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The topical effect of chlorhexidine and povidone-iodine in the repair of oral wounds. A review

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SUMMARY

Purpose. The aim of this paper was to review the current literature with regard to the use of chlorhexidine and povidone-iodine in the treatment of oral wounds.

Background. Oral mucosa is continuously subjected to physical or chemical injuries, where it becomes a common site for the occurrence of ulcerated lesions. These lesions are susceptible to infections that may delay healing.

Materials and methods. A search of the medical and dental literature was conducted in Medline/Pubmed and Scielo using a combination of the terms oral ulcer, oral wound, wound healing, povidone-iodine and chlorhexidine, to review their mechanism of action and their use in the healing of oral wounds.

Results and conclusion. The use of chlorhexidine and povidone-iodine is effective in the control of local infection in a concentration-dependent manner, exerting a positive influence on the tissue repair process. Oral antiseptics appear be a good alternative in the management of these lesions, since there is a low risk of systemic toxicity and allergies, and less clinical evidence of bacterial resistance.

Key words: Chlorhexidine, Povidone-Iodine, Wound Healing, Oral Wound.

INTRODUCTION

Oral wounds occur frequently and are usually accompanied by painful symptoms (1-3). They are mainly caused by physical or chemical traumatic agents, immunological disorders (e.g., recurrent aphthous stomatitis, lichen planus, pemphigus vulgaris), microbial infections, systemic diseases, chemotherapy and radiotherapy (4). The oral cavity is constantly subjected to traumatic injuries because of poorly adapted prostheses, inadequate brushing, teeth with sharp or fractured edges, use of acid or alkaline products or drugs, and surgical procedures, among others (2,5).

The repair of these lesions occurs as a cascade process of inflammation, proliferation and tissue remodeling, ending in wound healing (6-7). To obtain suitable tissue repair is of extreme importance for local homeostasis, but the oral microsystem can harbor from 800 to 1000 different bacterial species, making the lesions susceptible to infectious processes, mainly polymicrobial in nature (8). The physiological interactions of the microorganisms and the fact that the oral mucosa is exposed to constant trauma can modify the microbiome in these areas, favoring certain bacterial species, which exhibit local virulence factors, hindering the healing process (9-10). Thus, it is recommended to use substances or methods that promote local antisepsis or favor the tissue repair process (10-11). The methods described in the literature include low-level laser therapy, which promotes tissue biostimulation (12-14), and topical use of corticosteroids (15-17), antibiotics and antiseptics (18-20).

In the case of antiseptics, chlorhexidine (Chx) and povidone-iodine (PvI) exhibit broad-spectrum bactericidal effects, maintaining low numbers of microorganisms, which may aid in the wound healing process, whether oral or cutaneous (21-22). Chx is usually found in mouthwashes, gels and toothpaste for controlling plaque and gingivitis, and PvI in the form of a topical solution. On the other hand, although Chx and PvI have broad-spectrum germicidal effects, studies have demonstrated their

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cytotoxic and genotoxic effects in fibroblasts and osteoblasts in vitro, which could delay the repair process (23-24). Thus, it was observed the need to compare these antiseptics, in order to verify their efficacy in the treatment of oral wounds and to establish an adequate and easily accessible treatment. Therefore, the aim of this study was to review the use of Chx and PvI in the healing of oral lesions.

MATERIALS AND METHODS

The literature search was performed in the Medline/PubMed and Scielo databases using the terms "*oral ulcer", "oral wound", "wound healing", "povidone-iodine"* and *"chlorhexidine"*. The studies were selected according to the following inclusion criteria: articles published in English and Spanish between 1970 and 2017; in vivo studies (on human subjects or animals), clinical trials and reviews involving the application of chlorhexidine or povidone-iodine in the oral cavity focusing on the wound healing. In addition, in vitro studies on the cytotoxicity of these drugs have been included.

Chlorhexidine

Chx is an antimicrobial substance belonging to the bisbiguanide class. The most frequent oral preparation is water-soluble 0.12% chlorhexidine digluconate, which at physiological pH dissociates to release a positively charged molecule (25).

