Pemphigus vulgaris and laser therapy

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Summary

Introduction. Pemphigus vulgaris is a relatively rare, chronic, autoimmune vesiculobullous disorder characterized by formation of intraepithelial vesiculae and/or bullae in the skin and mucous membrane. Systemic steroids are considered to be the standard first-line therapy for pemphigus vulgaris. However, for patients unresponsive to standard therapy, the new treatment modalities are being sought. Low-level laser therapy has been accepted as an alternative or adjunctive treatment modality for many conditions in medicine and dentistry. Therefore, this study was aimed at presenting the effects of low-level laser therapy in the treatment of pemphigus vulgaris and to emphasize the crucial role of dentists in early recognition and diagnosis of pemphigus vulgaris. Material and Methods. The articles published until May 2013 were obtained from the Medline/PubMed online database, using following search terms and key words: “laser therapy” and “pemphigus vulgaris”, “low-level laser irradiation” and “pemphigus vulgaris”, “lasers” and “pemphigus vulgaris” and “pemphigus vulgaris”. Results. Low-level laser therapy could result in immediate and significant analgesia and improved wound healing within the observation period and follow-up. Furthermore, a decrease in patients’ discomfort as well as the absence of recurrence of the pemphigus vulgaris lesions has been claimed. Conclusion. Even though available literature suggests that low-level laser therapy can be efficiently used in treatment of oral pemphigus vulgaris, either independently or as a part of combined therapy approach, these results should be interpreted with caution since there are no solid evidence-based proofs to provide the guidelines for the treatment of pemphigus vulgaris with low-level laser therapy. Therefore, further long-term randomized controlled clinical studies are necessary in order to give any solid recommendations on the use of low-level laser therapy in the treatment of pemphigus vulgaris. Key words: Pemphigus; Laser Therapy; Dentistry; Laser Therapy, Low-Level; Skin Diseases, Vesiculobullous; Treatment Outcome

Sažetak


Ključne reči: Pemfigus; Laseroterapija; Stomatologija; Laserska terapija niskog nivoa; Vezikulobulozna oboljanja kože; Ishod lečenja

Introduction

Pemphigus is a group of relatively rare, chronic autoimmune disorders characterized by formation of intraepithelial bullae in the skin and mucous membrane [1, 2]. Pemphigus is divided into two major subtypes: pemphigus vulgaris and pemphigus foliaceus [1]. Having the incidence up to 80% of all...
pemphigus cases, pemphigus vulgaris (PV) is considered the most common form of disease [2]. PV can be divided into two subgroups: the mucosal type and mucocutaneous type [3]. PV affects the mucosa in nearly all cases and more importantly, the oral (mainly buccal and/or palatal) mucosa is the pace of the first lesions in the majority of cases [2]. It is characterized by immunoglobulin G auto antibodies against desmosome associated protein antigens (desmoglein 1 and/or 3) found in epithelial and epidermal intercellular substance. Since the desmosomes are the primary attachment mechanism between keratinocytes, this disease results in acantholysis in epidermis [1].

Typically, the patients suffering from PV have flaccid blisters (fluid filled bullae) that rupture easily provoked by even minimal trauma, further causing painful multiple erosions and ulcerations on the skin and mucous membranes, which spread to other mucosa and the skin [4]. Oral PV is usually associated with symptoms ranging from mild burning sensation to severe pain (in about 87.5% of patients with PV) affecting normal masticatory function [5]. Furthermore, due to the repeated cycles of blistering and healing, oral hygiene is usually compromised, leading to rapid breakdown of the dentition [3, 4]. A definitive diagnosis of PV is made when Nikolsky’s sign is positive, in the presence of acantholysis in histopathology and by direct immunofluorescence [2].

Although a number of different treatment modalities have been recommended so far, treatment of PV is usually symptomatic, therefore showing low predictability. Most treatment modalities are conservative/pharmacological, such as systemic corticosteroids, immunosuppressant or immunomodulatory agents, corticosteroids being widely accepted as the primary treatment of choice [1]. However, corticosteroids are limited by various time and dose dependent adverse effects. One of the main drawbacks of corticosteroids is the long-term application treatment, which can be difficult on the oral mucosa, causing frequent relapses upon the treatment’s cessation and often requiring steroid-sparing agents [6, 7]. Unfortunately, steroid-sparing agents are often associated with significant toxicity. Immunosuppressants used in the treatment of severe PV may increase the risk of infection and delayed healing, thus causing a problem in dental treatment procedures in this group of patients [9]. Less studied, emerging therapies include intravenous immunoglobulin, plasmapheresis, immunoadsorption, extracorporeal photochemotherapy, cholinergic agonists, rituximab, anti-CD20 monoclonal antibody therapy, tumor necrosis factor-α (TNF-α) inhibitors and other experimental therapies such as Desmoglein-3 peptides [10-12]. Since drugs used in the treatment of patients with PV have many drug-related side effects, the patients must be monitored carefully, their health status must be improved and they must be advised to exercise, diet and stop smoking. Though the majority of patients respond to these therapies, some patients will develop a recalcitrant disease [6]. Therefore, the need for better treatment alternatives was obvious, especially for patients unresponsive to standard therapy of PV.

