Angiogenesis and the prevention of alveolar osteitis: a review study

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Abstract

Angiogenesis is one of the essential processes that occur during wound healing. It is responsible for providing immunity as well as the regenerative cells, nutrition, and oxygen needed for the healing of the alveolar socket following tooth extraction. The inappropriate removal of formed blood clots causes the undesirable phenomenon of alveolar osteitis (AO) or dry socket. In this review, we aimed to investigate whether enhanced angiogenesis contributes to a more effective prevention of AO. The potential pro- or anti-angiogenic activity of different materials used for the treatment of AO were evaluated. An electronic search was performed in the PubMed, MEDLINE, and EMBASE databases via OVID from January 2000 to September 2016 using the keywords mentioned in the PubMed and MeSH (Medical Subject Headings) terms regarding the role of angiogenesis in the prevention of AO. Our initial search identified 408 articles using the keywords indicated above, with 38 of them meeting the inclusion criteria set for this review. Due to the undeniable role of angiogenesis in the socket healing process, it is beneficial if strategies for preventing AO are directed toward more proangiogenic materials and modalities.

Key words: Dry socket, Endothelial cells, Regeneration

I. Introduction

Alveolar osteitis (AO) or “dry socket” is a phenomenon that occurs following tooth extraction due to the disintegration of initial blood clots formed inside the alveolar socket and the failure of socket healing process1,2. The condition is also referred to as alveolalgia, localized osteitis, fibrinolytic alveolitis, alveolitis sicca dolorosa, and necrotic or septic socket3. The incidence of AO ranges from 1% to 4% following tooth extraction. In the case of mandibular third molar extraction, AO may occur in up to 45% of cases3,4. It is most commonly seen in patients aged between 40 years and 45 years5,6. The signs and symptoms of AO start with onset at two days to four days after tooth extraction, which includes severe and intense pain that mainly radiates to the ear and neck. The surrounding mucosa becomes erythematous, the alveolar socket is covered with a yellow-gray necrotic tissue layer, and halitosis or a putrid odor is also evident7.

The exact etiology of AO still remains largely unknown, but the most widely accepted theory is that it is the result of a partial or complete disintegration of formed blood clots by fibrinolysis8. Several contributing and risk factors have been identified that increase the incidence of AO. These include general factors such as sex8,9; smoking10; the use of oral contraceptives11; and local factors such as the site of extraction9,12, the presence of preoperative infection13, traumatic extraction14, a low level of operator experience15, inadequate postoperative irrigation16, and/or the use of local anesthetics with vasoconstrictors17. The management of AO includes preventive methods such as using clot-supporting agents3, antibiotics18,19, antifibrinolytic agents5, antiisepctic mouth rinses20, steroids22, and curative methods such as intra-alveolar dressings and medicaments25,26.
The role of pro- or anti-angiogenic materials used for the prevention of AO was considered. The main focus of this review was the beneficial proangiogenic potential of materials and/or methods used for the prevention of AO.

2. Inclusion and exclusion criteria

The inclusion criteria were (1) studies published in the English language; (2) studies accepted and published between January 2000 and September 2016; (3) scientific in vitro or in vivo articles, reviews, systematic reviews, case reports with controlled study design; and (4) studies that presented new methods and materials for the prevention of AO. The exclusion criteria were (1) studies that were published prior to January 2000 or after September 2016; (2) studies that evaluated the etiology or risk factors that contribute to AO; (3) studies that used different materials or methods for the management and related mechanisms of AO after occurrence; and (4) studies that investigated socket preservation methods for dental implant insertion.

3. Search methodology

As part of this study, electronic searches were performed in the PubMed, MEDLINE, and EMBASE databases via OVID using keywords mentioned in relevant PubMed and MeSH (Medical Subject Headings) terms, including the names of materials used for the prevention of AO.

4. Search strategy

In the electronic search of scientific papers in the PubMed, MEDLINE, and EMBASE databases in this study, the following keywords were used: “angiogenesis and alveolar osteitis,” “alveolar osteitis prevention,” “chlorhexidine gluconate and angiogenesis,” “tetracycline and angiogenesis,” “metronidazole and angiogenesis,” “azithromycin and angiogenesis,” “penicillin and angiogenesis,” “lincomycin and angiogenesis,” “amoxicillin and angiogenesis,” “eugenol and angiogenesis,” “platelet-rich fibrin and angiogenesis,” and “platelet-rich plasma and angiogenesis.” It should be noted that the search results obtained using the keywords “dry socket” and “alveolar osteitis” were similar, while the search results acquired using “alveolar osteitis” showed more results. Hence, we used “alveolar osteitis” as the main keyword in the electronic searches in the indicated databases. Relevant full-text articles and the reference lists of related articles were...
also evaluated to supplement the search. The assessment of the eligibility and the finding of related data were independently performed by two reviewers. There was no inconsistency with the two reviewers.

