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Photobiomodulation laser therapy in pemphigus vulgaris oral lesions: A randomized, double-blind, controlled study

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SUMMARY

Objective. Systemic corticosteroids are the mainstay treatment for PV oral lesions; the aim of this study is to evaluate the efficacy of PBMT with a 645 nm diode laser as a supportive topical therapy in patients with PV induced erosive-ulcerative oral lesions.

Materials and Methods. This double-blind placebo-controlled study divided patients into two groups: A, patients receiving laser therapy (Raffaello 980 Bio, Dental Medical Technologies, Italy with the following parameters: 100 mW power, 645 nm wave length, irradiation area 1 cm^2, application time 30 sec/cm^2, energy density 3 J/cm^2, scanning modality) and B, receiving sham therapy (placebo). All patients were being treated also with a systemic corticosteroid therapy i.e. prednisone 0.5 mg/Kg per day. Size of lesions, VAS and satisfaction were evaluated before the treatment (T0), after 4 weeks (T1) and after 8 weeks as a follow-up (T2).

Results. A total of 50 lesions were evaluated. About lesions size, there was a statistical significative difference between the two groups just at T2 ($p=0.0193$), though VAS significantly decreased both at T1 ($p=0.0198$) and at T2 ($p=0.0087$). In general, all patients were satisfied of the treatment received.

Conclusion. PBMT can be considered a validate supportive therapeutic option, even if further RCTs studies with wide sample sizes and standardized management protocols are suggested.

Keywords: oral ulcer, oral pemphigus, laser, pain.

INTRODUCTION

Pemphigus vulgaris (PV) is a rare, chronic, autoimmune, mucocutaneous, vesiculobullous disease (1). It has an incidence of 0.1-0.5/100000 new cases per year (2) and it usually occurs in both sexes, with a slice female predominance, and with a preference from the third to the sixth decade of life (3, 4).

Generally speaking, PV first begins with erosive-ulcerative lesions on the oral mucosa, preceded from vesicles that deteriorate quickly, sometimes (about 50% of the cases) followed by skin lesions (5, 6).

The pathogenesis of PV relies on IgG-targeting desmosomal proteins DSG1 and DSG3 (7). The blistering mechanism in PV can be explained through the binding of autoantibodies that can interfere with the cell adhesion ability of desmogleins (8). In addition to this, the autoantibodies induce clustering of the desmogleins leading to their depletion and signalling pathways determining acantholysis (9). The compromised intra epithelial adhesion leads to acantholysis and formation of vesicles, blisters and erosions on the skin and on mucosal membranes (10).

Oral blisters and vesicles are typically located on buccal mucosa, palate, tongue and lips, and quickly degrade with the appearance of very painful erosions and ulcers, which in turn lead to difficulties in food intake, swallowing and speech (11, 12).

Systemic corticosteroids (prednisone, maximum 1.5 mg/kg/day) are the PV mainstay treatment and, although they are quite effective in controlling the disease, they often have potentially serious side effects, partially causing its morbidity and mortality (6, 13-15). As supportive therapy, some topical treatment, such as corticosteroids gel (clobetasol diproprionate) for oral mucosa, can be useful in very painful refractory ulcers above all (16).

Complete remission at ten years after the diagnosis is testified in about 75% of patients (6).

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In the last years, low-level laser therapy (LLLT), recently referred as photobiomodulation therapy (PBMT), has been widely used in different medical fields as a non-pharmacological supportive therapy in chronic or acute painful situations with proven effectiveness and without any remarkable adverse consequences. In dentistry, PBMT has been widely used in many fields, oral pathology included, with good results, especially in supportive therapies for reducing pain due to oral mucosal lesions (17-19).

Anti-inflammatory and analgesic effect of PBMT can be explained in different ways: on one hand the absorption of laser light by photoacceptors chromophores in mitochondria causes an increase in the synthesis of ATP, growth factors, fibroblasts and collagen and on the other hand the increased microvascularity determines tissues repair. Moreover, laser light can detoxify oxygen free radicals during inflammation (20).

