Effect of Oxygen Releasing Oral Gel Compared to Chlorhexidine Gel in the Treatment of Periodontitis

R. Niveda¹ and Gurumoorthy Kaarthikeyan¹

¹Department of Periodontics, Saveetha Dental College and Hospital, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India.

Authors’ contributions

This work was carried out in collaboration between both authors. Author RN carried out the study, participated in the sequence alignment, statistical analysis and drafted the manuscript. Author GK conceived the study, participated in its design and coordinated and provided guidance to draft the manuscript. Both authors read and approved the manuscript.

ABSTRACT

The aim of the current study is to compare the effect of oxygen releasing oral gel and chlorhexidine gel in the treatment of periodontitis and the objective was to assess and compare the changes in clinical parameters such as Probing pocket depth, Bleeding on probing, Clinical attachment levels between oxygen releasing oral gel and chlorhexidine gel.

The current pilot study which compares oxygen releasing gel with chlorhexidine gel is a randomised split mouth clinical trial. All the patients included in the study were patients with moderate to severe periodontitis with no systemic diseases, not under any medication non smoking healthy patients. All the patients received supra and sub gingival scaling, pockets on molars with deeper probing depth on either maxillary or mandibular arch and the medication to be received by the patient were allotted randomly. Randomisation was performed using lot method. Oxygen releasing (Blue M gel) and chlorhexidine gel (Hexigel) was applied at the chosen site, patient was recalled for re application and was reassessed for clinical parameters Paired t test was done to compare the mean difference in probing depth in Blue M gel group and Hexigel group.

The mean probing depth at the day of drug delivery was for Blue M gel group was 7.2 mm SD+/-

*Corresponding author: E-mail: Kaarthikeyan@saveetha.com;
1. INTRODUCTION

It has been known that periodontal disease is induced by bacteria in biofilm. Specific microorganisms may be responsible for more aggressive forms of the disease. It is a chronic inflammatory disease caused by Gram negative anaerobic bacteria that have colonised the subgingival area. Despite the host’s protective mechanisms these microorganisms are responsible for the connective tissue breakdown and alveolar bone loss and tooth loss which are the basic characteristics of this disease [1]. Within the affected sulcus or periodontal pocket, the resident anaerobic bacteria interact with the host inflammatory reactions leading to a lower oxygen or hypoxic environment [2].

Keywords: Periodontitis; inflammation; oxygen therapy; topical oxygen; chlorhexidine.

Oxygen is an essential molecule for survival. Tissues depend on oxygen for electron transport, oxidative phosphorylation, and energy generation. Variations in tissue oxygen needs are attributed to a number of physiological or pathological states [3]. Cellular hypoxia, or lower concentration of oxygen in cells, could induce significant changes, they could be immediate or delayed responses and affect cell growth, cell proliferation and survival, they also affect pH regulation, metabolism, and angiogenesis [4–8]. Under a chronic inflammatory state, hypoxia induces protective cellular responses or a local defence. If the cause of inflammation cannot be eradicated, such hypoxic reactions can be the pathophysiology of inflammation leads to disease progression and pathogenesis of the disease [9]. Certain periodontopathogens like P. gingivalis under hypoxia increases oxidative stress in periodontal ligament fibroblasts and induces a collapse of the protective mechanisms causing the increase in reactive oxygen species (ROS) and the progression of inflammatory oral diseases [10].

It has been observed that oxygen is an important substrate during tissue healing. Oxygen is involved in multiple wound healing processes including oxidative killing of bacteria, reepithelialization, angiogenesis, and collagen synthesis [11]. Oxygen has been explored as a therapeutic modality to aid wound healing in either of topical or hyperbaric from to induce healing. The Potential benefits of oxygen on wound healing are as follows: Prevention of infection, increased reepithelialization, Collagen synthesis by induction of fibroblast growth, and angiogenesis [12]. Oxygen can be therapeutically administered by various methods. The widely known method of hyperbaric oxygen therapy has been associated with mutations in human blood DNA, apoptosis and arrested cell growth in fibroblasts, and hematopoietic cells and can be toxic [13].

