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Local Chlorhexidine Delivery for Periodontal Infection Therapy: A Short Review

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Abstract. Oral diseases affected more than half of the world’s population. Periodontitis is the second biggest threat to oral health after dental caries. Periodontitis is an inflammation inside periodontal pockets caused by pathogenic microbial colonies which lead to destruction of bone tissue and soft tissue. Chlorhexidine gluconate is an antimicrobial agent that effective to destroy pathogenic microbial and cure periodontitis. Chlorhexidine gluconate is given locally using a carrier material to the infected area. There are several materials that can be used to deliver Chlorhexidine gluconate to the infected periodontal tissue such as gel, liquid (mouthwash), and chip. This short review aims to describe the current methods to deliver Chlorhexidine gluconate to the infected periodontal tissue, including the advantages, disadvantages, and the future trend of the carrier materials used for periodontitis treatment. Future research about materials that can help to optimize tissue restorative after cure periodontitis would be beneficial.

Keywords: Carrier materials; Chlorhexidine; Local delivery; Periodontitis

1. Introduction

Periodontitis is an inflammation inside periodontal pockets caused by pathogenic microbial colonies which lead to destruction of bone tissue and soft tissue (Elsadek & Farahat 2022; Freire et al. 2020; Rizqillah 2022). Most bacteria that lived in human oral are categorized into Proteobacteria, Firmicutes, Actinobacteria, Bacteroidetes, Spirochaeter phyla, and Fusobacteria (Barzegar et al. 2022). Periodontitis classified into four stages (I-IV) (Tonetti, Greenwell & Kornman 2018) depend on destruction that occurs such as Bone Loss (BL), type of Bone Loss (Vertical and/or Horizontal), Probing-Pocket Depths (PPD), number of teeth lost due to periodontitis, and management complexity (Schwedicke et al. 2020). There are several periodontal diseases classification such as Abscesses of the periodontium, Gingivitis, Periodontitis, Aggressive Periodontitis, Chronic Periodontitis, Systemic Periodontitis and Necrotizing Periodontal Diseases (Highfield 2009). First stage before Periodontitis usually starts from gingivitis or soft tissue inflammation which if not treated in a timely manner can cause periodontitis and loss of connective tissue and alveolar bone resorption and lead to tooth loss (Aabed et al. 2022).

Chlorhexidine gluconate (CHX) is effective to destroy pathogenic microbial that cause periodontitis (Stähli et al 2021). CHX commonly used as adjunct with Scaling Root Planning (SRP) to help cure periodontitis. Using CHX with SRP resulting in less inflammation, improved tissue

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repair (Prietto et al. 2020), and reduction in pocket depth (Oh 2018). CHX can prevent the growth of bacteria (bacteriostatic), kill bacteria (bactericidal), and kill fungus (fungicidal) (Kotsailidi 2020). Positive charge from CHX will disrupt negative charge from cell membrane. Low CHX concentration will result in bacteriostatic effect, meanwhile high CHX concentration will result in bactericidal effect. This effect makes CHX is one of the commonly materials that used to cure periodontitis (Batool et al. 2019).

Local Drug Delivery is a method that deliver pharmacological compounds to local sites in a way that can safely achieve the desired therapeutic effect (Penmetsa et al. 2019; Fatriansyah, Rizqillah & Yandi). The carrier materials that commonly use to deliver CHX are in the form of gel, liquid, and chip. CHX in liquid form is usually as a mouthwash or mouth rinse. CHX delivered using a gel is usually injected into the periodontal pocket using a blunt needle syringe. CHX in the form of a chip is usually inserted into a periodontal pocket and allowed to dissolve while releasing CHX regularly. This short review aims to describe the current methods to deliver CHX to the infected periodontal tissue, including the advantages, disadvantages, and the future trend of the carrier materials used for periodontitis treatment (Ferreira-Fernandes et al. 2019; Amador-Medina et al. 2019; Agossa et al. 2020).

