Desquamative gingivitis: a systematic review of possible treatments.

Desquamative gingivitis: a systematic review of possible treatments.

Marco Cabras, Alessio Gambino, Roberto Broccoletti, Paolo G. Arduino.

Department of Surgical Sciences, Oral Medicine Section, CIR-Dental School, University of Turin, Turin, Italy

Short title: a systematic review on DG**.**

Computer system: Mac OS X, Version 10.13.2; Word-processor: Microsoft Word for Mac, Version 16.9.1

Corresponding author:

Dr. Marco Cabras

Department of Surgical Sciences; CIR - Dental School.

School of Medicine, University of Turin.

Oral Medicine Unit, Via Nizza 230, I-10126 Turin (Italy).

Telephone: + 390116631522; Fax: +39011618639.

E-mail: cabrasmarco300@gmail.com

Abstract

The occurrence of epithelial desquamation, erythema, and erosions on the gingival tissue could be described in literature as “desquamative gingivitis” (DG), mostly due to a wide range of autoimmune/dermatological disorders. The objective of this systematic review was to assess the efficiency of the different treatments for DG.

The research was conducted on the following databases: PubMed, Google Scholar, NIH (National Institute of Health), Up to Date, Scopus, Cochrane Library, Web of Science. The P.I.C.O. question was as follows: human patients with clinical-pathological diagnosis of DG (Patients); any topic, systemic medication, photobiomodulation or periodontal treatments (Intervention); no treatment, placebo or other drug (Comparison); and effectiveness in terms of improvement of symptoms (primary Outcome) and signs (secondary Outcome). The PROSPERO record is number CRD42018084531.

A total of 2174 potential results were acquired from the various databases, of which 998 were duplicates; the remaining 1176 studies were submitted to a first reading of title and abstract: 1137 articles had to be excluded, with 994 being not inherent to the purposes of this review, and 143 being published in languages other than English. The remaining 39 articles were subjected to full reading; 4 Randomized Controlled Trials were considered eligible but only 2 finally analysed.

To date, 0.05% clobetasol propionate ointment compared with placebo, in the management of signs and symptoms of DG, showed no statistically significant differences. Differently, a structured plaque control appeared to be successful in reducing plaque and improving signs and related pain, with statistically significant differences regarding related symptoms, plaque index and mucosal disease score.

Clinical relevance Based on our results, it is actually not possible to draw certain and positive conclusions as to the best management modalities for DG. Future research should be conducted in order to establish a proper therapy for this condition, primarily considering that it is mainly a characteristic clinical representation of dissimilar autoimmune bullous diseases. A promising field could be that of periodontal therapy but more data are however needed.

Key words: systematic review; desquamative gingivitis; gingival pain; therapy; outcome.

To the Editor,

Desquamative gingivitis (DG) is a characteristic clinical representation of many autoimmune diseases, such as oral lichen planus (OLP), mucous membrane pemphigoid (MMP), pemphigus vulgaris (PV), bullous pemphigoid, erythema multiforme, linear IgA disease, systemic lupus erythematosus, epidermolysis bullosa, and dermatitis herpetiformis. It can also arise as consequence of hypersensitivity reaction to some antigens contained in toothpastes, mouthrinses, chewing gum or foods, and less frequently in patients with plasma cell gingivitis, chronic ulcerative stomatitis and orofacial granulomatosis (1, 2).

DG usually presents with erythema, shedding and ulceration of both free and attached gingiva (mainly vestibular), and, differently from plaque-induced inflammation, it could extend beyond the marginal border, involving the full width of the gums and often the alveolar mucosa (3, 4).

To date, there are no generally established guidelines for the treatment of DG (1-4). Treatment should be undertaken with the goal of achieving control of symptoms with minimum side effects (1). In the last decade some evidence suggested that DG could play a role in increasing the long-term risk for periodontal tissue breakdown (5), detailing moreover that an inappropriate home oral hygiene could worsen the gingival status in DG patients, if compared to controls (6). For these reasons, some Authors have decided to start periodontal therapies for patients with DG (7).

Consequently, with such dissimilar conclusions at hand, we sought to systematically review therapies for DG to incorporate research in order to provide a base for the elaboration of more consistent and effective management approaches.

MATERIALS AND METHODS

From December 2016 to December 2017, two researchers (MC and PGA) carried out research on the treatment of DG.

The P.I.C.O. (Patient, Intervention, Control, Outcome) question [based on the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA)] for this investigation was: “In populations with DG, which intervention is effective in improving pain and/or relieving related symptoms compared to other intervention or placebo?”

The P.I.C.O. question was then developed as follows: human patients with clinical diagnosis of DG (Patients) related to any possible cause; any topic, systemic medication, photobiomodulation or periodontal treatments (Intervention); no treatment, placebo or other drug (Comparison); and effectiveness in terms of improvement of symptoms (primary Outcome) and clinical signs (secondary Outcome).

Inclusion criteria were: randomized and controlled clinical trials conducted on human beings affected by DG, treated by dentist / odontostomatologist, in the presence of a comparison group, under placebo or proper medications.