Mechanism of action

The bactericidal effect is due to rupture of the cell membrane and consequent loss of intracellular material such as potassium (at low concentrations) or by respiratory inhibition and loss of nucleic acids (at high concentrations) (25). Moreover, because of the interaction of Chx with cytoplasmic proteins, there is precipitation of proteins and nucleic acids (26). Chx inhibits glycosyltransferase and 2-phosphoenolpyruvate phosphotransferase, the latter being a vital enzyme for the function and maintenance of the bacterial glycolytic pathway (27). It is active against Gram-positive and Gram-negative bacteria and yeasts as well. Gram-positive bacteria are more sensitive than Gram-negative bacteria, probably due to the absence of an outer membrane and the presence of teichoic acids in their cell wall (25,28). Moreover, it exhibits a bacteriostatic effect due to its adsorption to oral surfaces, which allows prolonged release, conferring the characteristic of substantivity (29-30).

Clinical applications and oral wound healing

Clinical trials have demonstrated the bactericidal effect of Chx and its importance in pre-surgical preparation to decrease infections (31), dental plaque formation (32), postoperative discomfort and the occurrence of alveolitis (33). Torres-Lagares *et al*. (34) investigated the effect of 0.2% Chx gel on reduction of alveolar osteitis. Chx was applied to the interior of the alveolus immediately after exodontia. A 63.33% reduction in the incidence of osteitis was observed in comparison to the control group. On the other hand, Abu-Mostafa *et al*. (35) did not observe significant differences with intra-alveolar application of 0.2% Chx gel. However, in this study there was no placebo group. The control group used 0.12% Chx in the postoperative period twice a day for a week, which may explain the absence of any difference.

Fomete *et al*. (36) did not observe significant differences between 0.2% Chx and warm saline mouthwashes with regard to biofilm formation and microbial composition of third molar sutures. However, Chx mouthwash was used twice daily, while saline was used before and after each meal. In contrast, de Waal *et al*. (37) found that there was a significant reduction in anaerobic bacterial count with the use of a combination of 0.05% cetylpyridinium chloride and 0.12% Chx after surgical treatment for peri-implantitis. Furthermore, there was a loss of nine implants in the placebo group during the follow-up period, while no implant was lost in the test group. Such findings were explained by the efficient control of infection and local inflammation when the combination of antiseptics was employed.

In this perspective, preclinical studies have used animal models to evaluate clinically and histologically the healing of traumatic lesions induced in the oral mucosa (10, 18, 22, 38-40). Therefore, the study of different anatomical sites, drug concentrations and follow-up times has been described (Table 1). Table 1 shows that the best results are obtained with treatments of 7 to 21 days and depend, according to the authors, on the Chx concentration (between 0.12 and 2%). When the antiseptic was used in the form of a gel or paste, there was a longer contact time of the product with the operated area which could have contributed to the more favorable outcomes.

However, it should be emphasized that in vitro studies have demonstrated the cytotoxicity of this substance. The interaction of Chx with different cells of the oral mucosa and the mechanisms by which it could induce cell death have been investigated. Giannelli *et al*. (23) evaluated cell viability and cell death after contact of cells of the oral cavity with different concentrations of Chx. Cell viability was reduced in osteoblasts, fibroblasts and endothelial

cells by 0.01, 0.03 and 0.12% Chx, respectively. According to the authors, Chx exerts a toxic effect by inducing apoptosis and necrosis, also involving a decrease in mitochondrial membrane potential, intracellular increase in calcium ions levels and increase in oxidative stress, affecting vital conditions for cellular homeostasis. Faria *et al*. (24) observed apoptosis of L929 fibroblasts with 0.0005% Chx, which would occur via endoplasmic reticulum stress. Chx concentrations equal to or greater than 0.04% were shown to inhibit cell proliferation and cause morphological changes in human gingival fibroblasts. It is possible that the treated cells were blocked in the S phase of the cell cycle to repair the DNA damage induced by Chx and that some of these changes were not repaired, resulting in cell apoptosis (41).

Nevertheless, it is important to point out that the oral cavity has several sites for the adsorption of this substance, thus reducing the concentration that effectively comes into contact with the cells, which may explain its beneficial effect on the tissue repair process described in previous studies (10, 48-39).