Topical oxygen therapy, potentially less toxic topical oxygen is also much more convenient in that it can be done at home, is less expensive, and has fewer or no complications [14]. Considering all the above factors that oxygen could play a role in reducing the severity of chronic inflammatory condition like periodontitis and since previously we have worked on plenty of topics in periodontology [15–27]. The current study was done to compare and assess the effect of oxygen delivering agents in further research of topics in periodontology [15–27]. The current study was done to compare and assess the effect of oxygen delivering agents in further research of topics in periodontology.

2. MATERIALS AND METHODS

The participants of the study were selected from the outpatient department of periodontics, Saveetha Dental College and Hospitals.
Chennai, India. A randomized split mouth study was performed. 10 patients who were suffering from moderate to severe periodontitis were recruited for the study, of which 6 were males and 4 were females aged between 23-53 years.

The inclusion criteria was patients with generalised bleeding on probing and periodontal pocket over 5 mm and with no systemic diseases, not under medication non smoking healthy patients.

The exclusion criteria was patients with systemic diseases, patients under antibiotic and anti inflammatory medication, patients with habits like smoking and lactating mothers. At the first visit all the patients received a thorough scaling for 30-45 minutes, oral hygiene instructions were given using models and audiovisual aids. Patients were recalled after two weeks, in the recall visit oral hygiene maintenance was evaluated and the clinical parameters like probing depth, clinical attachment level and bleeding on probing were recorded as baseline values followed by thorough subgingival scaling and root planing under local anaesthesia and oral hygiene maintenance was reinforced. Patients were recalled after a week and clinical parameters were recorded. Single and same operator performed all the measurements at all the visits. The patients are blinded the patients were not aware of the treatment site. The oxygen releasing Blue M gel (Group A) was compared to chlorhexidine gel (Group B). Randomisation was performed using the lot method, the patient was asked to pick up a slip wherein the name of the drug to be given and the site of application has been enclosed in an envelope. Hexigel and Blue M gel were applied to either side of the bilateral deep pockets present in either of the maxillary or mandibular arch and the patient was recalled after two days and after a week for re-application of gels in the region of deep pocket oral hygiene maintenance was reinforced at all the visits, all the patients were recalled after 6 weeks and the clinical parameters were recorded. Sites with deep pockets after the first visit one from each arch either maxilla or mandibular arch one from each quadrant was assessed for the study.

Modified sulcular bleeding index by mombelli with scores 0,1,2,3 using periodontal probe to assess bleeding on probing. And clinical attachment levels was assessed using periodontal probe with fixed point on the teeth (CEJ).

3. RESULTS AND DISCUSSION
A total of 10 patients were involved in the study, 20 sites were assessed for evaluation of which 10 sites were treated with Blue M gel and the other 10 sites were treated with Hexigel. The overall baseline mean probing depth and bleeding on probing were assessed for both the groups. The overall mean probing depth was 5.8 mm SD+/− 0.4 mm, and overall mean for bleeding on probing was 0.7 SD+/− 0.3. The probing depth was measured at the site of drug delivery and the value was recorded at the baseline visit on the day of drug delivery, the probing depth was again measured during the reassessment and the measurement was recorded (Figs. 1 and 2).

Shapiro-wilk test was conducted to determine the normalcy of distribution between baseline probing depth and probing depth value after 6 weeks for both group A and B where the results obtained was non significant hence a parametric test was done to assess the difference in mean values. Paired t test with 95% confidence interval was done to compare the mean difference in probing depth in Blue M gel group and Hexigel group.

Intra group paired t test analysis was done between baseline and three weeks, three weeks and six weeks and between baseline and six weeks in both group A and group B.

The mean and standard deviation and P Value was analysed for clinical parameters like probing depth, clinical attachment level and bleeding on probing. The mean difference between baseline to 3 and 6 weeks for probing depth (Table 1), bleeding on probing (Table 3), clinical attachment level (Table 3) showed a statistically significant p value.

An inter group comparison of mean and standard deviation was calculated for probing depth, clinical attachment levels and bleeding on probing.