2. Methods

   Literature review method were used in this study. We use several search engines to collect information such as Google Search, Science Direct, PubMed, and Springer. Several keywords that we use while writing this short review are “Local Chlorhexidine Delivery for Periodontal Diseases”. Studies were included if the following conditions were met: using CHX as antibacterial; CHX used to reduce periodontal diseases; other papers that may be relevant to this study. Studies not reporting the relevant outcomes were excluded. This short review is based on 66 journals paper from 1998 to 2022.

3. Results and Discussion

3.1. Chlorhexadine

   Results CHX first developed in UK in 1940 as general disinfectant (Raszewski et al. 2019). CHX becomes antiplaque in 1970s (Reda et al. 2020), and mouthwash in 1976 (Deus & Ouanounou 2022). CHX is the most frequently used as skin disinfectant before regional anaesthesia (Rose et al. 2019). CHX is good for disinfectant both skin and mucous membrane (Kotsailidi 2020). CHX has anti-microbial properties, thus it is widely used for periodontal disease treatment (Bogdanovska et al. 2017).

   CHX has positive charge which creates a strong affinity to negative charge bacterial cell wall components that contains phosphates and sulphate groups (Szulc, Zakrzewska & Zborowski 2018). CHX then binds with the cell wall, affects the osmotic balance, and then leads to leakage of cytoplasm. If the concentration of CHX stabilizes or increases, it causes CHX enters the cell and rupture the cell wall. This rupture of the cell wall will lead to lysis and cell death (Bactericidal) (Deus & Ouanounou 2022).
FIGURE 1. The step of CHX kills the bacteria. (a) CHX with positive charge attracted with negative sites of the bacteria cell wall. (b) CHX binds with the cell wall and leads to leakage. (c) CHX enters the cell, ruptures its wall, and kills bacteria cell.

The use of CHX for up to 4 to 6 weeks prevents plaque formation and gingival inflammation (Dental Abstract, 2021a). Furthermore, CHX can also help reduce periodontal pocket and tissue attachment loss (Dental Abstract, 2021a). Liang described that the use of CHX in Perioperative oral care can help reduce incidence of Postoperative pneumonia (POP) in non-cardiac surgical (Liang et al. 2021). CHX can also used to medically compromised patients such as pregnancy (Silk et al. 2008), Type 2 Diabetes Mellistus (Shaheen et al. 2023), oral candidiasis (Manonmanipavithra, et al. 2020), HIV (Nittayananta, et al. 2008), and cancer (Cabrera-Jaime, et al. 2018).

Tooth staining is one of the side effects of the use of CHX in dental treatment (Badar et al. 2019). Other side effects may exist such as dry mouth (Pereira & Oliveira 2020), altered taste sensation (Tartaglia et al. 2019; Haydari et al. 2017), and discolored or coated tongue (Lakhani & Vandana 2016). Some patients also reported experiencing a burning sensation, swelling of the parotid gland, oral paraesthesia, and desquamation of the oral mucosa. Tooth staining also occurred when CHX mouth rinse used for a few weeks (Dental Abstract, 2021a). Build-up calculus (tartar), temporary damage to the lining of the mouth, temporary taste disturbance also reported to happen when using CHX (James et al. 2017). Using CHX to cure periodontitis must be precise and in a limited time because CHX is an antiseptic and antimicrobial agent. CHX should not be swallowed nor used in children under four years of age who have not acquired the necessary sputum mechanisms in case of swallowing or a false route (Kamdem et al. 2022).

