Treatment of minor recurrent aphthous ulceration through biostimulation mechanism by (650nm) diode laser

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Abstract

Recurrent aphthous stomatitis is the commonest oral mucosal disorder all over the world, including Iraq, without a known precise etiology or a specific efficacious therapy. Biostimulation with low level laser therapy was suggested as a safe, alternative therapeutic option. A randomized patient-blinded placebo- controlled therapeutic study were conducted to evaluate the efficacy and safety of low-power 650nm diode laser biostimulation in the management of patients with minor recurrent aphthous ulcerations. The 15 patients completed the study were distributed randomly into three groups: the placebo (A), lower dose laser (B) and higher dose laser (C) treated groups. Pain severity scores showed a comparable (and almost similar) reduction in the two laser irradiated groups which was better than those for the sham irradiated group. Reduction in the ulcers' sizes was most rapid in the higher dose laser group then the lower dose laser groups, and was least in the placebo group. Finally, the higher dose laser group was faster to yield complete healing than lower dose laser group which in turn showed shorter healing time than placebo treated group. Biostimulation of minor RAU using the (650 nm) diode laser with the doses studied seems to be a safe and, effective treatment tool in management of minor RAUs.

Keywords: Minor Recurrent Aphthous, Ulceration, Biostimulation, Diode Laser.

Introduction

Recurrent aphthous stomatitis remains the most common oral mucosal disorder in most communities of the world, including Iraq1. It is found in men and women of all ages, races, and geographic region1,2. The three classic forms of the lesions are minor, major, and herpetiform1-3. One-third of the total population seems to develop minor recurrent aphthous stomatitis (RAS) during their lifetime3. Considerable research attention has been devoted to elucidating the causes of these conditions, local and systemic conditions, genetic, immunologic, and microbial factors all may play a role in the pathogenesis of RAS. However, to date, no principal cause has been discovered1,3. Treatment of RAS includes the use of a long list including many topical and systemic (glucocorticoids, analgesics, antimicrobial, immunomodulatory and hormonal) medications; however, as its precise etiology (or etiologies) remains unknown, therapy is nonspecific and often of limited efficacy4,5.

Recently, low intensity laser therapy has been introduced as an alternative therapy, acting not only as a coadjutant but sometimes as a specific treatment6. He- Ne and diode lasers, with power ranging from 0.005 watts (5 mW) to 0.05 watts (50 mW), provide non thermal effect at wavelengths believed to stimulate circulation and cellular activity7,8. These lasers have been used to promote wound healing and reduce inflammation edema and pain with good to excellent results related to oral tissue healing7-9. They decrease the painful symptoms immediately and increase the reparation process of these lesions7,9. For RAS these two effects are highly desired, thus it may represent a safe, noninvasive treatment alternative to established therapeutic regimens in this indication6.

Patients & Methods

Over a period of 1 year, a randomized patient-blinded placebo- controlled therapeutic study were conducted to evaluate the efficacy and safety of low-power 650nm diode laser biostimulation in the management of patients with minor recurrent aphthous ulcerations (RAUs) using (Mini BioLas® Softlaser); a hand held, medical diode laser device emitting continuous wave, 5 mW power, 650 nm wavelength (visible red) laser light with 1mm beam diameter at output. It is a (class: IIa) laser device with laser protection class: 2M, no goggles required10.

After patients were informed about the nature of this treatment and a verbal consent were obtained, 20 patients with minor RAUs were enrolled in study. They were with early onset (within 3 days) ulcers and had unconvincing benefit from conventional therapy in previous attacks, but didn't use any kind of

medication in current attack before participating in the study.

Diagnosis was clinical. Patients suspected to have Behçet disease and other internal causes of oral ulcerations were excluded. The intensity of pain and burning sensation was measured using a modified visual analogue scale. Patients were asked to, daily, scale their pain-burning sensation on a 6 points scale graded from 0 to 5, where 0 is no burning and 5 is worst burning patient ever experienced. This modification from the standard 10-point visual analogue scale was suggested to facilitate pain estimation with this minor form of RAUs. Every patient kept a diary to record the pain and burning sensation severity on 2 separate modified visual analogue scales every day until the elimination of the symptoms. Patients were examined regarding number, site, size (average diameter) of the lesions and extent of surrounding erythema. Data from history and examination were recorded for each patient at their presentation.

The 15 patients completed the study were divided randomly into three groups A, B, C (each contained 5 patients): one placebo (the control) group A, and two laser-treated groups (the lower dose group B and the higher dose group C).

Number of irradiated ulcers in each group was 8.