The mean probing depth at the day of drug delivery was for Blue M gel group was 7.2 mm SD+/− 0.42 mm and the mean probing depth six week after drug delivery was 4.7 SD+/− 0.57 mm. The mean probing depth at the day of drug delivery was for Hexigel gel group was 7.0 mm SD+/− 0.57 mm and the mean probing depth six week after drug delivery was 5.7 SD+/− 0.64 mm (Table 4).
The mean clinical attachment levels at the day of drug delivery was for Blue M gel group was 4.70 mm SD +/- 0.43 mm and the mean clinical attachment levels six week after drug delivery was 2.50 SD +/- 0.52 mm. The mean clinical attachment levels at the day of drug delivery was for Hexigel gel group was 4.72 mm SD +/- 0.45 mm and the mean clinical attachment levels six week after drug delivery was 2.80 mm SD +/- 0.78 mm (Table 5).

The mean bleeding on probing levels at the day of drug delivery was for Blue M gel group was 2.30 mm SD +/- 0.48 mm and the mean bleeding on probing levels six week after drug delivery was 0.70 mm SD +/- 0.48 mm. The mean bleeding on probing levels at the day of drug delivery was for Hexigel gel group was 2.60 mm SD +/- 0.51 mm and the mean bleeding on probing levels six week after drug delivery was 1.40 mm SD +/- 0.51 mm (Table 6).

From the results it is seen that there is a significant difference in reduction in probing pocket depth. The mean difference between the probing depth reduction in group A (Blue M) from baseline to 6 week was 2.3 and The mean difference probing depth reduction in group B (Hexigel) from baseline to 6 week was 1.5. Group A showed better potential in probing depth reduction.

It has been suggested that the oxygen delivering gel commercially available as Blue M gel is used in various dental fields like implantology, Periodontology etc but there are very few clinical trials comparing the efficacy of topical oxygen therapy and conventional topical drug therapy. In this study we have found that the oxygen delivering gel showed increased probing depth reduction when compared to chlorhexidine gel. Most of the studies in this area is primarily based on studies conducted in animals and limited studies in human beings [28]. But it has been consistently implied that a sufficient oxygen supply to tissue is critical to the healing process and the avoidance of wound infection. In previous studies where the patients with acute necrotising ulcerative periodontitis were treated with antibiotics alone and antibiotics and adjunctive topical oxygen. It was found that in groups with adjunctive oxygen therapy, all patients showed a reduction of the microorganisms, resulting in more rapid improvements in clinical parameters with less periodontal destruction [29].

Various studies have proven the effect of chlorhexidine in tissues where they have indicated that more pain and swelling were recorded on the side treated with placebo gel, and more patients indicated that they preferred the chlorhexidine gel which indicates that healing was better with chlorhexidine gel [30]. Systematic review on chlorhexidine gels indicate that they have similar effects as any other forms of chlorhexidine and are mainly used in prevention and in healing process [31]. To substantiate the results of the current study, in an in vitro study it was found that higher concentrations of blue M gel presented with inhibitory halo similar to chlorhexidine digluconate [32], however the clinical trials are essential for utilisation.

This pilot study was undertaken to address the effectiveness of topical oxygen delivering agents in the form of gel which is less explored clinically and it was compared with Chlorhexidine gel whose efficiency was widely explored, it has been observed that both the groups showed significant reduction in probing depth.

Table 1. The mean difference in probing depth between baseline and 3 weeks was 0.6 with a p value of 0.001, and mean difference between 3 weeks and 6 weeks was 1.7 with a p value of 0.0001 and baseline and 6 weeks was 2.3 with a p value of 0.0001 in group A

| Group | Probing depth | Group B | Probing depth |
|-------|---------------|---------|---------------|
|       | Mean and standard deviation | P Value | Mean and standard deviation | P Value |
| Baseline and 3 weeks | 0.6 +/-0.516 | 0.005 | 0.7 +/-0.483 | 0.001 |
| 3 weeks and 6 weeks | 1.7 +/-0.483 | 0.0001 | 0.8 +/-0.422 | 0.0001 |
| Baseline and 6 weeks | 2.3 +/-0.482 | 0.0001 | 1.5 +/-0.527 | 0.0001 |

The mean difference in probing depth between baseline and 3 weeks was 0.7 with a p value of 0.001, and mean difference between 3 weeks and 6 weeks was 0.8 with a p value of 0.0001 and baseline and 6 weeks was 1.5 with a p value of 0.0001 in group B.
Fig. 1. The graph represents the changes in probing depth at the baseline, at 3 weeks and at 6 weeks, Blue M gel application was done at the third week.