III. Results

The initial search of the keywords indicated above resulted in 408 articles, with a final 38 of them meeting the inclusion criteria set for this review. The selected studies were directly related to the materials used for the prevention of AO. (Table 1)

IV. Discussion

In this section, we aim to discuss the proangiogenic potential of different materials used for the prevention of AO.

1. Antiseptics

The most commonly used and tested antiseptic for the prevention of AO is chlorhexidine gluconate (CHX). CHX is an antiseptic agent with a broad spectrum of activity, no associated development of resistance, good tolerability, substantivity, and slow release. CHX has been previously used at two concentrations of 0.2% and 0.12%, respectively, as a mouth rinse solution or in gel form.

1) Chlorhexidine gluconate solution

Shepherd performed a review study of 32 publications from 12 countries and concluded that, done preoperatively and at seven days postoperatively, rinsing the mouth with 0.12% CHX had a significant preventive effect on AO incidence. Sridhar et al. worked on 50 patients and reported similar results using 0.2% CHX solution twice daily at one day before and for seven days after surgical extraction.

Metin et al., in a prospective randomized clinical trial of 99 subjects, showed that a one-week-long postoperative mouth rinse with 0.2% CHX solution regimen was adequate and that there was no need to use CHX for a week before extraction. Caso et al., through their review of seven randomized prospective clinical trials, concluded that mouth rinsing with CHX solution post-extraction for several days reduced the incidence of AO. Delibiasi et al., in their study, worked on 177 subjects and showed that the effectiveness of 0.2% CHX solution was enhanced when used in combination with amoxicillin and clavulanic acid. (Table 1, Fig. 1)

2) Chlorhexidine gluconate gel

Torres-Lagares et al., in a pilot study of 30 patients, concluded that 0.2% CHX gel was a good prophylactic agent and that it can be applied only once in the intra-alveolar site after impacted third molar removal to reduce edema and AO incidence. Hita-Iglesias et al. compared the effectiveness of 0.2% CHX gel versus 0.12% CHX solution in the prevention of AO in 75 patients. They concluded that bioadhesive 0.2% CHX gel has more advantages and capabilities than does the CHX solution in reducing the incidence of AO. Abu-Mostafa et al., using 201 patients who underwent 301 extractions, also indicated that 0.2% CHX gel was more effective than 0.12% CHX solution. Mínguez-Serra et al. reviewed 12 clinical trials and reported similar results, and concluded that 0.2% CHX gel applied twice daily for seven days after tooth extraction was more effective than the use of 0.12% CHX mouth rinse. Torres-Lagares et al., in another study, showed that bioadhesive 0.2% CHX gel reduced the incidence of AO by up to 57.15% in patients with bleeding complications. Rodríguez-Pérez et al. reported that there were no differences between using 1% CHX and using 0.2% CHX gel twice daily for seven days with respect to reducing the incidence of AO in 88 subjects.

Barbar et al., in a randomized control trial study of 100 patients, showed a significant reduction in the incidence of AO using a single application of CHX gel following mandibular third molar surgery. Haraji and Rakhshan reported similar results regarding the effectiveness of a single-dose of intra-alveolar placement of 0.2% CHX gel in 45 patients. Jesudasan et al. worked with 270 patients and concluded that, although 0.2% CHX gel could reduce the incidence of AO, postoperative placement of a eugenol-based paste could eliminate AO completely. Yengopal and Mickenautsch, in a systematic review, compared six regimens of using CHX for the prevention of AO and concluded that a single application of 0.2% CHX gel placed inside the alveolar socket following tooth extraction and participating in mouth rinsing with 0.12% CHX solution twice a day for seven days after operation are the most effective regimens for the prevention of AO. Dodson, in a review study of 21 trials with 2,570 participants, showed similar results for these two regimens. Dodson also recommended that all members of the dental team be aware of the potential adverse side effects of CHX. Requena-Calla and Funes-Rumiche worked with 40 patients and applied 0.12% CHX gel, and reported no relationship between CHX gel and the reduction of AO incidence. However, Freudenthal et al., as part of their double-blinded randomized study with...
Table 1. Studies considered with respect to their discussion of the prevention of AO