Laser treated groups' patients were supplied with a laser device during treatment course, an initial treatment procedure presentation was performed and safety issues were carefully discussed initially.

Patients in group A were instructed to use a red light beam emitted from ordinary LED containing lighter with which they were supplied previously.

Patients in group B were instructed to apply the laser device beam (without a direct contact) at each of the four sides of the ulcer exposing both the ulcer bed and the surrounding mucosa to laser light for 1 minute (60 seconds). For ulcers with less than 5mm diameter, only two opposite sides were irradiated instead of four. Patients were instructed to repeat the procedure each night after mouth washing with water and drying ulcer floor with gauze.

Similar instructions were given to patients in group C except for longer irradiation time (3 minutes instead of 1minute).

In order to evaluate the progress of treatment, assessment of each patient was performed on days 1, 3, 5 from starting therapy and after complete resolution of the ulcer. During which, the records of pain and burning sensation severity were reviewed and the amount of epithelization (healing progress) and reduction in the diameter of the ulcers were assessed. The oral mucosa was also observed for local adverse reactions and the patients were questioned if they had experienced any side effects such as irritation or burning sensation in the mouth.

The response rate was estimated by calculating the percentage of change from baseline in the mean of pain severity scores, average ulcer diameter after 1,3 and 5 days of treatment.

Results

Patients

Of the 20 patients included in this study, 5 patients defaulted for unknown reasons; the remaining 15 patients completed the planned schedule of the study, 9 males (60%) and 6 females (40%). Their ages ranged between 21 and 46 years with a mean age of 32 (±SD 7) years. A Family history of a recurrent oral ulceration was obtainable in 4 (26%) patients.

Ulcers

Twenty-four ulcers were selected to be enrolled in this study, nine patients treated two ulcers and six patients treated one ulcer for each.

Regarding ulcer site, out of 24 ulcers, 13 were labial, 7 were buccal and 4 were sited at floor of mouth.

At presentation, the duration of ulcers varied between 1day (4 ulcers) to 3 days (4 ulcers), but majority were of 2 days' duration (16 ulcers). Considering symptomatic aspect, the pain-burning severity score, according to the suggested modified visual analogue scale for pain estimation, ranged between 2 (2 ulcers),3 (7 ulcers), 4 (9 ulcers) and 5 (6 ulcers) with an average 3.8 (± SD 0.9). The average diameter of studied ulcers ranged between (3mm) and (8mm) with an average 5.9 (± SD 1.6) mm.

Groups

The 5 patients in each group treated 8 ulcers collectively.

Group A ulcers ranged in their pain severity scores between 2 and 5 with a mean of 3.7 (± SD 1) and in their average diameters between 3 mm and 8 mm with a mean of 6 (± SD 1.8), while their duration at presentation ranged from 1 day to 3 days with a mean of 2 (± SD 0.5) days.

Pain-burning severity score of ulcers in group B ranged between 3 and 5 with a mean of 3.7 (± SD 0.7). Their average diameters ranged between 4.5 mm and 8 mm with a mean of 5.8 (± SD 1.2) mm, while duration of ulcers at presentation ranged from 1 day to 3 days with a mean of 1.8 (± SD 0.8) days.

Those in group C, their pain severity scores ranged between 2 and 5 with a mean of 3.8 (± SD 1.1). Average diameters ranged from 3 mm to 8 mm with a

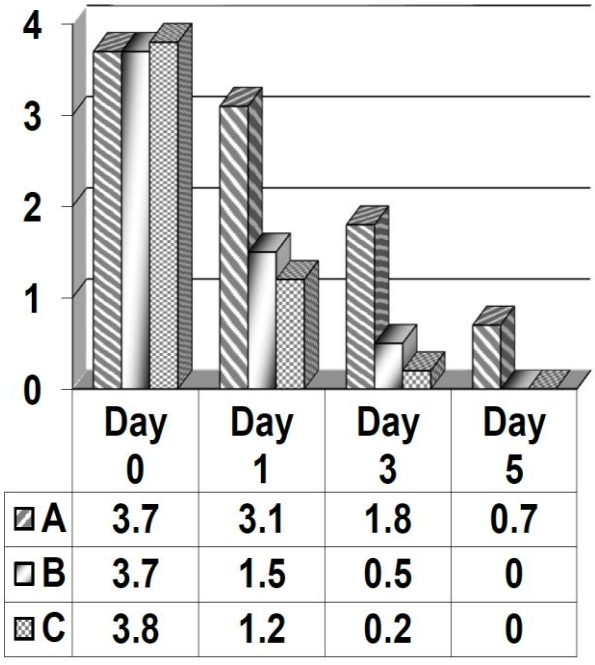
mean of 6 (± SD 1.9) mm, and ulcer duration till presentation ranged between 1 day and 3 days with a mean of 2 (± SD 0.5) days.