Fig. 2. The graph represents the changes in probing depth at the baseline, at 3 weeks and at 6 weeks, Hexigel application was done at the third week.

Table 2. The mean difference in bleeding on probing between baseline and 3 weeks was 1.1 with a p value of 0.0001, and mean difference between 3 weeks and 6 weeks was 0.5 with a p value of 0.015 and baseline and 6 weeks was 1.6 with a p value of 0.0001 in group A.

| Group   | Bleeding on probing |            |            |            |            |
|---------|---------------------|------------|------------|------------|------------|
|         | Mean and standard deviation | P Value | Mean and standard deviation | P Value |
| Group a | Baseline and 3 weeks | 1.1 +/-0.568 | 0.0001      | 0.7 +/-0.483 | 0.001      |
|         | 3 weeks and 6 weeks  | 0.5 +/-0.527 | 0.015      | 0.5 +/-0.527 | 0.015      |
|         | Baseline and 6 weeks | 1.6 +/-0.516 | 0.0001      | 1.2 +/-0.422 | 0.0001     |

The mean difference in bleeding on probing between baseline and 3 weeks was 0.7 with a p value of 0.001, and mean difference between 3 weeks and 6 weeks was 0.5 with a p value of 0.015 and baseline and 6 weeks was 1.2 with a p value of 0.0001 in group B.
Table 3. The mean difference in clinical attachment level between baseline and 3 weeks was 1.1 with a p value of 0.001, and mean difference between 3 weeks and 6 weeks was 0.8 with a p value of 0.011 and baseline and 6 weeks was 1.9 with a p value of 0.0001 in group A

| Group       | Clinical attachment level | Clinical attachment level |
|-------------|--------------------------|--------------------------|
|             | Mean and standard deviation | P Value | Mean and standard deviation | P Value |
| Baseline and 3 weeks | 1.1 +/-0.738 | 0.001 | 1.4 +/-0.699 | 0.0001 |
| 3 weeks and 6 weeks | 0.8 +/-0.789 | 0.011 | 0.8 +/-0.789 | 0.011 |
| Baseline and 6 weeks | 1.9 +/-0.876 | 0.0001 | 2.2 +/-0.789 | 0.0001 |

The mean difference in clinical attachment level between baseline and 3 weeks was 1.4 with a p value of 0.011, and mean difference between 3 weeks and 6 weeks was 0.8 with a p value of 0.011 and baseline and 6 weeks was 2.2 with a p value of 0.0001 in group B

Table 4. Inter group differences in probing depth between group A and group B

| Group       | Probing depth | Probing depth |
|-------------|---------------|---------------|
|             | Mean and standard deviation | Mean and standard deviation |
| Baseline    | 7.2 +/-0.42 | 7.0 +/-0.57 |
| 3 weeks     | 6.5 +/-0.40 | 6.4 +/-0.58 |
| 6 weeks     | 4.7 +/-0.57 | 5.7 +/-0.64 |

Table 5. Inter group differences in clinical attachment levels between group A and group B

| Group       | Clinical attachment levels | Clinical attachment levels |
|-------------|---------------------------|---------------------------|
|             | Mean and standard deviation | Mean and standard deviation |
| Baseline    | 4.70 +/-0.43 | 4.72 +/-0.45 |
| 3 weeks     | 3.30 +/-0.69 | 3.60 +/-0.48 |
| 6 weeks     | 2.50 +/-0.52 | 2.80 +/-0.78 |