Patients with delayed-type hypersensitivity to CHX may develop unpleasant reactions on mucosal exposure and be predisposed to develop Ig E-mediated (type 1) allergy; these patients should be advised to avoid CHX containing products (Rose et al. 2019). If CHX contact with people that have Ig E-mediated (type 1) allergy to CHX, it activates immune cells and release histamine into the tissue. This can result in a variety of symptoms including itching, hives (urticaria) and angioedema (swelling) (Pemberton & Gibson 2012). Chlorhexidine can also cause type 4 Hypersensitivity such as erythematous rash within 48 hours after treatment (Bhardwaj 2020).
3.2. **Liquid Delivery**

CHX can be delivered to the inflammation area using liquid such as mouthwash or mouth rinse. Mouth rinse CHX has widely used as anti-microbial not only by health care practitioners but also by public with or without oral disease (Brookes et al. 2021). There are mouth rinses containing 0.2% CHX and 0.12% CHX. Higher concentration CHX have a better plaque inhibiting effect (Haydari et al. 2017) while lower concentration CHX should decrease side effects (Najafi et al. 2012). There are no significant different in plaque prevention and controlling gingivitis between these two (Franco Neto et al. 2008). Mouth rinse is usually used twice a day for 30 seconds and limited for 2 to 4 weeks of usage (Dental Abstract, 2021a). CHX mouth rinses usually form in a base containing Purified water (Germiphene Corporation, 2015). Some CHX mouth rinse contain alcohol while other are alcohol free. CHX mouth rinse also contain PEG 40-sorbitan diisostearate as an emulsion. Other ingredients in CHX mouth rinse are glycerine as a humectant (Scodari & Chattman 1996), saccharin sodium, and FD&C Blue No. 1 as a coloring.

CHX mouth rinse is also reported to be used in patient upon gingival healing following scaling and root planning (SRP). Costa et al described the assignment of CHX upon SRP effectively reduced plaque build-up (de Costa et al. 2017) and lowered the risk of gingivitis (James et al. 2017). However, CHX mouth rinse is only recommended for patient with periodontitis stages I to III but not effective for patient with periodontitis stage IV (Dental Abstract, 2021b). This is because CHX mouth rinse cannot reach the bottom of periodontal pocket, so it is less effective.

The limitation of such delivery devices is that this method needs a high dose of CHX. CHX mouth rinse is easily diluted and eliminated due to saliva doing flushing action. CHX mouth rinse also hard to control to achieve therapeutic concentration in inflammation area. CHX mouth rinse also cannot reach bottom of the pocket due to permeation into and across the gingival tissue is poor (Ren et al. 2016).

3.3. **Gel Delivery**

CHX can be delivered to the inflammation area using gel. Gel is injected to inflammation area using syringe with blunt needle (Mamajiwala et al. 2019). This delivery system has several advantages such as simple and no discomfort from patient, can reach bottom of the pocket, can release CHX in targeted area, can be use in periodontal pocket depth less than 4mm. This gel needs to change into semi-solid or solid to prevent the formulation out from the pocket. There are many gels that can be used to deliver CHX to inflammation area such as Eudragit® L/dimethyl sulfoxide forming gel (Mahadlek et al 2022), poly (D,L-lactide-co-glycolide) (PLGA) microparticles (Sousa et al. 2021), Xanthan gel (Gautam, Manish & Kumar 2021), curdlan and polydopamine (PDA) hydrogels (Tong et al. 2020).

Xanthan based CHX gel has been reported and studied. This gel can be used as an adjunct to Scaling Root Planning (SRP). Using this gel with SRP show better result compared to SRP alone. The study showed a significant reduction in Plaque Index (PI), and Gingival index (GI) in 30 days (Gautam, Manish & Kumar 2021).

PDA hydrogels made by dopamine (DA) solution were gently stirred overnight at the 25°C temperature. The solution then oxidation and self-polymerization happen. Curdlan powder then added to PDA solution and gently stir until the powder dissolved. The thick solution then heated at 80°C for 15 min and cooled down. Tong et al. 2020 reported that curdlan and PDA hydrogels physiochemical properties could be precisely adjusted by changing PDA concentration. He also describes that this system is stable and biocompatible for human periodontal ligament cells. This gel can be used as a better strategy in treating periodontal disease.
The limitation of such delivery devices is relatively large dosing volumes (Wei et al. 2021). CHX gel may be used as adjutant, but SRP always plays dominate role to cure chronic periodontitis (Zhao, Hu & Zhao 2020). This material also easy to dilute compared to chip material.