| Study                      | Main aspect                                                                 | Conclusion                                                                 |
|----------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Shepherd                   | The effects of CHX solution in the prevention of AO                          | Used preoperatively and seven days postoperatively, mouth rinse with 0.12% CHX had a significant preventive effect on AO incidence |
| Sridhar et al.             | The effects of CHX solution in the prevention of AO                          | Use of 0.2% CHX solution twice daily, for one day before and seven days after surgical extraction, can be beneficial for the prevention of AO |
| Metin et al.               | The effects of CHX solution in the prevention of AO                          | A one-week postoperative mouth rinse with 0.2% CHX solution regimen was adequate and there was no need to use CHX for one week before extraction of AO |
| Caso et al.                | The effects of CHX solution in the prevention of AO                          | Rinsing of the mouth with CHX solution after the extraction for several days reduced the incidence of AO |
| Delibasi et al.            | The effects of CHX solution in the prevention of AO                          | The effectiveness of 0.2% CHX solution was enhanced when used in combination with amoxicillin and clavulanic acid |
| Torres-Lagares et al.      | The effects of CHX gel in the prevention of AO                               | 0.2% CHX gel was a good prophylactic agent and can be applied only once in the intra-alveolar site after impacted third molar extraction to reduce the edema and AO incidence |
| Hita-Iglesias et al.       | The effects of CHX gel in the prevention of AO                               | Bioadhesive 0.2% CHX gel has a larger advantage and capability in reducing the incidence of AO than the solution |
| Abu-Mostafa et al.         | The effects of CHX gel in the prevention of AO                               | 0.2% CHX gel was more effective than 0.12% CHX solution in reducing the incidence of AO |
| Minguez-Serra et al.       | The effects of CHX gel in the prevention of AO                               | 0.2% CHX gel applied twice daily for seven days after tooth extraction was more effective than 0.12% CHX mouth rinse in reducing the incidence of AO |
| Torres-Lagares et al.      | The effects of CHX gel in the prevention of AO                               | Bioadhesive 0.2% CHX gel reduced the incidence of AO by up to 57.15% in patients with bleeding complications |
| Rodríguez-Pérez et al.     | The effects of CHX gel in the prevention of AO                               | There were no differences seen with using 1% CHX or 0.2% CHX gel twice daily for seven days in terms of reducing the incidence of AO |
| Barbar et al.              | The effects of CHX gel in the prevention of AO                               | A significant reduction in incidence of AO by a single application of CHX gel following mandibular third molar surgery was seen |
| Haraji and Rakhshan        | The effects of CHX gel in the prevention of AO                               | A single-dose of intra-alveolar placement of 0.2% CHX gel can reduce the incidence of AO |
| Jesudasan et al.           | The effects of CHX gel in the prevention of AO                               | The use of 0.2% CHX gel could reduce incidence of AO, but postoperative placement of eugenol-based paste could eliminate AO completely |
| Yengopal and Mickenautsch  | The effects of CHX gel in the prevention of AO                               | A single application of 0.2% CHX gel placed inside the alveolar socket following tooth extraction and rinsing the mouth with 0.12% CHX solution twice a day for seven days after surgery are the most effective regimens for the prevention of AO |
| Dodson                    | The effects of CHX gel in the prevention of AO                               | The single application of 0.2% CHX gel placed inside the alveolar socket and mouth rinsing with 0.12% CHX solution twice a day for seven days after surgery are the most effective regimens for the prevention of AO |
| Requena-Calla and Funes-Rumiche | The effects of CHX gel in the prevention of AO                           | There is no relationship between 0.12% CHX gel application and the reduction of AO incidence |
| Freudenthal et al.         | The effects of CHX gel in the prevention of AO                               | There is doubt regarding the application of CHX gel for the prevention of AO and patients’ postoperative analgesic consumption reproduced the development of AO |
| Hedström and Sjögren       | The effects of antibiotic agents in the prevention of AO                    | Local treatment of the extraction site with tetracycline showed a great reduction of risk of AO |
| Bosco et al.               | The effects of antibiotic agents in the prevention of AO                    | Tetracycline could reduce the occurrence of AO and cause significant changes in the microbiota of the extraction site by decreasing the number of anaerobes while increasing the amount of tetracycline-resistant and multi-resistant microorganisms |
| Sanchis et al.             | The effects of antibiotic agents in the prevention of AO                    | Intra-alveolar placement of tetracycline compound did not affect the incidence of AO |
| Bergdahl and Hedström      | The effects of antibiotic agents in the prevention of AO                    | The use of 1,600 mg of metronidazole did not significantly reduce the incidence of AO |
| Reekie et al.              | The effects of antibiotic agents in the prevention of AO                    | The use of topical metronidazole did not significantly reduce the incidence of AO |

100 extraction cases, did not verify the same observation and casted doubt upon the application of CHX gel for the prevention of AO. These authors claimed that patients' postoperative analgesic consumption reproduced the development of AO. (Table 1, Fig. 1)

3) The proangiogenic effects of chlorhexidine gluconate
The proangiogenic effects of CHX have not been previously evaluated. Saghiri et al. reported that 2% CHX may exhibit cytotoxic effects on dental pulp stem cells. Considering the levels of CHX and povidone iodine used routinely in the
oral cavity, these results suggest that CHX has a higher cytotoxicity profile than povidone iodine. This observation might have some clinical relevance regarding the potential utility of povidone iodine in the prevention of AO. CHX complications such as bad taste, alterations in taste, numbness in the tongue, and staining of dentures and oral cavity tissues have been reported. In addition, anaphylactic reaction to CHX has been recently observed.