Exclusion criteria were: case reports, case series, reviews, open clinical trials, prospective or retrospective studies, letters to editors concerning DG therapy, as well as studies published in non-English language, and "non-inherent" studies, defined as such when:

- Not performed on humans;
- DG was not mentioned in any way;
- DG was simply cited as one of the many clinical manifestations observed in patients, without further specification;

- DG was documented and treated together with other atrophic-erosive oral lesions, without offering any distinctive data on the efficacy and/or tolerability of a given therapeutic protocol in the management of DG alone.

The PROSPERO record is number CRD42018084531.

Search Strategy

The research was conducted on the following databases: PubMed, Google Scholar, NIH (National Institute of Health), Up to Date, Scopus, Cochrane Library, Web of Science. Initially, there were no restrictions regarding the language, with not-in-English studies excluded in the first phase of study selection.

Conversely, no restriction regarding the publishing year was applied whatsoever.

Study selection and data extraction

References were exported into the EndNote® program (Thomson Reuters). Two reviewers (PGA and MC), independently from one another, proceeded to classify the various results. Any disagreements were resolved by consulting other reviewers (RB and AG) until a consensus was reached.

After excluding not-inherent and not-in-English studies, based on the reading of titles and abstracts, full text of the remaining articles was acquired and read; later, their classification was carried out, based on the eligibility criteria mentioned above.

Quality assessment

The reviewers (PGA and MC) proceeded to assess the quality of the studies included through the PEDro scale, applied in previous systematic reviews, up to the current year.

This scale considers the following parameters: random allocation, concealed allocation, similarity between the groups at baseline, subject, therapist and assessors blinding, less than 15% dropouts, intention-to-treat analysis, statistical comparisons between the groups, point measures and variability data.

According to this scale, controlled clinical trial can be considered of good quality if PEDro score is ≥6 with a maximum score of 10.

Data synthesis

Through the compilation of the Excel sheet, information was extracted from each of the selected studies regarding study design, main characteristics of the selected sample (country of origin, size, distribution by gender and age), type of therapeutic protocol, duration of the intervention and results.

In the light of the limited number of RCTs and the high degree of diversification regarding both methods and therapies, a meta-analysis could not be performed: therefore, a narrative description of the results has been presented in this current review.

RESULTS

A total of 2174 potential results were acquired from the various databases, of which 998 were duplicates.

The remaining 1176 studies were submitted to a first reading of title and abstract: 1137 articles had to be excluded, with 994 being not inherent to the purposes of this review, and 143 being published in languages other than English.

The remaining 39 articles were subjected to full reading: 2 Randomized Controlled Trials were considered eligible for this review (12, 16).

On the other hand, 11 case reports, 7 case-series, 6 pilot studies, 5 reviews, 4 open clinical trials, 2 not-inherent RCT, 1 retrospective study and 1 letter to Publisher were also excluded (Figure 1).

Table I summarizes the main characteristics of the two included trials.

Quality assessment

The quality assessment using the PEDro scale revealed values ranging from 6 to 10 with the scale ranging from 0 to 10. The grade 6 of the study conducted by Stone and co-workers was due to the absence of a blinding approach (Table II).

General characteristics of the sample

The size of the trial samples varies from 22 to 82, with an age-range between 25 and 78 years, and an approximate female to male ratio of 6:1.

In 2009, Motta and co-workers (16) carried out an 8-week double-blind, crossover, placebo-controlled clinical trial in 22 Brazilian patients, divided in two groups in order to compare the efficacy of 0.05% clobetasol propionate ointment with placebo (hydroxyethyl cellulose) in the management of signs and symptoms of DG, showing no statistically significant differences ($p>0.05$). Group 1 was a sample of five PV female patients, treated systemically with prednisone and/or azathioprine in the previous six months, whereas group 2 consisted of nine patients with OLP, five with MMP and three with PV, thus consisting of a total of 17 patients.

Later, in 2015, Stone and co-workers (12) conducted a 20-week randomized controlled trial on 82 British patients affected by OLP-related DG, in order to determine the clinical efficacy of structured plaque control, provided to 43 patients, through the addition of a powered toothbrush and inter-dental cleaning aids TePe®

extra soft inter-dental brushes (TePe Munhygienprodukter, Malmo, Sweden) ranging from ISO size 1–6 or Oral-B dental floss (Procter & Gamble, Weybridge, UK). Such addition, when compared to the normal plaque control regimen maintained by the 39 control cases, appeared to be successful in reducing plaque and improving signs and symptoms of DG, with statistically significant differences regarding related symptoms, plaque index and mucosal disease score.

DISCUSSION

The aim of this systematic review was to investigate the current state of the art regarding the therapy of DG. Based on these current results, it is actually not possible to draw certain and encouraging conclusions as to the best management modalities.

Corrocher and co-workers' RCT (8) was excluded due to the questionable eligibility criteria provided as well as Stone and co-workers' RCT (9), due to the incompatibility of its outcomes with the P.I.C.O. question of the present review.

