



# Angiogenesis and the prevention of alveolar osteitis: a review study

Mohammad Ali Saghiri<sup>1,2</sup>, Armen Asatourian<sup>3</sup>, Nader Sheibani<sup>1,2</sup>

*Departments of<sup>1</sup>Ophthalmology and Visual Sciences and<sup>2</sup>Biomedical Engineering, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA, <sup>3</sup>Angiogenesis Regenerative Medicine Sector, Dr. H. Afsar Lajevardi Research Cluster (DHALC), Shiraz, Iran*

**Abstract** (J Korean Assoc Oral Maxillofac Surg 2018;44:93-102)

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

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## 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 process<sup>1,2</sup>. The condition is also referred to as alveolgia, localized osteitis, fibrinolytic alveolitis, alveolitis sicca dolorosa, and necrotic or septic socket<sup>3</sup>. 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 cases<sup>3,4</sup>. It is most

commonly seen in patients aged between 40 years and 45 years<sup>5,6</sup>. 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 evident<sup>7</sup>.

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 fibrinolysis<sup>8</sup>. Several contributing and risk factors have been identified that increase the incidence of AO. These include general factors such as sex<sup>8,9</sup>; smoking<sup>10</sup>; the use of oral contraceptives<sup>11</sup>; and local factors such as the site of extraction<sup>9,12</sup>, the presence of preoperative infection<sup>13</sup>, traumatic extraction<sup>14</sup>, a low level of operator experience<sup>15</sup>, inadequate postoperative irrigation<sup>16</sup>, and/or the use of local anesthetics with vasoconstrictors<sup>17</sup>. The management of AO includes preventive methods such as using clot-supporting agents<sup>3</sup>, antibiotics<sup>18,19</sup>, antifibrinolytic agents<sup>20</sup>, antiseptic mouth rinses<sup>21-23</sup>, steroids<sup>24</sup>, and curative methods such as intra-alveolar dressings and medicaments<sup>25,26</sup>.

### Mohammad Ali Saghiri

*Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health, 1111 Highland Avenue, 9418 WIMR, Madison, WI 53705, USA*

TEL: +1-608-263-3345

E-mail: [saghiri@wisc.edu](mailto:saghiri@wisc.edu)

ORCID: <https://orcid.org/0000-0002-5064-7828>

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The healing process of alveolar socket after tooth extraction is divided into three overlapping stages, specifically the inflammatory, proliferative, and remodeling stages. During the inflammatory stage, first, the blood clot is formed from the hemorrhage that occurs due to tooth extraction. At two days to three days, numerous inflammatory cells migrate to the socket to clean the area. A granulation tissue is then formed by sprouting angiogenesis and the migration of immature fibroblasts. Subsequently, in the proliferative stage, the granulation tissue becomes rich in collagen fibers and cells, which provide a connective tissue matrix for rapid tissue formation. In this stage, several vessels and osteogenic cells are present and woven bone formation is initiated. Woven bone is a temporary type of bone with no load-bearing potential that can be present at up to two weeks after the extraction. In addition, in the proliferative stage, the oral epithelial cell migration begins from the marginal gingiva to form the epithelial coverage. During the bone remodeling stage, the architecture and shape of the woven bone changes and is replaced with lamellar bone and bone marrow, a process that may take several months to years<sup>27</sup>. Choukroun et al.<sup>28</sup> indicated that the most important and crucial aspects of healing include angiogenesis, immunity, the recruitment of circulating stem cells, and the assurance of wound protection by epithelial coverage.

Angiogenesis is defined as the formation of new blood vessels from preexisting capillaries through endothelial cell sprouting<sup>29-31</sup>. During the socket healing process, the fibrin matrix inside the blood clot provides a provisional matrix that supports the migration of sprouting endothelial cells<sup>32</sup>. Angiogenesis is one of the essential events that occurs during the socket healing process and provides the inflammatory cells, growth factors, and progenitor cells that are required in the inflammatory and proliferative stages of socket healing. In addition, the regeneration and wound healing of alveolar bone is directly dependent on the angiogenesis process. In the present review, we provide an overview of the angiogenic potential of materials commonly used for the treatment and prevention of AO. Our intentions were to evaluate whether the angiogenic characteristics of these materials are advantageous.

## II. Materials and Methods

### 1. The review purpose

The present review was performed to evaluate whether angiogenesis is associated with favorable prevention of AO.