Effect of treatment on pain severity score

Group A ranged, in its pain severity scores, at presentation (day 0) between 2 and 5 with a mean of 3.7 (± SD 1), the second day (day1) between 2 to 4 with a mean of 3.1 ((± SD 0.8), two days later (day 3) between 1 and 3 with a mean of 1.8 (± SD 0.6), and at (day 5) between zero and 1 with a mean of 0.7 (± SD 0.4). (Figure1)

Pain severity scores for group B at presentation (day 0) ranged between 3 and 5 with a mean of 3.7 (± SD 0.7). Next day (day1) after laser irradiation, these changed to a range of 1 to 3 with a mean of 1.5 (± SD 3.6), just to drop two days later (day 3) to a range of 0 to 1 with a mean of 0.5 (± SD 0.5), and to end all in (zero) five days after start of daily laser irradiation (day 5). (Figure 1)

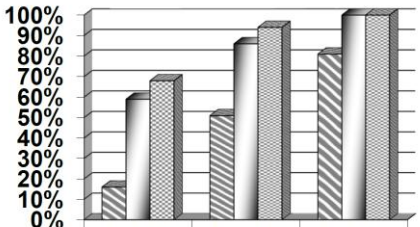
For group C, pain severity scores at presentation (day 0) ranged between 2 and 5 with a mean of 3.8 (± SD 1.1). The second day (day1) they ranged from 1 to 2 with a mean of 1.2 (± SD 0.4), and declined two days later (day 3) to range between 0 and 1 with a mean of 0.2 (± SD 0.4), while all scores were (zero) five days after start of daily laser irradiation (day 5). (Figure 1)



	Day 0	Day 1	Day 3	Day 5
A	3.7	3.1	1.8	0.7
B	3.7	1.5	0.5	0
C	3.8	1.2	0.2	0

Figure-1: Mean pain severity scores in the three groups A-C

The estimated response rate, by calculating the percentage of change from baseline of the mean of pain severity scores after 1, 3 and 5 days of treatment were as shown in figure 2.



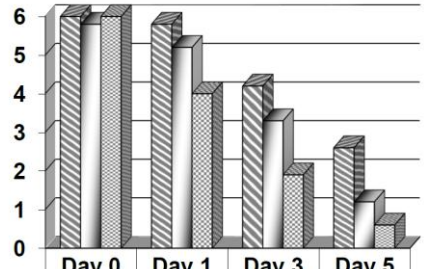
	Day 1	Day 3	Day 5
A	16%	51%	81%
B	59%	86%	100%
C	68%	94%	100%

Figure-2: Response rate of pain severity score in the three groups A-C

Effect of treatment on average Ulcers' diameters

Average Ulcers' diameters for group A at presentation (day 0) ranged between 3 and 7.5 mm with a mean of 6 (± SD 1.8) mm. Next day (day1) after laser irradiation, these still ranged from 3 to 7.5 mm but with a mean of 5.8 (± SD 1.6) mm, just to change two days later (day 3) to a range of 2 to 6.5 mm with a mean of 4.2 (± SD 1.6) mm, and to end at (day 5) in a range of 1.5 to 4.5 mm with a mean + SD of 2.6 + 1 mm. (Figure 3).Group B ranged, in its average Ulcers' diameters, at presentation (day 0) between 4.5 and 8mm with a mean 5.8 (± SD 1.2) mm, the second day (day1) between 3 to 7 mm with a mean of 5.2 (± SD 1.3) mm, two days later (day 3) between 2.5 and 5.5 mm with a mean of 3.3 (± SD 0.9) mm, and at (day 5) between zero and 3 mm with a mean of 1.2 (± SD 0.8).

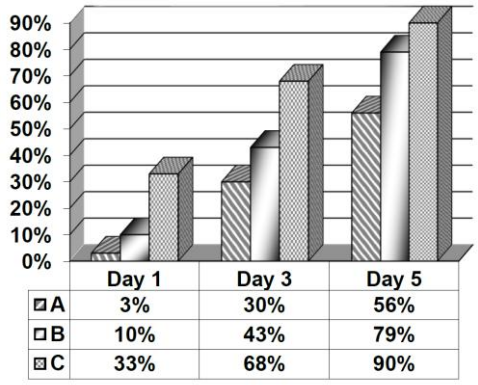
For group C, average Ulcers' diameters at presentation (day 0) ranged between 3 and 8 mm with a mean 6 (± SD 1.9) mm. The second day (day1) they ranged from 2 to 5.5 mm with a mean of 4 (± SD 1.4) mm, and declined two days later (day 3) to range between 0.5 and 2.5 mm with a mean of 1.9 (± SD 0.8) mm, while they ranged between zero and 1.5 mm with a mean of 0.6 (± SD 0.5) mm five days after start of daily laser irradiation (day 5). (Figure 3)