Povidone-iodine

PvI is an iodine complex with polyvinylpyrrolidone, which is water soluble. The bactericidal component is free iodine (usually 1 ppm), which is released gradually, and its most common formulation is a 10% solution. It has a germicidal effect on Gram-positive and Gram-negative bacteria, bacterial spores, fungi, viruses and protozoa, showing the broadest spectrum of activity among oral antiseptics (42-43).

Table 1. Pre-clinical studies involving topical application of chlorhexidine on oral wounds

Authors	Concentration	Wound size/ site	n	Experimental time	Results
Kozlovsky *et al.* (2007) (38)	0.12% chlorhexidine digluconate solution - 1% chlorhexidine digluconate gel	5 mm diameter/ Palatal mucosa	Wistar rats 0.12% ChxG: 24 (6 per experimental time) 1% ChxG: 24 (6 per experimental time)	3, 7, 14 and 21 days	14, 21 days: 1% ChxG showed a significant rate of wound epithelialization ($p<0.05$) compared with placebo group. 0.12% ChxG no significant difference between any of the experimental times.
Hammad *et al.* (2011) (39)	0.12% chlorhexidine digluconate gel	3 mm diameter/ Palatal mucosa	Wistar albino rats ChxG: 24 (6 per experimental time)	3, 7, 14 and 21 days	7, 14, 21 days: ChxG showed a greater reduction in the wound area ($p<0.05$) in relation to control group. 7 days: ChxG showed a significant rate of wound epithelialization ($p<0.05$).
Al-Mobeeriek (2011) (18)	0.2% chlorhexidine digluconate solution	5 mm length/ Right buccal mucosa	Sprague-Dawley rats ChxG: 25 (5 per experimental time)	1, 2, 7, 15 and 30 days	No significant difference in the ChxG compared to the control group at all experimental times.
Alsadat Hashemipour *et al.* (2013) (22)	Not given	2 mm diameter/ Palatal mucosa	Wistar rats ChxG: 16 (4 per experimental time)	2, 4, 6 and 8 days	2, 4 days: higher count of PMNs in ChxG ($p<0.05$) 2, 4, 6, 8 days: Chx alone had no significant effect on the area of the ulcer, the thickness of the epithelium nor the rate of epithelialization.
Kovalik *et al.* (2014) (40)	2% chlorhexidine digluconate gel	4 mm diameter/ Palatal mucosa	Wistar rats ChxG: 32 (8 per experimental time)	3, 7, 15 and 21 days	No significant difference in the ChxG compared to the control group at all experimental times. At 15 days, the ChxG showed a delay in the pattern of repair compared with baseline wound.
Mariano *et al.* (2015) (10)	2% chlorhexidine paste	4 mm diameter/ Palatal mucosa	Wistar rats ChxG: 9 (3 per experimental time	3, 6 and 10 days	3, 6 and 10 days: Significant difference in tissue repair in 2% ChxG compared with control group.

ChxG – chlorhexidine group, PMNs – polymorphonuclear cells.

Mechanism of action

Its basic mechanism of action is the oxidation of amino acids and nucleic acids, through the perturbation of various microbial metabolic pathways, as well as destabilization of the cell membrane, causing irreversible damage to the microbial organism (11). Furthermore, it exerts an effect on bacterial exotoxins, enzymes and proteins, which directly influence tissue repair and inflammation (44).

Clinical applications and oral wound healing

Several literature reviews have demonstrated the effects of the PvI application in the treatment and prevention of infection in cutaneous wounds, both acute and chronic, showing good clinical results (45-46). In the oral cavity, the use of PvI has been restricted to the treatment of oral mucositis (OM), to pre-surgical preparation and as an adjuvant to periodontal therapy (11,47).

OM is a common complication of radiotherapy, chemotherapy or the combination of the two. The main clinical signs are erythema in the mucosa and painful ulcers, which make eating difficult and can lead to interruption of cancer treatment due to the high risk of infections (48). Accordingly, several clinical studies have investigated the effect of PvI in the prevention and treatment of OM during chemoradiotherapy (47,49-52). Table 2 presents the main clinical studies in which PvI was used in cancer patients with OM. The findings suggest a positive effect of the antiseptic, mainly in relation to the severity, incidence and duration of the lesions. Most authors highlight the antimicrobial efficacy of this antiseptic as the main reason for recommending its use in the prevention and treatment of OM.