3.3. Chip Delivery

Another method for delivery of CHX to inflammation area is by using chip. A CHX contained-chip can be inserted into the periodontal pocket, releasing a controlled amount of CHX over a week period. Compared to mouthwash, CHX chips show a clinical benefit to treat an inflammation area locally with controlled releases of CHX (Ma & Diao 2020).

Several materials from biodegradable and non-degradable based have been used to fabricate periodontal chips. Non-degradable material such as polyacrylates (Pillai & Panchagnula 2001) and polydimethylsiloxane (Uskoković et al. 2022) also have been reported for the application of periodontal chips. This material has greater control over the time of CHX release to the periodontal pocket because the therapist controls the removal of the chip. However, non-degradable material is less popular and barely current studies. This is because of its limitation such as patient need to visit therapist to remove the chip.

Degradable polymer have also been employed for the application of periodontal chips. One of the main benefit of degradable chips over non-degradable one is that they degrade after their function have been fulfilled. Thus, a second appointment to remove the chips is unnecessary. Degradable synthetic polymers include Poly(ε-caprolactone) (PCL) (Davoodi et al 2018; Márquez Lobato et al. 2017), Polyethylene glycol (PEG 400) (Lim et al. 2020), and polyamines (Uskoković et al. 2022). PCL chips were developed and reported as a drug delivery for periodontal diseases. polylactide (PLA) microfibers were used to reinforce PCL chip (Márquez Lobato et al. 2017). PCL/PLA reinforce chip release 90% of CHX in about 400 to 1800 minutes depend on its configuration. PEG 400 chip were developed and reported. PEG 400 chip show no significant increase CHX release after 1 hour. This make the CHX concentration is not enough to kill bacteria. This chip may be effective for patient to reduce the progression of debilitating symptoms. Both PCL/PLA and PEG 400 chip can be used as a drug deliver for periodontal disease. The use of these chip must be adjusted to patient condition because of its CHX releases different.

Natural polymers have also been used such as Corn Starch (Queiroz et al. 2020), collagen (John et al. 2015) and gelatine (John et al. 2015; Tan, Safii & Razali 2019). Corn starch chip was developed and met the requirement for drug delivery. This material can be produced from a cheap, simple, and reproduceable process. CHX can be mix well with the matrix and active up to 500h (Queiroz et al. 2020). CHX chip made of collagen has been used as an adjunctive treatment for Scaling Root Planning (SRP). Study showed improvement in clinical parameter and microbiological profile. Study also showed a better reduction of probing pocket depth and subgingival microflora of chronic periodontitis (John et al. 2015).

CHX chip made of gelatine has been used as an adjunctive treatment for Scaling Root Planning (SRP) (Ma & Diao 2020). The study reported by Ma and Diao 2020 showed that in 6 months follow-up, the treatment with SRP and CHX chips resulted a better response in Periodontal Pocket Depth (PDD) reduction than those with SRP alone. The combined treatment also showed a better Gingival inflammation improvement and significant reduction of microbial pathogens such as Treponema denticola, Tannarella forsythia, and Porphyromonas gingivalis.

The limitation of such delivery devices is this method only effective in periodontitis with pocket depth more than 5 mm (Rosa et al. 2021). Less than 5 mm, this method would be less effective. For comparison advantages and disadvantages between liquid, gel and chip can be seen on table 1.
Table 1: Comparison Between Liquid, Gel and Chip.