	Day 0	Day 1	Day 3	Day 5
A	6	5.8	4.2	2.6
B	5.8	5.2	3.3	1.2
C	6	4	1.9	0.6

Figure-3: Mean of average ulcers' diameters (mm) in the three groups A-C

The estimated response rate, by calculating the percentage of change from baseline of the mean of average ulcers' diameters after 1, 3 and 5 days of treatment were as shown in figure 4.



	Day 1	Day 3	Day 5
A	3%	30%	56%
B	10%	43%	79%
C	33%	68%	90%

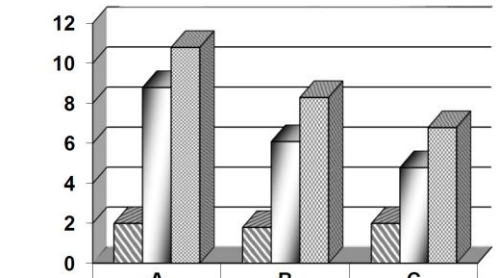
Figure-4: Response rate of average ulcers' diameters in the three groups

Effect of treatment on healing duration

Group A ulcers ranged in their duration at presentation from 1 to 3 days with a mean of 2 (± SD 0.5) days, while their durations after treatment till complete healing ranged between 7 and 11 days with a mean of 8.8 (± SD 1.2) days resulting in a total healing duration range of 9 to 13 day with a mean of 10.8 (± SD 1.3) days.

Ulcers' duration at presentation in group B ranged between 1 and 3 days with a mean of 1.8 (± SD 0.8) days, while their durations after treatment till complete healing ranged between 5 and 7 days with a mean of 6.1 (± SD 0.6) days resulting in a total healing duration range of 7 to 9 days with a mean of 8.3 (± SD 0.7) days.

At presentation, ulcers' duration in group C ranged from 1 to 3 days with a mean of 2 (± SD 0.5) days, while their durations after treatment till complete healing ranged between 4 and 6 days with a mean of 4.8 (± SD 0.8) days resulting in a total healing duration range of 6 to 8 days with a mean of 6.8 (± SD 0.8) days. (Figure 5)



	A	B	C
Before	2	1.8	2
After	8.8	6.1	4.8
Total	10.8	8.3	6.8

Figure-5: Means of healing duration (days) in the three groups A-C

Effect of treatment on erythema and edema

Regarding edema presence and the extent of surrounding erythema, they showed a tendency for resolution during treatment-observation course without measurable difference between the three groups. In addition to a sort of fluctuation exhibited by some ulcers in all groups.

Side Effects

No significant side effects were noticed, nor reported, in all patients of the three groups regarding ulceration site, oral mucosa or eye exposure.

Discussion

The low level laser has been used for wound healing for more than 30 years with a documented beneficial effect on mucous membrane and skin (the types of problem it is best suited to)11. Helium-neon lasers are used to treat skin wounds, wounds to mucous membrane, herpes simplex, herpes zoster (shingles), gingivitis, pains in skin and mucous membrane, conjunctivitis, etc7,8. However, while much of the work has been done with helium-neon gas lasers, an identical laser wavelength (632 nm) can now be produced by diode laser devices and it was as effective as the gas helium-neon laser (632 nm) in significantly speeding the rate of healing12,13.

Evaluating the literature describing clinical applications of low-intensity laser therapy (LLLT) is complicated by the wide variations in methodology and dosimetry between different studies. Not only have a range of different wavelengths been examined, but exposure times and the frequency of treatments also vary12,13.

In this study we evaluated the influence of low-intensity laser therapy on symptomatology and healing process of minor RAU among Iraqi patients in a placebo-controlled trial design. The inclusion of sham-irradiated controls in clinical studies is an important element, since placebo effects can be dramatic, particularly in terms of the level of pain experienced following treatment11,12.

Out of the twenty patient enrolled in the study, 15 patients completed its suggested course. The relative differences in their ages and sex distribution from the published epidemiologic data can be explained to some extent by the selection criteria regarding duration of lesions at presentation and the use of previous medication(s), in addition to patients' desire to participates in the study.

Twenty-four ulcers in the fifteen patients were selected to be enrolled in this study, nine patients treated two ulcers and six patients treated one ulcer. Regarding ulcer site, out of 24 ulcers, 13 were labial, 7 were buccal and 4 were sited at floor of mouth.