A reduction in microorganism counts following the use of PvI mouthwash is well documented in the literature (11), with an effect lasting up to four hours (53). Cherry *et al*. (54) investigated the effect of mouthwash with 7.5% PvI on systemic bacteremia after periodontal treatment. Oral-derived bacteremia

Table 2. Controlled clinical studies involving topical application of povidone-iodine (PvI) for prevention or treatment of oral mucositis (OM)

Authors	Cancer treatment modality	Treatment or prevention regimen for OM with PvI	n	Comments
Rahn *et al.* (1997) (49)	C/RT (carboplatin in the 1st and 5th week of RT, total radiation dose of 71.3 Gy)	Rinses with 10% PvI (diluted 1:8), four time a day, started simultaneously with RT (approximately 8 weeks)	20 patients per group	PvI significantly reduced incidence ($p<0.05$), severity ($p<0.005$) and duration ($p<0.001$) of chemoradiation-induced OM.
Vokurka *et al.* (2005) (50)	CT (BEAM: carmustine, etoposide, cytarabine, melphalan or HD-L-PAM: melphalan) in the 1st week, followed by autologous peripheral stem cell transplantation.	Rinses with 10% PvI (diluted 1:100), four times a day, started simultaneously with CT (time of treatment not specified)	67 patients in PvI group	Overall incidence, severity and duration of OM were not significantly different between the control group and PvI group. Mouthwash with PvI was significantly less tolerated ($p= 0.02$).
Madan *et al.* (2008) (47)	RT (total dose of 60 Gy)	Rinses with 1% PvI, twice a day, started simultaneously with RT (6 weeks)	20 patients per group	A significant difference in the mean OM scores was observed between the PvI group and the control group ($p<0.01$) at the end of each study week. PvI also significantly reduced onset of OM. $p=0.005$).
Roopashri *et al.* (2011) (51)	RT (total dose of 66 Gy)	Rinses with 5% PvI, four times a day, started after two weeks of RT (4 weeks)	25 patients per group	PvI reduced the severity of OM and pain, without significant difference in relation to the control group (0.15% Benzydamine hydrochloride).
Rao *et al.* (2014) (52)	C/RT (carboplatin once a week, totaling 7 sessions/ total dose of 70 Gy) or only RT.	Rinses with 10% PvI (diluted 1:100), twice a day, started simultaneously with C/RT (7 weeks)	40 patients per group	PvI was used as the gold standard for treatment of OM. The test group used mouthwash with curcuma, 6 times a day, showing a reduction in the incidence and severity of the lesions ($p<0.001$).

RT – radiotherapy, CT – chemotherapy, C/RT – chemoradiotherapy.

occurred in 33% of subjects in the control group and 10% in the PvI group. Additionally, studies have shown that PvI has an anti-inflammatory, hemostatic effect and causes reduction in postoperative edema and trismus. Kumar *et al*. (55) evaluated the effect of irrigation with PvI after apicoectomy of anterior teeth in reducing bleeding and the inflammatory process. PvI significantly reduced bleeding time, total dose of non-steroidal anti-inflammatory drugs, and postoperative edema in relation to the control group. Chemical cauterization promoted by the PvI complex might have been the reason for cessation of bleeding (56). The authors suggested that PvI had anti-inflammatory action because it decreases the availability of cytochrome oxidase, thereby altering the synthesis of prostaglandins and influencing the initial stages of wound healing. Arakeri and Brennan (57), in a randomized clinical trial, evaluated the effect of irrigation with PvI (0.5%) during lower third molar extraction, in reducing postoperative edema. There was a significant reduction in facial edema in relation to the control group on the first and seventh day after surgery. Such findings may be explained by a possible inhibitory effect on leukotriene B4 synthesis and leukocyte chemotaxis.