Low-level laser therapy (LLLT; photobiostimulation) has been widely used as an alternative or supplementary treatment modality; thus, its applications in modern medicine and dentistry are numerous. The aim of this review article was to give the insight into the literature published so far regarding the effects of LLLT used for treatment of patients with PV and to remind on the crucial role of dentists in early recognition of PV.

Material and Methods

The articles published until May 2013 were obtained from the Medline/PubMed online database, using following search terms and key words: ”laser therapy” and ”pemphigus vulgaris”, ”low-level laser irradiation” and ”pemphigus vulgaris”, ”lasers” and ”pemphigus vulgaris” and ”pemphigus vulgaris”. Two authors performed both the screening and selection of studies independently in order to ensure impartiality when selecting the studies. Secondary sources included papers cited by articles retrieved from the above mentioned studies. The corresponding authors were contacted in case of missing and insufficient data reported originally in the studies. The authors of this study measured and compared the symptoms (pain, discomfort), signs (enhanced healing) and recurrence of the PV lesions.

Results

The author of this article knows of only three publications that deal with the effects of LLLT on pemphigus vulgaris.

Table 1. The basic information of selected studies

<table>
<thead>
<tr>
<th>Author and the year of the publication (reference)</th>
<th>Study design Vrsta studije</th>
<th>Number of patients Broj pacijenata</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bharadwaj A. et al. (6)</td>
<td>Case report/Prikaz slučaja</td>
<td>2</td>
</tr>
<tr>
<td>Minicucci EM. et al. (7)</td>
<td>Case report/Prikaz slučaja</td>
<td>2</td>
</tr>
<tr>
<td>Zand N. et al. (8)</td>
<td>Before/after clinical trial Pre/posle klinička studija</td>
<td>10</td>
</tr>
</tbody>
</table>
oral pemphigus vulgaris (Table 1). Minicucci et al. [7] reported two cases of oral and cutaneous PV treated with conventional steroid therapy prednisone and dapsone (diamino-diphenyl sulfone) combined with the low-level diode laser therapy and its effects on pain and faster wound healing. The following diode laser parameters were used: wavelength 660 nm, output power 100 mW, fluency 35 J/cm² and time duration of 20 s per point. The laser was applied at the distance of 6 mm from the oral mucosa and the treatment was repeated daily until the pain, being the main symptom, disappeared. The immediate analgesic effect in oral lesions (70% after the first laser therapy session) and accelerated oral wound healing were evident; thus, the authors suggested LLLT as a promising supplementary treatment modality for patients with PV. On the other hand, Bhardway et al. [6] used only low-level CO₂ laser irradiation in the treatment of recalcitrant oral PV lesions (previously unsuccessfully treated with pulse therapy of methyl-prednisolone and cyclophosphamide for 6-8 months). The following laser parameters were used: wavelength 10 600 nm, continuous wave, output power of 1-1.5 W. The authors proved immediate analgesia, reduced discomfort with no recurrence of the lesions and improved wound healing within 1, 3 and 5 months of follow-up [6]. Similarly, Zand et al. reported immediate and significant analgesia following low-level CO₂ (10 600 nm, continuous wave) laser irradiation in the treatment of recalcitrant painful PV lesions [8]. Both studies employed CO₂ laser in a defocused mode to scan rapidly over oral PV lesions at the distance of 5-6 mm from oral lesions for about 5-10 s [6,8]. However, Zand et al. used a thick layer (3-4 mm) of transparent non-anesthetic gel with high water content to reduce the beam absorption by the tissue, thus significantly reducing the output power from 1 W to 2-5 mW [8].

Discussion

Pemphigus vulgaris is a painful, and, if neglected, a potentially life-threatening blistering disease. The therapy is mainly focused on increasing oral comfort (e.g. eating, swallowing, speaking, sleeping, wearing dental prostheses…) and reducing the duration and severity of symptomatic outbreaks, especially during the periods of quiescence and exacerbation (period of increased pain and sensitivity) of PV lesions. It is widely accepted that the first line therapy for oral PV are systemic corticosteroids. However, LLLT has been introduced as a new treatment option for patients with PV lesions unresponsive to conventional therapy. LLLT is a non-destructive, non-thermal and painless procedure with no thermal damage effects visible in the oral mucosa. It has biostimulatory effects on the surrounding tissues and cells during high-level laser irradiation, such as an increase of systemic microcirculation and tissue oxygenation, cell metabolism and/or tissue regeneration and potential tissue healing, without side effects [13, 14]. LLLT has also been proven to reduce the pain of various etiologies [15]. Even though several theories have been proposed to explain the positive effects of LLLT, the exact underlying mechanism by which LLLT helps healing of the tissue and alleviation of pain is still unknown. So far, in vitro and in vivo studies have demonstrated enhanced fibroblast, keratinocyte and endothelial cells metabolism, migration and proliferation [16, 17]. Furthermore, an increase in the activity of cytokines and growth factors as well as protein synthesis and secretion following LLLT irradiation has been proved [18]. In addition, LLLT is claimed to reduce the prostaglandin E₂ level and inhibit cyclooxygenase, bradykinin and substance P activity [19, 20].