Selection of ulcers to be treated was dependent to a large extent on the duration of ulceration presence at presentation, easy applicability of the treatment modality (determined by number of ulcers for a single patient and their approachable sites) according to patient abilities.

Daily application was used, and it was applicable since patient was not obligate to visit clinic to obtain their dose and it was recommended that daily dosing yields better results than alternate day or twice weekly dosing.

Regarding the effect of treatment on pain-discomfort severity scores, the two laser irradiated groups (group B and group C) showed a comparable (and almost similar) reduction in their scores which was better than those for the sham irradiated (placebo treated group A). They showed (by calculating the percentage of change from baseline of the mean of pain severity scores) estimated response rates of (59% and 61%) at day 1, (86% and 94%) at day 3, and (100% and 100%) at day 5 for groups B and C respectively which were noticeably better than those of group A (16%, 51% and 81%) at days 1, 3, and 5 respectively. At day 5 all pain severity scores were zero (completely free of pain and discomfort) for both laser-treated groups (B and C) while patients in the placebo group A were still feeling discomfort in all but two ulcers.

Concerning effect on average ulcers' diameters, the sham irradiated placebo treated group A ulcers showed a response rates of 3% at day 1 in comparisons to 10% versus 33% for the laser treated groups (B and C) respectively. At day 3, the response rates of the three groups were 30%, 43% and 68% to be (i.e. the response rate) 56%, 79% and 90% two days later (at day 5) for groups A, B and C respectively. Thus it is obvious that group C showed more rapid reduction in the average ulcers' diameters (and thus ulcers' sizes) than those in group B, which showed in turn still more rapid reduction in its ulcers' sizes than those in the placebo treated group A.

Mean of time required for ulcers till complete healing was 10.8 ± 1.3 days for group A, 8.3 ± 0.7 days for group B, and 6.8 ± 0.8 days for group C. This shows that laser treatment dose in group C was faster to yield complete healing than that used for group B ulcers which in turn showed shorter healing time than placebo treated group A ulcer. These findings are consistent with some of the available data from literature which showed in an open study that the stimulatory effect of LLLT at 660nm is dose dependent for exposure to energy densities of 2.4 - 7.2 J/cm2, the upper end of the range being most effective and with 9.6 J/cm2 proving to be less effective than 7.2 J/cm2. However, detailed comparable clinical studies were unfortunately none too easy to find11.

This athermic phototherapeutic modality represents a safe treatment since none of the patient complained of any sort of side effect at the ulcer site or all oral mucosa. In addition to that, no accident of visual complication to laser beam exposure was reported6,9. It seems that a proper patient selection and a careful discussion regarding safety issues is enough for safe use of such laser device.

Though our study was not concerned with following up recurrence rate, it is worth mention that 4 of our pretreated patients were seen again with the same complaint while we were testing different (non mentioned) treatment schedules thus criticizing the preventive claims of laser biostimulation for RAS which were in fact the prime important point that patients concern about1-4.

Diode laser pointers are very common and are becoming more available. They are prevalent in lecture halls and classrooms. Currently the most common and inexpensive laser pointer emitting continuous wave visible bright red beam with a wavelength ranging from 630 - 680 nm and 5Mw power can be thought about as a cheap and widely available alternative to obtain the beneficial effect shown in present study with an easily achievable non-expensive laser source, (thereby lowering treatment expense), that can be applied by patient himself, (in order to simplify treatment course and avoid frequent clinic attendance for this highly common disorder), with an acceptable safety standard for the general community thereby needs just simple understandable safety precautions.

Conclusions

Biostimulation of minor RAU using the (650 nm) diode laser with the doses studied in the current study seems to be a safe and, effective treatment tool for reducing aphthous ulcer pain and lesion size, in this Iraqi patient cohort. It might be considered as an alternative to established therapeutic regimens in this indication.

Both doses used in the treatment groups showed almost similarly effective and equivalent analgesic effect which is felt to be non-dose dependent. In contrast ulcers' healing progression and lesions' size reduction, showing dose dependency, were faster with the higher dose of laser biostimulation than the lower dose which in turn were faster than the sham irradiation.

Further large well-designed clinical trials are required to optimize doses, demonstrate effectiveness for other types of RAU It is essential that treatment protocols are based on the results of randomized controlled clinical trials. There is an urgent need for more of these studies to be undertaken, and for the

results of these to be disseminated widely to clinicians using LLLT. Only then will the aura of controversy and the stigma of anecdote and empiricism be removed from this area of clinical practice.

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