Despite the good clinical results and the various beneficial effects of PvI on the inflammatory process, in vitro studies have demonstrated deleterious effects on gingival fibroblasts, keratinocytes and human osteoblasts. PvI has a non-selective cytotoxic effect; high concentrations (greater than 10%) can induce tissue necrosis and low concentrations, cellular apoptosis (58). Flemingson *et al*. (59) evaluated the effect of three oral antiseptics (0.2% Chx, Listerine® and 1% PvI) on the proliferation of human gingival fibroblasts. Several dilutions of each drug were tested, and cell cultures were evaluated after 1, 5 and 15 minutes. In all three groups, the inhibition of fibroblast proliferation was dependent on the concentration used and independent of the exposure time. Among the products tested, PvI demonstrated the lowest cytotoxicity. Regarding the effect on keratinocytes, PvI induced necrosis and apoptosis in human epithelial cells (HeLa) in a dose-dependent manner. In addition, when tested in cells from the oral mucosa of rats, there was a significant reduction in epithelial tissue layers as well as changes in the cytoplasm after the first day of exposure (60).

Cabral and Fernandes (61) compared the effect of Chx and PvI on cell proliferation and functional activity of human alveolar bone cells. A short exposure (2 minutes) resulted in cell death at 0.12 and 2% (1.2 and 20 mg/mL) Chx and 5 and 10% (50 and 100 mg/mL) PvI. Chx at levels up to 0.005 mg/mL and PvI at levels up to 0.5 mg/mL did not result in significant effects on adhesion and cell morphology. The results suggested higher cytotoxicity of Chx to osteoblastic cells.

Although in vitro studies demonstrate that PvI inhibits cell proliferation, it should be considered that the oral cavity is a complex environment composed of several tissues, structures and substrates, which together with salivary flow promote a certain dilution of the antiseptic, reducing the concentration which actually reaches the cells of the surgical bed, for example. In view of these findings, the use of PvI at a low concentration should be considered, since it exhibits a bactericidal effect at concentrations around 0.001% (58).

FINAL CONSIDERATIONS

The management of oral wounds is complex because of the various structures involved and the highly contaminated environment to which these lesions are exposed. In this paper, we discussed studies involving the oral mucosa and adjacent bone structures, injured by physical or chemical traumatic agents. PvI appears to be the most effective antiseptic in oral wound repair, due to its antimicrobial, anti-inflammatory and antioxidant properties. However, rinses with povidone-iodine cause yellow-brown stains on the tooth surface and soft tissues, which could contraindicate its use. The choice of antiseptic should consider the location, size and etiology of the wound. Oral antiseptics have proven to be a good alternative for the management of these lesions, since there is a low risk of systemic toxicity or allergies and less clinical evidence of bacterial resistance. However, such findings are mainly from laboratory studies, and clinical trials are lacking.

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CONFLICTS OF INTERESTS

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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REFERENCES