Table 6. Inter group differences in bleeding on probing between group A and group B

| Group       | bleeding on probing | bleeding on probing |
|-------------|---------------------|---------------------|
|             | Mean and standard deviation | Mean and standard deviation |
| Baseline    | 2.30 +/-0.48 | 2.60 +/-0.51 |
| 3 weeks     | 1.20 +/-0.42 | 1.90 +/-0.31 |
| 6 weeks     | 0.70 +/-0.48 | 1.4 +/-0.51 |

4. CONCLUSION

Within the limitations of the study from the results it is seen that there is a significant difference in reduction in probing pocket depth. The mean difference between the probing depth reduction in group A (Blue M ) from baseline to 6 week was 2.3 and The mean difference probing depth reduction in group B (Hexigel ) from baseline to 6 week was 1.5. Group A showed better potential in probing depth reduction. It emphasises the fact that thorough sub gingival scaling and root planing along with adjuvant topical oxygen therapy aid in reducing the periodontal pockets further research has to be done to assess the effect of oxygen delivering agents in future.

DISCLAIMER

The products used for this research are commonly and predominantly used products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

The study was conducted after obtaining approval by the Institutional Ethical and Review
Board, Savetha Dental College and Hospitals, Chennai. All the procedures were done after obtaining consent from the patients.

**COMPETING INTERESTS**

Authors have declared that no competing interests exist.