So far, LLLT has been used effectively in the treatment of oral lichen planus, leukoplakia, aphthous ulcers, epidermolysis bullosa and even oral manifestations of HIV [21-24]. Therefore, it was reasonable to expect PV lesions would respond to LLLT in oral PV therapy. The present review was aimed at evaluating the available literature on the effects of LLLT in the treatment of PV and it has been concluded that LLLT is efficient in the treatment of recalcitrant oral PV lesions, either used alone [6, 8] or as an adjunct to conventional treatment modalities [7]. LLLT resulted in the immediate and significant analgesia with enhanced wound healing, decrease in patients’ discomfort and no recurrence of PV lesions during the observation period and follow-up (Table 2). However, the results of this study should be interpreted with caution and evaluated more thoroughly because the literature data published on this issue are rather scarce; furthermore, a different set of laser parameters was applied and the length of observation and follow-up period were not the same.

In order to determine the real efficacy of laser therapy (the optimal set of laser irradiation parameters and well-defined duration and thermal effect intervals), further carefully designed long-term clinical studies with a larger number of patients (possibly international) are necessary as well as prolonged follow-up period. It is suggested that further research should be performed with standardized outcome measures (such as patients’ subjective assessment) using different wavelengths and/or laser parameter combinations in order to determine the most efficient irradiation conditions for the best PV treatment outcome. Even though the advances in laser technology have improved the site-specific delivery of laser energy, there is enough space for further improvement of the oral application of lasers, designed for different spot sizes and in variety of shapes for better handling.

After prolonged history of oral lesions, 75%-80% of the patients with PV will experience initial lesions in the oral cavity [25, 26]. Since oral PV lesions can appear similarly to other mucocutaneous disease lesions present in oral mucosa, their diagnosis can be very difficult. Therefore, the definite diagnose of PV
is often made with a significant delay. Oral manifestations of PV may occur independently or precede cutaneous involvement by a year or more, suggesting that oral cavity can be considered a place for potential diagnosis of PV [27, 28]. Dentists are, therefore, in a unique position to recognize the oral signs and symptoms of PV in its initial stages, to establish an early definitive diagnosis and to initiate the therapy in order to prevent the serious disease progression and morbidity that may result from the disease [29]. They can put PV disease under control and ensure patients’ comfort by maintaining oral hygiene and providing prosthetic rehabilitation if necessary [30].

Apart from dentists, management of these patients requires multidisciplinary approach of other physicians (e.g. dermatologist, gastroenterologist, family physician and nurses) in order to establish an appropriate diagnostic and therapeutic plan.

Table 2. Effects on laser therapy in treatment of pemphigus vulgaris

<table>
<thead>
<tr>
<th>Author and the year of the publication (reference)/Autor i godina publikacije (referenca)</th>
<th>Laser device</th>
<th>Laser application</th>
<th>Laser output power</th>
<th>Main outcome measures</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhardwaj A. et al (6)</td>
<td>CO2 laser (10 600 nm)</td>
<td>Laser only</td>
<td>100 mW</td>
<td>Symptoms: pain, discomfort</td>
<td>Immediate analgesia Trenutna analgezija</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Simptom: bol, nelagodnost Sign: enhanced healing</td>
<td>Less patients’ discomfort Smanjena nelagodnost</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Znak: ubrzano zastanjenje</td>
<td>Accelerated oral wound healing Ubrzano zastanje rana u ustima</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recurrence of the lesions/Ponovno javljanje lezija</td>
<td>No recurrence of lesions Nema ponovnog javljanja lezija</td>
</tr>
<tr>
<td>Minicucci EM. et al (7)</td>
<td>diode laser (660 nm)</td>
<td>Laser+systemic corticosteroids</td>
<td>1-1.5 W</td>
<td>Symptom: pain</td>
<td>Immediate analgesia Trenutna analgezija</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Laser+sistemski kortikosteroidi</td>
<td></td>
<td>Simptom: bol Sign: enhanced healing/Znak: ubrzano zastanjenje</td>
<td>Accelerated oral wound healing Ubrzano zastanje rana u ustima</td>
</tr>
<tr>
<td>Zand N. et al (8)</td>
<td>CO2 laser (10 600 nm)</td>
<td>Laser only</td>
<td>1 W</td>
<td>Symptom: pain</td>
<td>Immediate and significant analgesia Trenutna i značajna analgezija</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Simptom: bol</td>
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</tr>
</tbody>
</table>

Conclusion

Available literature suggests that low-level laser therapy can be used efficiently in the treatment of oral pemphigus vulgaris either independently or as an adjunct to the conventional therapy approaches. Since there have been no solid evidence-based proofs so far which would undoubtedly corroborate the effectiveness of low-level laser therapy in the treatment of oral pemphigus vulgaris, it is rather difficult to recommend the low-level laser therapy in this conclusion as superior to other available therapy options. Therefore, further long-term randomized controlled clinical studies are necessary to give a solid recommendation on the use of low-level laser therapy in the treatment of pemphigus vulgaris.

References