1. Bascones-Martínez A, Figuero-Ruiz E, Esparza-Gómez GC. Úlceras orales. *Med Clin* (Barc) 2005;125:590-7.
2. Muñoz-Corcuera M, Esparza-Gómez G, González-Moles MA, Bascones-Martínez A. Oral ulcers: clinical aspects. A tool for dermatologists. Part I. Acute ulcers. *Clin Exp Dermatol* 2009;34:289-94.
3. Nico MM, Nagano CP, Fernandes JD, Lourenço SV. A destructive ulcer on the lower lip. *Clin Exp Dermatol* 2010;35:e180-81.
4. Field EA, Allan RB. Review article: oral ulceration - aetiopathogenesis, clinical diagnosis and management in the gastrointestinal clinic. *Aliment Pharmacol Ther* 2003;18:949-62.
5. Gonzalez-Moles MA, Bagan-Sebastian JV. Alendronate-related oral mucosa ulcerations. *J Oral Pathol Med* 2000;29:514-8.
6. Enoch S, Leaper DJ. Basic science of wound healing. *Surgery* (Oxford) 2005;23:37-42.
7. Young A, McNaught C. The physiology of wound healing. *Surgery* (Oxford) 2011;29:475-79.
8. Gomez A, Nelson KE. The Oral microbiome of children: development, disease, and implications beyond oral health. *Microb Ecol* 2017;73:492-503.
9. Hijazi K, Lowe T, Meharg C, Berry SH, Foley J, Hold GL. Mucosal microbiome in patients with recurrent aphthous stomatitis. *J Dent Res* 2015;94:87S-94S.
10. Mariano RC, Oliveira MR, Silva LC, Ferreira S, Garcia Júnior IR, de Carvalho Silva A. Effect of topical application of chlorhexidine and metronidazole on the tissue repair of palatal wounds of rats: a clinical and histomorphometric study. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2015;119:505-13.
11. Kanagalingam J, Feliciano R, Hah JH, Labib H, Le TA, Lin JC. Practical use of povidone-iodine antiseptic in the maintenance of oral health and in the prevention and treatment of common oropharyngeal infections. *Int J Clin Pract* 2015;69:1247-56.
12. Cooper CE, Springett R. Measurement of cytochrome oxidase and mitochondrial energetics by near-infrared spectroscopy. *Philos Trans R Soc Lond B Biol Sci* 1997;352:669-76.
13. Alexandratou E, Yova D, Handris P, Kletsas D, Loukas S. Human fibroblast alterations induced by low power laser irradiation at the single cell level using confocal microscopy. *Photochem Photobiol Sci* 2002;1:547-52.
14. Dillenburg CS, Almeida LO, Martins MD, Squarize CH, Castilho RM. Laser phototherapy triggers the production of reactive oxygen species in oral epithelial cells without inducing DNA damage. *J Biomed Opt* 2014;19:048002.
15. Lima AAS, Grégio AMT, Tanaka O, Machado MAN, França BHS. Treatment of the mouth traumatic ulcers caused by orthodontic appliances. *Rev Dent Press Ortodon Ortop Facial* 2005;10:30-6.
16. Belenguer-Guallar I, Jiménez-Soriano Y, Claramunt-Lozano A. Treatment of recurrent aphthous stomatitis. A literature review. *J Clin Exp Dent* 2014;6:e168-74.
17. Schemel-Suárez M, López-López J, Chimenos-Küstner E. [Oral ulcers: Differential diagnosis and treatment] [Article in Spanish]. *Med Clin* (Barc) 2015;145:499-503.
18. Al-Mobeeriek A. Effects of myrrh on intra-oral mucosal wounds compared with tetracycline- and chlorhexidine-based mouthwashes. *Clin Cosmet Investig Dent* 2011;3:53-8.