2. Antibiotics

1) Tetracycline

Hedström and Sjögren, in a systematic review of 32 randomized controlled trials, showed that local treatment of the extraction site with tetracycline prompted a great reduction in risk for AO. Bosco et al. used local tetracycline for the prevention of AO in rats and concluded that tetracycline could reduce the occurrence of AO. This treatment also caused significant changes in the microbiota of the extraction site by decreasing the number of anaerobes while increasing the amount of tetracycline-resistant and multi-resistant microorganisms. Sanchis et al., in a postoperative study of 200 impacted mandibular third molar extractions, concluded that intra-alveolar placement of tetracycline compound did not affect the incidence of AO.

2) Metronidazole

Bergdahl and Hedström, in a randomized controlled trial of 119 patients, showed that the administration of 1,600 mg of metronidazole did not significantly reduce the incidence of AO. Reekie et al., in a randomized study of 302 patients seen in three general dental practices by general dental prac-
Tactors working in England during the time period of 2000 to 2003, concluded that topical metronidazole did not significantly reduce the incidence of AO. Neugebauer et al., in an intra-individual study on 100 patients, showed that antimicrobial photodynamic therapy can be used for the prevention of AO.

3) Azithromycin

Ishihama et al., in a retrospective single-center review of 45 patients, concluded that the usage of azithromycin as a prophylactic agent for the prevention of AO did not significantly reduce the rate of AO. Bascones-Martinez et al., in a clinical trial of 400 women using tobacco and oral contraceptives, showed that azithromycin was significantly superior for post-extraction treatment versus saline for the prevention of AO.

4) Systemic antibiotics

Halpern and Dodson, in their study of 118 subjects who used systemic antibiotics (e.g., penicillin or clindamycin for penicillin-allergic subjects) in an intravenous form, concluded a significant reduction in AO or surgical site infection occurred with drug administration. Ren and Malmström, in a meta-analysis of 16 randomized controlled clinical trials including 2,932 patients, reported that systemic antibiotics used prior to surgery could effectively reduce the frequency of AO.

5) Lincomycin

Wiśniewska et al., in a study of 80 patients, showed that lincomycin could significantly prevent the incidence of AO.

6) Amoxicillin

Olusanya et al., in a randomized experiment including 42 patients, employed a five-day regimen of oral 500 mg amoxicillin capsules and 400 mg metronidazole tablets three times daily. These authors concluded that, while a single bolus antibiotic prophylaxis may be effective in the reduction of pain, swelling, and trismus, in case of reducing the risk of AO, five-day postoperative consumption is advisable. Marcussen et al., in a systematic review of randomized controlled trials, reported that the prophylactic use of amoxicillin for reducing the risk of
AO was only effective when it was used in combination with clavulanic acid. (Table 1, Fig. 1)

7) The proangiogenic effects of antibiotics

There are few studies available to date that have investigated the proangiogenic effects of antibiotics used for the prevention of AO. Mathe et al.\(^6\) showed that tetracycline can increase the expression of vascular endothelial growth factor and prompt better revascularization of the treated tissues. Rawal and Rawal\(^7\) evaluated the nonantimicrobial properties of tetracycline and reported that it can regulate the angiogenesis processes, stimulate osteoblastic bone formation, and inhibit osteoclast function.

3. Other materials

Bloomer\(^7\), in his study of 100 patients, indicated that the immediate packing of the extraction site with filament gauze containing 9% eugenol, 36% balsam of Peru, and 55% petroleum jelly could reduce the risk of AO. Poor et al.\(^2\), in a retrospective investigation, showed that SaliCept patches containing Acemannan hydrogel (Carrington Laboratories, Irving, TX, USA) placed after extraction could significantly reduce the incidence of AO as compared with the placement of clindamycin-soaked Gelfoam (Pharmacia and Upjohn, Kalamazoo, MI, USA). Rutkowski et al.\(^7\), in their analysis of 904 extraction cases, suggested that the application of platelet-rich plasma (PRP) at the extraction site could be used as a cost-effective technique for the prevention of AO. (Fig. 2) However, Barona-Dorado et al.\(^7\), after performing a systematic review including 101 articles, concluded that more clinical trials must be conducted before the recommendation of PRP for the treatment of the extraction site after operation can be taken seriously. Tek et al.\(^7\), in their study of 100 extraction cases, found that the application of platelet-rich fibrin (PRF) could significantly decrease the incidence of AO. (Table 1, Fig. 2)