SATISFACTION QUESTIONNAIRE

1)What is your instruction level?
- Elementary school
- Secondary school
- Under-graduate
- Graduate

2) In general, are you satisfied about the laser therapy?
- 0 (non satisfied)
- 1 (not very satisfied)
- 2 (discreetly satisfied)
- 3 (quite satisfied)
- 4 (extremely satisfied)

3) How much are you satisfied about the need of multiple appointment?
- 0 (non satisfied)
- 1 (not very satisfied)
- 2 (discreetly satisfied)
- 3 (quite satisfied)
- 4 (extremely satisfied)

Fig. 1. Satisfaction questionnaire

As today literature is poor of reports about the use of laser light on PV oral lesions (20-22), the aim of this study is to evaluate the efficacy of PBMT with a 645 nm diode laser as a supportive therapy in patients with PV induced erosive-ulcerative oral lesions.

MATERIALS AND METHODS

Sample selection

This study was carried out at the Department of Oral Medicine of the Dental Clinic of Spedali Civili of Brescia (Italy). Patients were consecutively enrolled from September 2020 till December 2020.

Inclusion criteria were:

a) clinic, serologic and histologic diagnosis of Pemphigus Vulgaris according to the conventional WHO criteria (24),

b) presence of erosive-ulcerative oral lesions with a diameter >1.5 cm,

c) symptomatic lesions (d) acceptance of participating in the study by signing the informed consent.

Exclusion criteria were:

a) chronic diseases (e.g. coeliac disease, diabetes, etc.),

b) neoplastic diseases,

c) drug intake (e.g. antibiotics, antifungals, anti-inflammatory, hormone therapies, etc.) or pregnancy.

Study design

This study was designed as a double-blind placebo-controlled study. This research has been performed in accordance of the principles of Helsinki Declaration revised in 1983 and has been approved by the Ethic Committee (February, 20th 2020), NP: 3952.

Patients were randomized into two groups by a computer code: group A which included patients receiving laser therapy and group B receiving sham therapy (placebo), i.e. the device was switched on but the hand piece did not work. All patients were being treated also with a systemic corticosteroid therapy i.e. prednisone 0.5 mg/Kg per day, full dosage for two weeks and half dosage for the next two weeks.

Patients were evaluated before the treatment (T0), after 4 weeks (T1) and after 8 weeks as a follow-up (T2).

PV clinical course was assessed by measuring severity of pain and the lesions size, besides the patient satisfaction of the therapy. Clinicians who evaluated the outcomes were blinded to the allocation group.

Laser equipment and treatment timing

The device used for this study (Raffaello 980 Bio, Dental Medical Tecnologies, Italy) had the following

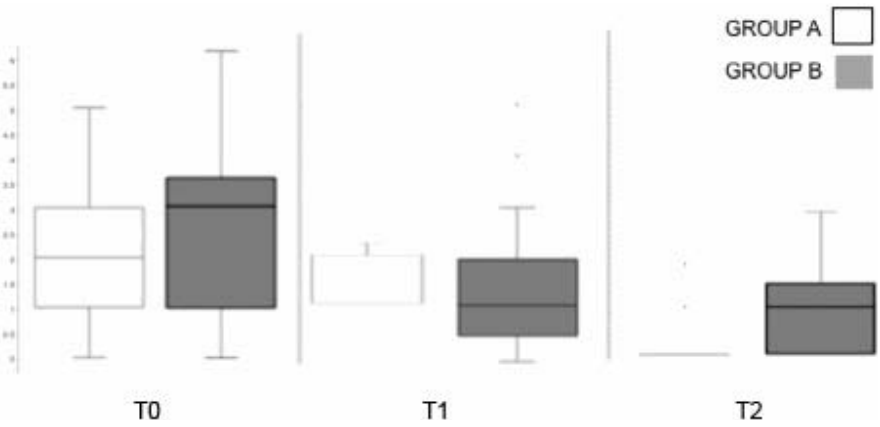

Fig. 2. Boxplot of VAS at T0, T1, T2 in Group A and Group B

parameters: 100 mW power, 645 nm wave length, irradiation area 1 cm^2, application time 30 sec/cm^2, energy density 3 J/cm^2, scanning modality.