19. Soylu Özler G, Okuyucu Ş, Akoğlu E. The Efficacy of sucralfate and chlorhexidine as an oral rinse in patients with recurrent aphthous stomatitis. *Adv Med* 2014;2014:986203.
20. Laugisch O, Ramseier CA, Salvi GE, Hägi TT, Bürgin W, Eick S, et al. Effects of two different post-surgical protocols including either 0.05% chlorhexidine herbal extract or 0.1% chlorhexidine on post-surgical plaque control, early wound healing and patient acceptance following standard periodontal surgery and implant placement. *Clin Oral Investig* 2016;20:2175-83.
21. Kramer SA. Effect of povidone-iodine on wound healing: a review. *J Vasc Nurs* 1999;17:17-23.
22. Alsadat Hashemipour M, Borna R, Gandjaliphan Nassab A. Effects of mucoadhessive paste of chlorhexidine and betamethasone on oral ulcer recovery process in rats. *Wounds* 2013;25:104-12.
23. Giannelli M, Chellini F, Margheri M, Tonelli P, Tani A. Effect of chlorhexidine digluconate on different cell types: a molecular and ultrastructural investigation. *Toxicol In Vitro* 2008;22:308-17.
24. Faria G, Cardoso CR, Larson RE, Silva JS, Rossi MA. Chlorhexidine-induced apoptosis or necrosis in L929 fibroblasts: A role for endoplasmic reticulum stress. *Toxicol Appl Pharmacol* 2009; 234:256-65.
25. Hidalgo E, Dominguez C. Mechanisms underlying chlorhexidine-induced cytotoxicity. *Toxicol In Vitro* 2001;15:271-6.
26. Gomes BP, Souza SF, Ferraz CC, Teixeira FB, Zaia AA, Valdrighi L, et al. Effectiveness of 2% chlorhexidine gel and calcium hydroxide against Enterococcus faecalis in bovine root dentine in vitro. *Int Endod J* 2003;36:267-25.
27. Ribeiro LG, Hashizume LN, Maltz M. The effect of different formulations of chlorhexidine in reducing levels of mutans streptococci in the oral cavity: A systematic review of the literature. *J Dent* 2007;35:359-70.
28. Greenstein G, Berman C, Jaffin R. Chlorhexidine. An adjunct to periodontal therapy. *J Periodontol* 1986;57:370-7.
29. Bonesvoll P. Oral pharmacology of chlorhexidine. J *Clin Periodontol* 1977;4:49-65.
30. Khademi AA, Mohammadi Z, Havaee A. Evaluation of the antibacterial substantivity of several intra-canal agents. *Aust Endod J* 2006;32:112-5.
31. Kosutic D, Uglesic V, Perkovic D, Persic Z, Solman L, Lupi-Ferandin S, et al. Preoperative antiseptics in clean/contaminated maxillofacial and oral surgery: prospective randomized study. *Int J Oral Maxillofac Surg* 2009;38:160-5.
32. Charles CH, Mostler KM, Bartels LL, Mankodi SM. Comparative antiplaque and antigingivitis effectiveness of a chlorhexidine and an essential oil mouthrinse: 6-month clinical trial. *J Clin Periodontol* 2004;31:878-84.
33. Haraji A, Rakhshan V. Chlorhexidine gel and less difficult surgeries might reduce post-operative pain, controlling for dry socket, infection and analgesic consumption: a split-mouth controlled randomised clinical trial. *J Oral Rehabil* 2015;42:209-19.
34. Torres-Lagares D, Gutierrez-Perez JL, Infante-Cossio P, Garcia-Calderon M, Romero-Ruiz MM, Serrera-Figallo MA. Randomized, double-blind study on effectiveness of intra-alveolar chlorhexidine gel in reducing the incidence of alveolar osteitis in mandibular third molar surgery. *Int J Oral Maxillofac Surg* 2006;35:348-51.
35. Abu-Mostafa NA, Alqahtani A, Abu-Hasna M, Alhokail