<table>
<thead>
<tr>
<th>Materials</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liquid</strong></td>
<td>• easy to use.</td>
<td>• needs high dose of CHX.</td>
</tr>
<tr>
<td></td>
<td>• easily diluted and eliminated due to saliva doing flushing action.</td>
<td></td>
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<tr>
<td></td>
<td>• hard to control to achieve therapeutic concentration in inflammation area.</td>
<td></td>
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<tr>
<td></td>
<td>• cannot reach bottom of the pocket due to permeation into and across the gingival tissue is poor.</td>
<td></td>
</tr>
<tr>
<td><strong>Gel</strong></td>
<td>• simple and no discomfort from patient.</td>
<td>• relatively large dosing volumes.</td>
</tr>
<tr>
<td></td>
<td>• can releases chlorhexidine in inflammation area.</td>
<td>• chlorhexidine gel may be diluted before the gel release all the chlorhexidine.</td>
</tr>
<tr>
<td></td>
<td>• can reach bottom of the pocket.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• can be used for periodontitis with pocket depth less than 5mm.</td>
<td></td>
</tr>
<tr>
<td><strong>Chip</strong></td>
<td>• Controlled releases of Chlorhexidine in inflammation area up to 7 days.</td>
<td>• effective only for periodontitis with pocket depth more than 5mm.</td>
</tr>
<tr>
<td></td>
<td>• Effective to kill bacteria compare to other method.</td>
<td>• Need to visit therapist to remove the chip if using non-degradable chip.</td>
</tr>
<tr>
<td></td>
<td>• Can reach bottom of the pocket.</td>
<td></td>
</tr>
</tbody>
</table>

3.4. Future Research

In the future, research about local CHX delivery for periodontal infection should be focus on tissue restorative and managing the disadvantages that happen in current method. CHX should be combine with adjunctive material that can help minimize the disadvantages such as tooth staining. Guided Tissue Regeneration (GTR) also need further research to optimize tissue restorative after cure periodontitis (Mirzaeei et al. 2022).

4. Conclusions

CHX has been used as adjunctive to cure periodontal diseases. There are three kinds of material used to deliver CHX to inflammation area such as liquid, gel, and chip. Every material has its advantages and disadvantages. That material used depends on patient’s condition to get a better result and minimize the side effect. This short review can be used for researcher that wants to research about several materials that can be used to deliver chlorhexidine to help reduce periodontitis. Further research is needed to find any other materials that not only cure periodontitis but also optimize tissue restorative after the cure of periodontitis.
References


Fatriansyah, JF, Rizqillah, RK & Yandi, MY, 2022, ‘Molecular docking and molecular dynamics simulation of fisetin, galangin, hesperetin, hesperidin, myricetin, and naringenin against polymerase of dengue virus’, *Journal of Tropical Medicine*, vol. 2022, DOI: 10.1155/2022/7254990


*Germiphene Corporation*, 2015, ‘Product Monograph Chlorhexidine Gluconate 0.12% Oral Rinse’, USP

Haydari, M, Bardakci, AG, Koldsland, OC, Aass, AM, Sandvik, L & Preus, HR, 2017, ‘Comparing the effect of 0.06% -, 0.12% and 0.2% Chlorhexidine on plaque, bleeding and side effects in an experimental gingivitis model: A parallel group, double masked randomized clinical trial’, *BMC Oral Health*, vol. 17, no. 1,DOI:10.1186/s12903-017-0400-7.


Oh, TJ, 2018, ‘Adjunctive Use of Chlorhexidine Mouthwash to Nonsurgical Periodontal Therapy May Enhance Periodontal Pocket Depth Reduction’, *Journal of Evidence Based Dental Practice*, vol. 18, no.4, pp. 358-359, DOI: 10.1016/j.jebdp.2018.10.004


Rizqillah, RK, 2022, ‘Material Selection of Below-knee Leg Prosthetics’, *Journal of Materials Exploration and Findings (JMEF)*, vol. 1, no 1, DOI: 10.7454/jmef.v1i1.1004