1) The proangiogenic effects of these other materials

Manikandan et al.\(^7\) showed that eugenol is a phytochemical agent with remarkable abilities to alter the equilibrium between pro- and anti-angiogenic proteins and to disturb the balance between the stimulators and inhibitors of angiogen-

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**Fig. 2.** A schematic presentation of the mechanisms of action of hemostatic agents placed inside the alveolar socket for the prevention of AO. (PRP: platelet-rich plasma, PRF: platelet-rich fibrin, VEGF: vascular endothelial growth factor, FGF: fibroblast growth factor, AO: alveolar osteitis).

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esis at the application site. Kobayashi et al. reported that PRP and PRF can act both as scaffolding and reservoirs for angiogenic factors during the wound-healing period. One of the limitations of the present study is its exclusive attention paid to the biomaterials used for AO treatment without the consideration of the quality or nature of the studies (i.e., in vivo, in vitro, case report, review).

V. Conclusion

In this review, the proangiogenic impacts of materials used for the prevention of AO were discussed. According to the reviewed studies, the following conclusions can be drawn:

- The proangiogenic properties of CHX have not been evaluated thus far. However, CHX has several cytotoxic effects.
- Among antibiotics used for the prevention of AO, only the proangiogenic effects of tetracycline were investigated, with promising effects identified. However, there is still a lack of information about the proangiogenic properties of other antibiotics.
- PRP and PRF are other beneficial and proangiogenic materials used for the prevention of AO.
- Generally speaking, angiogenesis is of great importance during the socket-healing period occurring after extraction, and it is beneficial if preventive strategies of AO are directed toward more proangiogenic materials and modalities.

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Authors’ Contributions

M.A.S. participated in study design, preparation of figures, and manuscript writing. A.A. participated in data collection and writing the manuscript. N.S. participated in data analysis, coordination and helped in manuscript writing and edition. All authors read and approved the final manuscript.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

References

1. Dohan DM, Choudrouk J, Diss A, Dohan SL, Dohan AJ, Mouhyi J, et al. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part III: leukocyte activation: a new feature for platelet concentrates? Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;101:e51-5.
2. Huesch RF, Coleman RD, Frandsen AM, Becks H. The healing process following molar extraction. I. Normal male rats (long-evans strain). Oral Surg Oral Med Oral Pathol 1952;5:864-76.
3. Blum IR. Contemporary views on dry socket (alveolar osteitis): a clinical appraisal of standardization, aetiology and management: a critical review. Int J Oral Maxillofac Surg 2002;31:309-17.
4. Fazakerley M, Field E.A. Dry socket: a painful post-extraction complication (a review). Dent Update 1991;18:31-4.
5. Rood JP, Danford M. Metronidazole in the treatment of “dry socket”. Int J Oral Surg 1981;10:345-7.
6. Rud J. Removal of impacted lower third molars with acute pericoronitis and necrotising gingivitis. Br J Oral Surg 1970;7:153-60.
7. Swanson AE. A double-blind study on the effectiveness of tetracycline in reducing the incidence of fibrinolytic alveolitis. J Oral Maxillofac Surg 1989;47:165-7.
8. Birn H. Etiology and pathogenesis of fibrinolytic alveolitis (“dry socket”). Int J Oral Surg 1973;2:211-63.
9. MacGregor AJ. Aetiology of dry socket: a clinical investigation. Br J Oral Surg 1968;4:49-58.
10. Sweet JB, Butler DP. The relationship of smoking to localized osteitis. J Oral Surg 1979;37:732-5.
11. Catellani JE, Harvey S, Erickson SH, Cherkin D. Effect of oral contraceptive cycle on dry socket (localized alveolar osteitis). J Am Dent Assoc 1980;101:777-80.
12. Oginni FO, Fatusi OA, Alagbe AO. A clinical evaluation of dry socket in a Nigerian teaching hospital. J Oral Maxillofac Surg 2003;61:871-6.
13. el-Khateeb TL, el-Marsafi AI, Butler NP. The relationship between the indications for the surgical removal of impacted third molars and the incidence of alveolar osteitis. J Oral Maxillofac Surg 1991;49:141-5; discussion 145-6.
14. Lilly GE, Osbon DB, Rael EM, Samuels HS, Jones JC. Alveolar osteitis associated with mandibular third molar extractions. J Am Dent Assoc 1974;88:802-6.
15. Alexander RE. Dental extraction wound management: a case against medicating postextraction sockets. J Oral Maxillofac Surg 2000;58:538-51.
16. Butler DP, Sweet JB. Effect of lavage on the incidence of localized osteitis in mandibular third molar extraction sites. Oral Surg Oral Med Oral Pathol 1977;44:14-20.
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17. Meechan JG, Venchard GR, Rogers SN, Hobson RS, Prior I, Tavares C, et al. Local anaesthesia and dry socket. A clinical investigation of single extractions in male patients. Int J Oral Maxillofac Surg 1987;16:279-84.