A, Aladsani A. A randomized clinical trial compared the effect of intra-alveolar 0.2% Chlorohexidine bio-adhesive gel versus 0.12% Chlorohexidine rinse in reducing alveolar osteitis following molar teeth extractions. *Med Oral Patol Oral Cir Bucal* 2015;20:e82-7.
36. Fomete B, Saheeb BD, Obiadazie AC. A prospective clinical evaluation of the effects of chlorhexidine, warm saline mouth washes and microbial growth on intraoral sutures. *J Maxillofac Oral Surg* 2015;14:448-53.
37. de Waal YC, Raghoebar GM, Huddleston Slater JJ, Meijer HJ, Winkel EG, van Winkelhoff AJ. Implant decontamination during surgical peri-implantitis treatment: a randomized, double-blind, placebo-controlled trial. *J Clin Periodontol* 2013;40:186-95.
38. Kozlovsky A, Artzi Z, Hirshberg A, Israeli-Tobias C, Reich L. Effect of local antimicrobial agents on excisional palatal wound healing: a clinical and histomorphometric study in rats. *J Clin Periodontol* 2007;34:164-71.
39. Hammad HM, Hammad MM, Abdelhadi IN, Khalifeh MS. Effects of topically applied agents on intra-oral wound healing in a rat model: a clinical and histomorphometric study. *Int J Dent Hyg* 2011;9:9-16.
40. Kovalik AC, Bisetto P, Pochapski MT, Campagnoli EB, Pilatti GL, Santos FA. Effects of an orabase formulation with ethanolic extract of Malva sylvestris L. in oral wound healing in rats. *J Med Food* 2014;17:618-24.
41. Wyganowska-Swiatkowska M, Kotwicka M, Urbaniak P, Nowak A, Skrzypczak-Jankun E, Jankun J. Clinical implications of the growth-suppressive effects of chlorhexidine at low and high concentrations on human gingival fibroblasts and changes in morphology. *Int J Mol Med* 2016;37:1594-600.
42. Flynn J. Povidone-iodine as a topical antiseptic for treating and preventing wound infection: a literature review. *Br J Community Nurs* 2003;8:S36-42.
43. Sauerbrei A, Wutzler P. Virucidal efficacy of povidone-iodine-containing disinfectants. *Lett Appl Microbiol* 2010;51:158-63.
44. König B, Reimer K, Fleischer W, König W. Effects of Betaisodona on parameters of host defense. *Dermatology* 1997;195:42-48.
45. Burks RI. Povidone-iodine solution in wound treatment. *Phys Ther* 1998;78:212-8.
46. Campbell N, Campbell D. Evaluation of a non-adherent, povidone-iodine dressing in a case series of chronic wounds. *J Wound Care* 2013;22:401-2, 404-6.
47. Madan PD, Sequeira PS, Shenoy K, Shetty J. The effect of three mouthwashes on radiation-induced oral mucositis in patients with head and neck malignancies: a randomized control trial. *J Cancer Res Ther* 2008;4:3-8.
48. Lalla RV, Sonis ST, Peterson DE. Management of oral mucositis in patients who have cancer. *Dent Clin North Am* 2008;52:61-77.
49. Rahn R, Adamietz IA, Boettcher HD, Schaefer V, Reimer K, Fleischer W. Povidone-iodine to prevent mucositis in patients during antineoplastic radiochemotherapy. *Dermatology* 1997;195:57-61.
50. Vokurka S, Bystrická E, Koza V, Scudlová J, Pavlicová V, Valentová D, et al. The comparative effects of povidone-iodine and normal saline mouthwashes on oral mucositis in patients after high-dose chemotherapy and APBSCT--results of a randomized multicentre study. *Support Care Cancer* 2005;13:554-8.
51. Roopashri G, Jayanthi K, Guruprasad R. Efficacy of benzydamine hydrochloride, chlorhexidine, and povidone iodine in the treatment of oral mucositis among patients undergoing radiotherapy in head and neck malignancies: A drug trail. *Contemp Clin Dent* 2011;2:8-12.
52. Rao S, Dinkar C, Vaishnav LK, Rao P, Rai MP, Fayad R, et al. The Indian Spice Turmeric Delays and Mitigates Radiation-Induced Oral Mucositis in Patients Undergoing Treatment for Head and Neck Cancer: An Investigational Study. *Integr Cancer Ther* 2014;13:201-10.
53. Domingo MA, Farrales MS, Loya RM, Pura MA, Uy H. The effect of 1% povidone iodine as a pre-procedural mouthrinse in 20 patients with varying degrees of oral hygiene. *J Philipp Dent Assoc* 1996;48:31-8.
54. Cherry M, Daly CG, Mitchell D, Highfield J. Effect of rinsing with povidone-iodine on bacteraemia due to scaling: a randomized-controlled trial. *J Clin Periodontol* 2007;34:148-55.
55. Kumar KS, Reddy GV, Naidu G, Pandiarajan R. Role of povidone iodine in periapical surgeries: Hemostyptic and anti-inflammatory? *Ann Maxillofac Surg* 2011;1:107-11.
56. Kumar BP, Maddi A, Ramesh KV, Baliga MJ, Rao SN, Meenakshi. Is povidone-iodine a hemostyptic? A clinical study. *Int J Oral Maxillofac Surg* 2006;35:765-6.
57. Arakeri G, Brennan PA. Povidone-iodine: an anti-oedematous agent? *Int J Oral Maxillofac Surg* 2011;40:173-6.
58. Woo KY. Management of non-healable or maintenance wounds with topical povidone iodine. *Int Wound J* 2014;11:622-6.
59. Flemingson, Emmadi P, Ambalavanan N, Ramakrishnan T, Vijayalakshmi R. Effect of three commercial mouth rinses on cultured human gingival fibroblast: an in vitro study. *Indian J Dent Res* 2008;19:29-35.
60. Sato S, Miyake M, Hazama A, Omori K. Povidone-iodine-induced cell death in cultured human epithelial HeLa cells and rat oral mucosal tissue. *Drug Chem Toxicol* 2014;37:268-75.
61. Cabral CT, Fernandes MH. In vitro comparison of chlorhexidine and povidone-iodine on the long-term proliferation and functional activity of human alveolar bone cells. *Clin Oral Investig* 2007;11:155-64.

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