On the other hand, the double-blind, crossover, placebo-controlled trial published by Motta and co-workers (10), assessing the efficacy of topical clobetasol propionate on DG patients, met our criteria of inclusion, showing a slight, not-significant improvement of clinical signs and symptoms between topical steroid and placebo. On the other hand, Stone and co-workers (11) reported a statistically significant improvement through a structured plaque control both in plaque control and oro-mucosal disease ($p<0.001$ for Plaque Index and Escudier index), with no statistically significant changes regarding perception of pain ($p>0.05$ for OHIP and VAS).

The present systematic review reveals a substantial lack in current understanding of the pathogenesis and risk factors of DG. Hence, further clinical trials in large samples of patients are required to establish at first if clobetasol propionate is just as unreliable as showed by Motta et al. not only on patients with OLP-related DG, but also PV/PMM-related DG, where DG tends to persist, despite the healing of the cutaneous and oral signs.

On the other hand, to assess the role of periodontal therapy in the management of DG, although our group provided evidence of microbiologic alterations in subgingival plaque between autoimmune and plaque-induced gingivitis (12), further and wider randomized prospective studies are needed to investigate this fascinating association.

Compliance with Ethical Standards

Conflict of Interest: All authors declare: no support from any organisation for he submitted work; no financial relationships with any organisations that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Funding: The work was supported by the Department of Surgical Sciences, School of Medicine, University of Turin, Turin, Italy.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent: For this type of study, formal consent is not required.

Author contribution: Authors were all involved in the design of the study. Marco Cabras, Alessio Gambino and Paolo G. Arduino conducted the database searches and drafted the paper. Marco Cabras and Paolo G. Arduino analysed the data. All of the authors were involved in making editing the paper.

References

1. Arduino PG. Oral complications of dermatologic disorders. Atlas Oral Maxillofac Surg Clin North Am 2017; 25:221-8.
2. Mustafa MB, Porter SR, Smoller BR, Sitaru C. Oral mucosa manifestations of autoimmune skin diseases. Autoimmunity Rev 2015; 14: 930–51.
3. Lo Russo L, Fedele S, Guiglia R, et al. Diagnostic pathways and clinical significance of desquamative gingivitis. J Periodontol 2008; 79:4-24.
4. Arduino PG, Broccoletti R, Sciannameo V, Scully C. A practical clinical recording system for cases of desquamative gingivitis. Br J Dermatol 2017; 177:299-301.
5. Lo Russo L, Guiglia R, Pizzo G, et al. Effect of desquamative gingivitis on periodontal status: a pilot study. Oral Dis 2010; 16:102-7.
6. Lo Russo L, Gallo C, Pellegrino G, et al. Periodontal clinical and microbiological data in desquamative gingivitis patients. Clin Oral Investig 2014; 18:917-25.
7. Guiglia R, Di Liberto C, Pizzo G, et al. A combined treatment regimen for desquamative gingivitis in patients with oral lichen planus. J Oral Pathol Med 2007; 36:110-6.
8. Corrocher G, Di Lorenzo G, Mansueto P, et al. Comparison of topical tacrolimus 0.1 % in pectin ointment with clobetasol 0.5% ointment in adults with moderate to severe desquamative gingivitis: A 4-week, randomized, double-blind clinical trial. Clin Ther 2006; 28:1296-302.
9. Stone SJ, McCracken GI, Heasman PA, Staines KS, Pennington M. Cost-effectiveness of personalized plaque control for managing the gingival

manifestations of oral lichen planus: a randomized controlled study. J Clin Periodontol 2013; 40:859-67.

10. Motta AC, Domaneschi C, Komesu MC, Souza Cda S, Aoki V, Migliari DA. Double-blind, crossover, placebo-controlled clinical trial with clobetasol propionate in desquamative gingivitis. Braz Dent J 2009; 20:231-6.
11. Stone SJ, Heasman PA, Staines KS, McCracken GI. The impact of structured plaque control for patients with gingival manifestations of oral lichen planus: a randomized controlled study. J Clin Periodontol 2015; 42:356-62.
12. Arduino PG, Romano F, Sasia D, et al. Subgingival microbiota in white patients with desquamative gingivitis: a cross-sectional study. J Periodontol 2017; 88:643-50.

Table I. Characteristics of RCT examining treatment on patients with Desquamative Gingivitis

Authors, year	Country	Oral disease	Sample	Groups under comparison	Duration	Drug/dose
Motta *et al.* 2009	Brazil	PV, MMP, OLP	22 (17 F)	5 vs 17	8 wks	0,05% propionate clobetasol ointment Vs hydroxylhetyl cellulose
Stone *et al.* 2015	UK	OLP	82 data from 79 patients	39 vs 43	20 wks	Powered toothbrush/interdental cleaning aids Vs normal plaque control

Table II. Quality assessment PEDro scale

Authors, year	1	2	3	4	5	6	7	8	9	10	11	Total
Motta *et al.* 2009	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9 of 10
Stone *et al.* 2015	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6 of 10

FIGURE 1. Flow-chart of systematic review synthesis