18. Krekmanov L. Alveolitis after operative removal of third molars in the mandible. Int J Oral Surg 1981;10:173-9.

19. Rood JP, Murgatrody J. Metronidazole in the prevention of ‘dry socket’. Br J Oral Surg 1979;17:62-70.

20. Ritzau M, Swangsilpa K. The prophylactic use of propylc ester of p-hydrobenzoic acid on alveolitis sicca dolorosa. A preliminary report. Oral Surg Oral Med Oral Pathol 1977;43:32-7.

21. Sweet JB, Macynski AA. Effect of antimicrobial mouth rinses on the incidence of localized alveolitis and infection following mandibular third molar oral surgery. Oral Surg Oral Med Oral Pathol 1985;59:24-6.

22. Field EA, Nind D, Varga E, Martin MV. The effect of chlorhexidine irrigation on the incidence of dry socket: a pilot study. Br J Oral Maxillofac Surg 1988;26:395-401.

23. Ragno Jr Jr, Szkatunik AJ. Evaluation of 0.12% chlorhexidine rinse on the prevention of alveolar osteitis. Oral Surg Oral Med Oral Pathol 1991;72:524-6.

24. Swanson AE. Prevention of dry socket: an overview. Oral Surg Oral Med Oral Pathol 1990;70:131-6.

25. Poor MR, Hall JE, Poor AS. Reduction in the incidence of alveolar osteitis in patients treated with the SalifCept patch, containing Acsmann hydrogel. J Oral Maxillofac Surg 2002;60:374-9; discussion 379.

26. Nitzan DW. On the genesis of ‘dry socket’. J Oral Maxillofac Surg 1983;41:706-10.

27. Araiyo MG, Silva CO, Misawa M, Sukavaka F. Alveolar socket healing: what can we learn? Periodontol 2000 2015;68:122-34.

28. Choukroun J, Diss A, Simonpietri A, Girard MO, Schoeffler C, Dohan SL, et al. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part IV: clinical effects on tissue healing. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;101:e56-60.

29. Saghiri MA, Asatourian A, Sorenson CM, Sheibani N. Role of angiogenesis in endodontics: contributions of stem cells and proangiogenic and antiangiogenic factors to dental pulp regeneration. Int Endod J 2015;41:797-803.

30. Saghiri MA, Asatourian A, Garcia-Godoy F, Sheibani N. The role of angiogenesis in implant dentistry part II: the effect of bone-grafting and barrier membrane materials on angiogenesis. Med Oral Patol Oral Cir Bucal 2016;21:e526-37.

31. Saghiri MA, Asatourian A, Garcia-Godoy F, Sheibani N. The role of angiogenesis in implant dentistry part I: review of titanium alloys, surface characteristics and treatments. Med Oral Patol Oral Cir Bucal 2016;21:e514-25.

32. Dvorak HF, Harvey VS, Estrella P, Brown LF, McDonagh J, Dvorak AM. Fibrin containing gels induce angiogenesis. Implications for tumor stroma generation and wound healing. Lab Invest 1987;57:673-86.

33. Seymour RA, Heasman PA. Anti-plaque and anti-calculus agents. In: Seymour RA, Heasman PA, MacGregor ID, eds. Drugs, diseases, and the periodontium. Oxford and New York: Oxford University Press; 1992:153-79.

34. Shepherd J. Pre-operative chlorhexidine mouth rinses reduce the incidence of dry socket. Evid Based Dent 2007;8:43.

35. Sridhar V, Wali GG, Shyla HN. Evaluation of the perioperative use of 0.2% chlorhexidine gluconate for the prevention of alveolar osteitis after the extraction of impacted mandibular third molars: a clinical study. J Maxillofac Oral Surg 2011;10:101-11.

36. Metin M, Tek M, Sener I. Comparison of two chlorhexidine rinse protocols on the incidence of alveolar osteitis following the surgical removal of impacted third molars. J Contemp Dent Pract 2006;7:79-86.

37. Caso A, Hung LK, Beirne OR. Prevention of alveolar osteitis with chlorhexidine: a meta-analytic review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;99:155-9.

38. Delibiasi C, Saracoglu U, Keskini A. Effects of 0.2% chlorhexidine gluconate and amoxicillin plus clavulanic acid on the prevention of alveolar osteitis following mandibular third molar extractions. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002;94:301-4.