Laser treatment/placebo were performed without local anaesthesia 2 times a week for 4 weeks by trained clinicians, following international safety procedures (clinicians and patient wore protective glasses).

Size of the lesions

The lesion size was defined as the longest distance in mm of the main diameter of the worst erosive lesion of PV, measured with a periodontal probe. The scoring was performed by two calibrated clinicians.

Pain scoring

The severity of pain was determined using a visual analogue scale (VAS) from 0 to 10 where 0 corresponds to "no pain" and 10 to "the worst possible pain".

Clinicians who performed laser/sham therapy did not participate in the scoring of oral lesions.

Satisfaction/discomfort questionnaire

At the end of the study (T2) level of satisfaction of PBMT was evaluated through an ad hoc questionnaire. The questionnaire contained three questions regarding: one about instruction level and two about laser therapy satisfaction; at the two satisfaction questions, 5 choices were possible (Fig. 1).

Statistical analysis

All collected data were recorded in a Microsoft Excel database and statistical analysis was performed using IBM SPSS Statistics (v.25, SPSS Inc., Chicago, IL, USA).

Statistical analysis was descriptive, including mean, median, standard deviation and percentiles for variables such as sex and age. Concordance or differences in the frequency distribution between the two groups were tested using the Student *t* test. For data not exhibiting normal distribution, the non-parametric test U-Mann Whitney was used, evaluating the difference in pain and clinical diameter.

A *p* value less than 0.05 was considered statistically significative.

Sample dimension

Clinical experience and the literature set the significative reduction of PV lesion after 4 weeks at a percentage of 30% in the cases following conventional therapy and at the 70% in the lesions treated also with PBMT; assuming α error 5% and a study power of 80%, and considering that PV is quite a rare disease, the number of oral lesions to be investigate in the study is calculated to be 50 (minimum 25 per group).

RESULTS

Twenty-three patients (14 female and 9 male) were enrolled in this study with a total of 50 oral lesions; the mean age (±SD) was 43.5 (±14.62) years, range 21-82 years. Educational level was so distributed: 3 people had elementary license, 5 people finished the secondary school, 7 were under-graduated and 8 patients were graduated or more. Group A and group B consisted of 25 lesions each.

Size of the lesions

Medians values are displayed in Table. The reduction in lesions diameter resulted not statistically significative both at T0 and at T1.

There was a statistical significative difference between the two groups just at T2, after 8 weeks (p=0.0193) (Table) when lesions in group treated by PBMT totally disappeared.

Table 1. Results for lesions size at T0, T1, T2

	GROUP A median (PBMT+ systemic therapy)	GROUP B median (sham+systemic therapy)	Z score (U-Mann Whitney test)	p-value
T0	6	6.5	0.4850	0.6276
T1	1	1	0.5335	0.5936
T2	0	0.5	-2.3380	0.0193*

* – result is significant.

Pain scoring

VAS median for group A were: 3.5 at T0, 0 at T1 and 0 at T2; for group B: 5 at T0, 2 at T1 and 1 at T2. The difference in VAS value

was statistically significative both at T1 (p=0.0198) and at T2 (p=0.0087). Results for VAS are displayed in Fig. 2.

Satisfaction Questionnaire

No differences in satisfaction resulted through the different education degree.

For the second question, about the satisfaction of laser/sham therapy, most patients in both groups were "discreetly" and "quite satisfied"; no difference between the two groups was noted (p>0.05).

About the need of multiple appointments, satisfaction was lower, in fact, most patients complained to be "not very satisfied" or "discreetly satisfied" in both groups, without significative difference (p>0.05).