**REFERENCES**

1. Genco RJ. Current view of risk factors for periodontal diseases. J Periodontol. 1996;67(Suppl 10S):1041–1049.
2. Wang XX, Chen Y, Leung WK. Role of the Hypoxia-Inducible Factor in Periodontal Inflammation. Hypoxia and Human Diseases. 2017:285.
3. Piruat JI, López-Barneo J. Oxygen tension regulates mitochondrial DNA-encoded complex I gene expression. Journal of Biological Chemistry. 2005;280:42676–42684.
4. Semba H, Takeda N, Isagawa T, et al. HIF-1α-PDK1 axis-induced active glycolysis plays an essential role in macrophage migratory capacity. Nat Commun. 2016;7:11635.
5. Wu D, Chen B, Cui F, et al. Hypoxia-induced microRNA-301b regulates apoptosis by targeting Bim in lung cancer. Cell Proliferation. 2016;49:476–483.
6. Li X, Liu Y, Ma H, et al. Enhancement of glucose metabolism via PGC-1α participates in the cardioprotection of chronic intermittent hypobaria hypoxia. Frontiers in Physiology. 2016;7:Epub ahead of Print. DOI: 10.3389/fphys.2016.00219
7. Katayama K, Ishida K, Saito M, et al. Hypoxia attenuates cardiopulmonary reflex control of sympathetic nerve activity during mild dynamic leg exercise. Experimental Physiology. 2016;101:377–386.
8. Hyun S-W, Jung Y-S. Hypoxia induces FoxO3a-mediated dysfunction of blood–brain barrier. Biochemical and Biophysical Research Communications. 2014;450:1638–1642.
9. Semenza GL. Oxygen sensing, hypoxia-inducible factors, and disease pathophysiology. Annu Rev Pathol. 2014;9:47–71.
10. Götz L, Memmert S, Rath-Deschner B, et al. LPS from *P. gingivalis* and hypoxia increases oxidative stress in periodontal ligament fibroblasts and contributes to periodontitis. Mediators of Inflammation. 2014;2014:1–13.
11. Knighton D, Hunt T, Scheuenstuhl H, et al. Oxygen tension regulates the expression of angiogenesis factor by macrophages. Science. 1983;221:1283–1285.
12. Rodriguez PG, Felix FN, Woodley DT, et al. The role of oxygen in wound healing: A review of the literature. Dermatologic Surgery. 2008;34:1159–1169.
13. Conconi MT, Baiguera S, Guidolin D, et al. Effects of hyperbaric oxygen on proliferative and apoptotic activities and reactive oxygen species generation in mouse fibroblast 3T3/J2 cell line. Journal of Investigative Medicine. 2003;51:227–232.
14. Kalliainen LK, Gordillo GM, Schlanger R, et al. Topical oxygen as an adjunct to wound healing: A clinical case series. Pathophysiology. 2003;9:81–87.
15. Ezhlaras D, Apoorva VS, Ashok Vardhan N. *Syzygium cumini* extract induced reactive oxygen species-mediated apoptosis in human oral squamous carcinoma cells. J Oral Pathol Med. 2019;48:115–121.
16. Kaarthikeyan G, Jayakumar ND, Sivakumar D. Comparative evaluation of bone formation between PRF and blood clot alone as the sole sinus-filling material in maxillary sinus augmentation with the implant as a tent pole: A randomized split-mouth study. J Long Term Eff Med Implants. 2019;29:105–111.
17. Arjunkumar R. Nanomaterials for the management of periodontal diseases. In: Chaughule RS, (Ed.). Dental Applications of Nanotechnology. Cham; Springer International Publishing. 2018:203–215.
18. Ravi S, Malaiappan S, Varghese S, et al. Additive effect of plasma rich in growth factors with guided tissue regeneration in treatment of intrabony defects in patients with chronic periodontitis: A split-mouth randomized controlled clinical trial. J Periodontol. 2017;88:839–845.
19. Kavarthapu A, Malaiappan S. Comparative evaluation of demineralized bone matrix and type II collagen membrane versus eggshell powder as a graft material and membrane in rat model. Indian J Dent Res. 2019;30:877–880.
20. Murthykumar K, Arjunkumar R, Jayaseelan VP. Association of vitamin D receptor gene
polymorphism (rs10735810) and chronic periodontitis. J Investig Clin Dent. 2019;10:e12440.
21. Ramesh A, Vellayappan R, Ravi S, et al. Esthetic lip repositioning: A cosmetic approach for correction of gummy smile - A case series. J Indian Soc Periodontol. 2019;23:290–294.
22. Ramesh A, Varghese S, Jayakumar ND, et al. Comparative estimation of sulfiredoxin levels between chronic periodontitis and healthy patients - A case-control study. J Periodontol. 2018;89:1241–1248.
23. Kavarthapu A, Thamaraiselvan M. Assessing the variation in course and position of inferior alveolar nerve among south Indian population: A cone beam computed tomographic study. Indian J Dent Res. 2018;29:405–409.
24. Ramesh A, Ravi S, Kaarthikeyan G. Comprehensive rehabilitation using dental implants in generalized aggressive periodontitis. J Indian Soc Periodontol. 2017;21:160–163.
25. Jain M, Nazar N. Comparative evaluation of the efficacy of intraligamentary and supraperioosteal injections in the extraction of maxillary teeth: A randomized controlled clinical trial. J Contemp Dent Pract. 2018;19:1117–1121.
26. Vijayashree Priyadharsini J. In silico validation of the non-antibiotic drugs acetaminophen and ibuprofen as antibacterial agents against red complex pathogens. J Periodontol. 2019;90:1441–1448.
27. Ramamurthy J, Mg V. Comparison of effect of hiora mouthwash versus chlorhexidine mouthwash in gingivitis patients: A clinical Trial. Asian J Pharm Clin Res. 2018;11:84–88.
28. Fries RB, Wallace WA, Roy S, et al. Dermal excisional wound healing in pigs following treatment with topically applied pure oxygen. Mutation Research/ Fundamental and Molecular Mechanisms of Mutagenesis. 2005;579:172–181.
29. Gaggl AJ, Rainer H, Grund E, et al. Local oxygen therapy for treating acute necrotizing periodontal disease in smokers. J Periodontol. 2006;77:31–38.
30. Bakaen GS, Strahan JD. Effects of a 1% chlorhexidine gel during the healing phase after inverse bevel mucogingival flap surgery. Journal of Clinical Periodontology. 1980;7:20–25.
31. Fiorillo L. Chlorhexidine gel use in the oral district: A systematic review. Gels; 5. 2019; Epub ahead of print. DOI: 10.3390/gels5020031
32. Deliberador TM, Weiss SG, Rychuv F, et al. Comparative analysis in vitro of the application of blue®m oral gel versus chlorhexidine on Porphyromonas gingivalis: A pilot study. Advances in Microbiology. 2020;10:194–201.

© 2020 Niveda and Kaarthikeyan; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdtarticle4.com/review-history/59828