39. Torres-Lagares D, Infante-Cossio P, Gutierrez-Perez JL, Romero-Ruiz MM, Garcia-Calderon M, Serrera-Figallo MA. Intra-alveolar chlorhexidine gel for the prevention of dry socket in mandibular third molar surgery. A pilot study. Med Oral Patol Oral Cir Bucal 2006;11:E179-84.

40. Hidalgolesias P, Torres-Lagares D, Flores-Ruiz R, Magallanes-Abad N, Basalote-Gonzalez M, Gutierrez-Perez JL. Effectiveness of chlorhexidine gel versus chlorhexidine rinse in reducing alveolar osteitis in mandibular third molar surgery. J Maxillofac Surg 2008;66:441-5.

41. Abu-Mostoafa NA, Aqlahtani A, Abu-Hasna M, Alhokai A, Aladsani A. A randomized clinical trial compared the effect of intra-alveolar 0.2 % chlorhexidine bio-adhesive gel versus 0.12% chlorhexidine rinse in reducing alveolar osteitis following molar teeth extractions. Med Oral Patol Oral Cir Bucal 2015;20:e82-7.

42. Miguez-Serra MP, Salort-Llorca C, Silvestre-Donat FJ. Chlorhexidine in the prevention of dry socket: effectiveness of different dosage forms and regimens. Med Oral Patol Oral Cir Bucal 2009;14:e445-9.

43. 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;35:548-51.

44. Rodrigue-Perez M, Bravo-Perez M, Sanchez-Lopez JD, Muoz-Soto E, Romero-olid MN, Baca-Garcia P. Effectiveness of 1% versus 0.2% chlorhexidine gels in reducing alveolar osteitis from mandibular third molar surgery: a randomiz, double-blind clinical trial. 2013;18:e693-700.

45. Babar A, Ibrahim MW, Baig NJ, Shah I, Amin E. Efficacy of intra-alveolar chlorhexidine gel in reducing frequency of alveolar osteitis in mandibular third molar surgery. J Coll Physicians Surg Pak 2012;22:91-4.

46. Harangi A, Rakshan V. Single-dose intra-alveolar chlorhexidine gel application, easier surgeries, and younger ages are associated with reduced dry socket risk. J Oral Maxillofac Surg 2014;72:259-65.

47. Jesusadan JS, Wahab PU, Sekhar MR. Effectiveness of 0.2% chlorhexidine gel and a eugenol-based paste on postoperative alveolar osteitis in patients having third molars extracted: a randomised controlled clinical trial. Br J Oral Maxillofac Surg 2015;53:826-30.

48. Yengopol V, Mickenatsch S. Chlorhexidine for the prevention of alveolar osteitis. Int J Oral Maxillofac Surg 2012;41:1253-64.

49. Dodson T. Prevention and treatment of dry socket. Evid Based Dent 2013;14:13-4.

50. Requena-Calla S, Funes-Rumiche I. Effectiveness of intra-alveolar chlorhexidine gel in reducing dry socket following surgical extraction of lower third molars. A pilot study. J Clin Exp Dent 2016;8:e160-3.

51. Freudenthal N, Sternudd M, Jansson L, Wannfors K. A double-blind randomized study evaluating the effect of intra-alveolar chlorhexidine gel on alveolar osteitis after removal of mandibular third molars. J Oral Maxillofac Surg 2015;73:600-5.

52. Saghiri MA, Asatourian A, Garcia-Godoy F, Sheibani N. Effect of biomaterials on angiogenesis during vital pulp therapy. Dent Mater J 2016;35:701-9.

53. 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.