DISCUSSION

Pemphigus Vulgaris is a painful blistering disease, causing discomfort in feeding, drinking, eating and speaking (12). Systemic corticosteroids remain the gold standard therapy, but refractoriness of oral lesions and pain lead the research to alternative and supportive therapies (20, 24). PBMT, already used in other medical fields with good results, has been proposed to increase oral tissue healing, since it determines faster lesions reduction, quicker re-epithelization and proliferation of organized collagen fibers and fibroblasts (21, 14, 25).

Though in literature several studies can be find about PBMT and different oral lesions (26-29), to the best of our knowledge there are just a few researches on PBMT and oral PV (11, 19, 20-22). In this before-after clinical trial, authors decided to investigate a diode device, considering the results of previous studies on oral mucosa healing (17, 18).

Minicucci *et al.* (11) used a diode laser with parameters similar to this trial, but with a different timing (daily, until the pain disappeared); they found an analgesic effect since the first laser session with evident lesions healing. These data are just partially in accordance to those issued in the present research: pain significatively decreased, but after 4 weeks from the beginning of treatment and also at follow up evaluation (8 weeks). We can speculate that this discrepancy in results can be due to the consistent difference in the sample; in fact, Minicucci *et al.* analysed just two cases, suggesting a wide sample research (11) and also considering oral and cutaneous lesions. Other few papers are available to study the effect on pain of the photobiomodulation therapy on PV lesions, but all used low-level CO_2 laser irradiation. In particular, Yousefi *et al.* (21) examined cutaneous recalcitrant lesions though Zand *et al.* (16) only oral lesions. Zand and colleagues used a non-ablative, non-thermal, CO_2 laser therapy (NTCLT), operated at 1 W power, in a continuous defocused mode, about 5 mm distant from the surface of the lesion, previously covered with a thick layer of a transparent gel with high water content, in 14 patients. Authors found a significative pain decrease in nearly all patients immediately after the first laser session and till the end of the follow-up (16). In this case, CO_2 laser can be considered a low level therapy because it was delivered by a defocused circular manner, in addition with a thick water gel layer, which reduces the beam absorption avoiding tissue injury (16).

On the other hand, in the case report of Bhardwaj and colleagues, recalcitrant oral PV lesions were treated through CO_2 laser, in a classical surgical mode. Even if the laser power was low (1-1.5 W in defocused mode for 5-10 sec), it was in the range of thermal surgical laser; however, authors reported decrease in pain and lesions healing (22). This case report is the unique that investigates, behind the pain, also the wound healing, but not in terms of diameter, so the comparison with the present research is not possible.

According to the literature, the relief of pain after PBMT is quite immediate (11, 16, 19-21). On the contrary, our results show a significant improvement of symptoms only after 4 weeks. The reason of this discordance may be found in the different devices and protocols used. Minicucci *et al.*. reported a prompt analgesic effect using a similar device but they treated just two cases of PV (11). The sample of this study is one of the largest treated so far, thus the slower but effective action of PBMT on these ulcerative lesions seems reliable.

PBMT is believed to exert a double effect. The first phase is immediate and occurs as a result of direct irradiation of cell components, while the second is a delayed response that occurs after hours or days. Its effects are the result of activation of endogenous chromophores, light absorption by intercellular water, and several mediators: growth factors (TGF-β1), pro- and anti-inflammatory cytokines, matrix metalloproteinases, and small molecules, such as ATP and reactive oxygen species. These mediators guide cell proliferation, differentiation, angiogenesis, and immune activation, modulate apoptosis and improve cell survival, explaining the pain relief and significant reduction in lesions observed when PBMT is used to treat PV (30). The increased microcirculation and the faster wound healing could justify the good acceptance of the treatment, as demonstrated by our study; patients gladly accepted the therapy, even if it required more appointments. In addition, PBMT did not required anaesthesia and was well tolerated

in all the sessions, also in patients with recalcitrant oral ulcerative lesions.

CONCLUSION

In conclusion, although systemic steroids remain the mainstay in oral PV treatment, PBMT can be considered as a validate supportive therapeutic option, recommending further RCTs studies with wide sample sizes and standardized management protocols.

STATEMENT OF CONFLICTS OF INTEREST

The authors state no conflict of interest.

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