cells and hence anti-inflammatory efficacy of LLLT.²² Therefore, further well-designed studies with accurate laser parameters are required in order to clearly understand the efficacy of LLLT in the removal of OLP lesions.

Some other discrepancies were observed among the included studies in terms of inclusion of systemic diseases such as diabetes mellitus, hypertension, and inclusion of smokers. Patients with OLP should be monitored for potential comorbidities. One study¹¹ included patients with diabetes mellitus, and in one study,¹⁴ the systemic health status of the participants remained unaddressed. It is known that wound healing is delayed among patients with persistent hyperglycemia as compared to normoglycemic individuals.²³ In addition, in patients with chronic hyperglycemia (such as patients with poorly controlled diabetes mellitus), increased levels of advanced glycation end products (AGEs) in serum may accelerate tissue injury through elevated oxidative stress mechanism.²⁴ These AGEs are responsible for the production of various pro-inflammatory cytokines such as IL-6 and TNF- α , which are involved in jeopardizing normal tissue structures²⁵ and hence the compromised outcomes. Furthermore, tobacco smoking is a risk factor for the outcomes of wound healing and through suppression of immune system.²⁶

The following limitations should be taken into account when considering the conclusions of the present review. The present systematic review only considered studies in English language. This may have resulted in publication bias with potential relevant studies published in other language being missed.^{27,28} The authors suggest that to determine the clinical outcomes in the management of OLP, the follow-up period seems inadequate and longer follow-up periods could have yielded different outcomes. Therefore, further studies with follow-up periods of up to 1 year or more are recommended in order to witness changes in the clinical severity of OLP after laser application. In addition, a high risk of bias was found in almost 80% of the included studies^{11-14,20} mainly on the sections: sample size calculation, masking of assessors, and internal validity (selection bias). These methodological shortcomings should be cautiously considered when interpreting the findings of the present study. Moreover, it is of essential also to understand the cost of the treatment, expertise/ training in the use of lasers, and need to review the patients in recall appointments once or twice weekly to ensure proper compliance. To date, the steroid therapy is still the gold standard therapy and LLLT seems to be the promising therapy but for limited patients.

A number of review data published recently indicated weak evidence for the effectiveness of LLLT for OLP suggesting further clinical trials to be conducted in order to obtain strong conclusions in this regard.^{29,30} The present systematic review is the first study to compare the efficacy of two treatment modalities such as LLLT and steroid therapy. In the light of other methodological aspects in the included studies,^{11-14,20} such as non-standardized laser parameters and short-term follow-up, it is suggested that the role of LLLT in improving clinical signs and symptoms of OLP as compared to steroid therapy is still debatable. Therefore, studies with long-term follow-up, exclusion of systemic disease, and standardization of LLLT parameters are recommended to reliably assess the efficacy of LLLT in the reduction in signs and symptoms of OLP against steroid therapy.

5 | CONCLUSION

It remains debatable whether LLLT is more effective as compared to corticosteroids in the treatment of OLP in adult patients, given that the scientific evidence is weak. Further randomized clinical trials with long follow-up period and standardized laser parameters are recommended to assess the efficacy of LLLT in the treatment of OLP.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest and all authors have read and approved the final draft.

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