54. Pemberton MN. Allergy to chlorhexidine. Dent Update 2016;43:272-4.

55. Hedström L, Sjögren P. Effect estimates and methodological qual-
ity of randomized controlled trials about prevention of alveolar osteitis following tooth extraction: a systematic review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103:8-15.
56. Bosco JM, de Oliveira SR, Bosco AF, Schweitzer CM, Jardim Júnior EG. Influence of local tetracycline on the microbiota of alveolar osteitis in rats. Braz Dent J 2008;19:119-23.
57. Sanchis JM, Sáez U, Peñarrocha M, Gay C. Tetracycline compound placement to prevent dry socket: a postoperative study of 200 impacted mandibular third molars. J Oral Maxillofac Surg 2004;62:587-91.
58. Bergdahl M, Hedström L. Metronidazole for the prevention of dry socket after removal of partially impacted mandibular third molar: a randomised controlled trial. Br J Oral Maxillofac Surg 2004;42:555-8.
59. Reekie D, Downes P, Devlin CV, Nixon GM, Devlin H. The prevention of 'dry socket' with topical metronidazole in general dental practice. Br Dent J 2006;200:210-3.
60. Neugebauer J, Jozua M, Kübler A. [Antimicrobial photodynamic therapy for prevention of alveolar ostitis and post-extraction pain]. Mund Kiefer Gesichtschir 2004;8:350-5. German.
61. Ishihama K, Kimura T, Yasui Y, Komaki M, Ota Y. Azithromycin as prophylaxis for the prevention of postoperative infection in impacted mandibular third-molar surgery. J Infect Chemother 2006;12:31-5.
62. Bascones-Martinez A, Reche I, Manso F, González-Moles MA, Bravo M. Prevention of alveolar osteitis with azithromycin in women according to use of tobacco and oral contraceptives. Quintessence Int 2007;38:295-300.
63. Halpern LR, Dodson TB. Does prophylactic administration of systemic antibiotics prevent postoperative inflammatory complications after third molar surgery? J Oral Maxillofac Surg 2007;65:177-85.
64. Ren YF, Malmstrom HS. Effectiveness of antibiotic prophylaxis in third molar surgery: a meta-analysis of randomized controlled clinical trials. J Oral Maxillofac Surg 2007;65:1909-21.
65. Wiśniewska I, Słosarczyk A, Myśliwiec L, Sporniak-Tutak K. [Lincomycin applied to the alveolus on TCP carrier and its effect on wound healing after surgical extraction of a third molar]. Ann Acad Med Silesi 2009;55:59-64. Polish.
66. Olusanya AA, Arotiba JT, Fasola OA, Akadiri AO. Prophylaxis versus pre-emptive antibiotics in third molar surgery: a randomised control study. Niger Postgrad Med J 2011;18:105-10.
67. Marcusen KB, Lautlund AS, Jørgensen HL, Pinholt EM. A systematic review on effect of single-dose preoperative antibiotics at surgical osteotomy extraction of lower third molars. J Oral Maxillofac Surg 2016;74:693-703.
68. Arteagoitia MI, Barbier L, Santamaria J, Santamaria G, Ramos E. Efficacy of amoxicillin and amoxicillin/clavulanic acid in the prevention of infection and dry socket after third molar extraction. A systematic review and meta-analysis. Med Oral Patol Oral Cir Bucal 2016;21:e494-504.
69. Mathé Z, Dupraz P, Rinsch C, Thorens B, Bosco D, Zbinden M, et al. Tetracycline-regulated expression of VEGF-A in beta cells induces angiogenesis: improvement of engraftment following transplantation. Cell Transplant 2006;15:621-36.
70. Rawal SY, Rawal YB. Non-antimicrobial properties of tetracyclines--dental and medical implications. West Indian Med J 2001;50:105-8.
71. Bloomer CR. Alveolar osteitis prevention by immediate placement of medicated packing. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000;90:282-4.
72. Rutkowski JL, Fennell JW, Kern JC, Madison DE, Johnson DA. Inhibition of alveolar osteitis in mandibular tooth extraction sites using platelet-rich plasma. J Oral Implantol 2007;33:116-21.
73. Barona-Dorado C, González-Regueiro I, Martín-Ares M, Arias-Irimia O, Martínez-González JM. Efficacy of platelet-rich plasma applied to post-extraction retained lower third molar alveoli. A systematic review. Med Oral Patol Oral Cir Bucal 2014;19:e142-8.
74. Tek M, Akkas I, Toptas O, Ozan F, Sener I, Bereket C. Effects of the topical hemostatic agent Ankaferd Blood Stopper on the incidence of alveolar osteitis following tooth extraction. Br J Oral Maxillofac Surg 2015;53:328-31.
75. Eshghpour M, Dastmalchi P, Nekooei AH, Nejat A. Effect of platelet-rich fibrin on frequency of alveolar ostitis following mandibular third molar surgery: a double-blinded randomized clinical trial. J Oral Maxillofac Surg 2014;72:1463-7.
76. Manikandan P, Murugan RS, Priyadarisini RV, Vinothini G, Nagini S. Eugenol induces apoptosis and inhibits invasion and angiogenesis in a rat model of gastric carcinogenesis induced by MNNG. Life Sci 2010;86:936-41.
77. Kobayashi M, Kawase T, Okuda K, Wolff LF, Yoshie H. In vitro immunological and biological evaluations of the angiogenic potential of platelet-rich fibrin preparations: a standardized comparison with PRP preparations. Int J Implant Dent 2015;1:31.
78. Saghir MA, Saghir AM. In memoriam: Dr. Hajar Afsar Lajevardi MD, MSc, MS (1955-2015). Iran J Pediatr 2017;27:e8093.