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<sup>33</sup>. 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<sup>34</sup> 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.<sup>35</sup> 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.<sup>36</sup>, 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.<sup>37</sup>, 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. Delilbasi et al.<sup>38</sup>, 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.<sup>39</sup>, 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.<sup>40</sup> compared the effectiveness of 0.2% CHX gel versus 0.12% CHX solution in the prevention of AO in 73 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.<sup>41</sup>, 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.<sup>42</sup> 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.<sup>43</sup>, 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.<sup>44</sup> 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.<sup>45</sup>, 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<sup>46</sup> 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.<sup>47</sup> 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<sup>48</sup>, 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<sup>49</sup>, in a review study of 21 trials with 2,570 participants, showed similar results for these two regimens. Dodson<sup>49</sup> also recommended that all members of the dental team be aware of the potential adverse side effects of CHX. Requena-Calla and Funes-Rumiche<sup>50</sup> 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.<sup>51</sup>, 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 <sup>34</sup>	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. <sup>35</sup>	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. <sup>36</sup>	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
Caso et al. <sup>37</sup>	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
Delilbasi et al. <sup>38</sup>	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. <sup>39</sup>	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. <sup>40</sup>	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. <sup>41</sup>	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
Mínguez-Serra et al. <sup>42</sup>	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. <sup>43</sup>	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. <sup>44</sup>	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. <sup>45</sup>	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 <sup>46</sup>	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. <sup>47</sup>	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 <sup>48</sup>	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 <sup>49</sup>	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 <sup>50</sup>	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. <sup>51</sup>	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 <sup>55</sup>	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. <sup>56</sup>	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. <sup>57</sup>	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 <sup>58</sup>	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. <sup>59</sup>	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.<sup>52</sup> 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

**Table 1.** Continued

Study	Main aspect	Conclusion
Neugebauer et al. <sup>60</sup>	The effects of antibiotic agents in the prevention of AO	Antimicrobial photodynamic therapy can be used for the prevention of AO
Ishihama et al. <sup>61</sup>	The effects of antibiotic agents in the prevention of AO	Azithromycin as a prophylactic agent for the prevention of AO did not significantly reduce the rate of AO
Bascones-Martinez et al. <sup>62</sup>	The effects of antibiotic agents in the prevention of AO	Azithromycin was a significantly superior post-extraction treatment as compared with saline for the prevention of AO
Halpern and Dodson <sup>63</sup>	The effects of antibiotic agents in the prevention of AO	The use of systemic antibiotics (e.g., penicillin or clindamycin for penicillin-allergic subjects) in intravenous form could significantly reduce the incidence of AO and surgical site infection
Ren and Malmstrom <sup>64</sup>	The effects of antibiotic agents in the prevention of AO	Systemic antibiotics used before surgery could effectively reduce the frequency of AO
Wiśniewska et al. <sup>65</sup>	The effects of antibiotic agents in the prevention of AO	Lincomycin could significantly prevent the incidence of AO
Olusanya et al. <sup>66</sup>	The effects of antibiotic agents in the prevention of AO	Five-day postoperative consumption of oral 500 mg amoxicillin capsules three times daily and 400 mg metronidazole tablets three times daily is advisable for reducing the risk of AO
Marcussen et al. <sup>67</sup>	The effects of antibiotic agents in the prevention of AO	A single oral dose of 2 g of amoxicillin can effectively reduce the risk of surgical site infection and a single dose of 0.8 g of phenoxymethylpenicillin can significantly reduce the risk of AO
Arteagoitia et al. <sup>68</sup>	The effects of antibiotic agents in the prevention of AO	Prophylactic use of amoxicillin for reducing the risk of AO was only effective when it was used in combination with clavulanic acid
Bloomer <sup>71</sup>	The effects of different agents in the prevention of AO	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. <sup>25</sup>	The effects of different agents in the prevention of AO	SaliCept patches containing Acemannan hydrogel (Carrington Laboratories) placed after extraction could significantly reduce the incidence of AO in comparison with the use of clindamycin-soaked Gelfoam (Pharmacia and Upjohn)
Rutkowski et al. <sup>72</sup>	The effects of different agents in the prevention of AO	The application of PRP at the extraction site can be used as a cost-effective technique for the prevention of AO
Barona-Dorado et al. <sup>73</sup>	The effects of different agents in the prevention of AO	There should be more clinical trials conducted before the recommendation of PRP for the treatment of extraction site after operation can be made
Tek et al. <sup>74</sup>	The effects of antibiotic agents in the prevention of AO	The application of Ankaferd BloodStopper (Ankaferd Health Products) as a hemostatic agent did not significantly decrease the risk of AO
Eshghpour et al. <sup>75</sup>	The effects of antibiotic agents in the prevention of AO	PRF could significantly decrease the incidence of AO

(AO: alveolar osteitis, CHX: chlorhexidine gluconate, PRP: platelet-rich plasma, PRF: platelet-rich fibrin)

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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<sup>53</sup>. CHX complications such as bad taste, alterations in taste, numbness in the tongue, and staining of dentures and oral cavity tissues have been reported<sup>36,38</sup>. In addition, anaphylactic reaction to CHX has been recently observed<sup>54</sup>.

## 2. Antibiotics

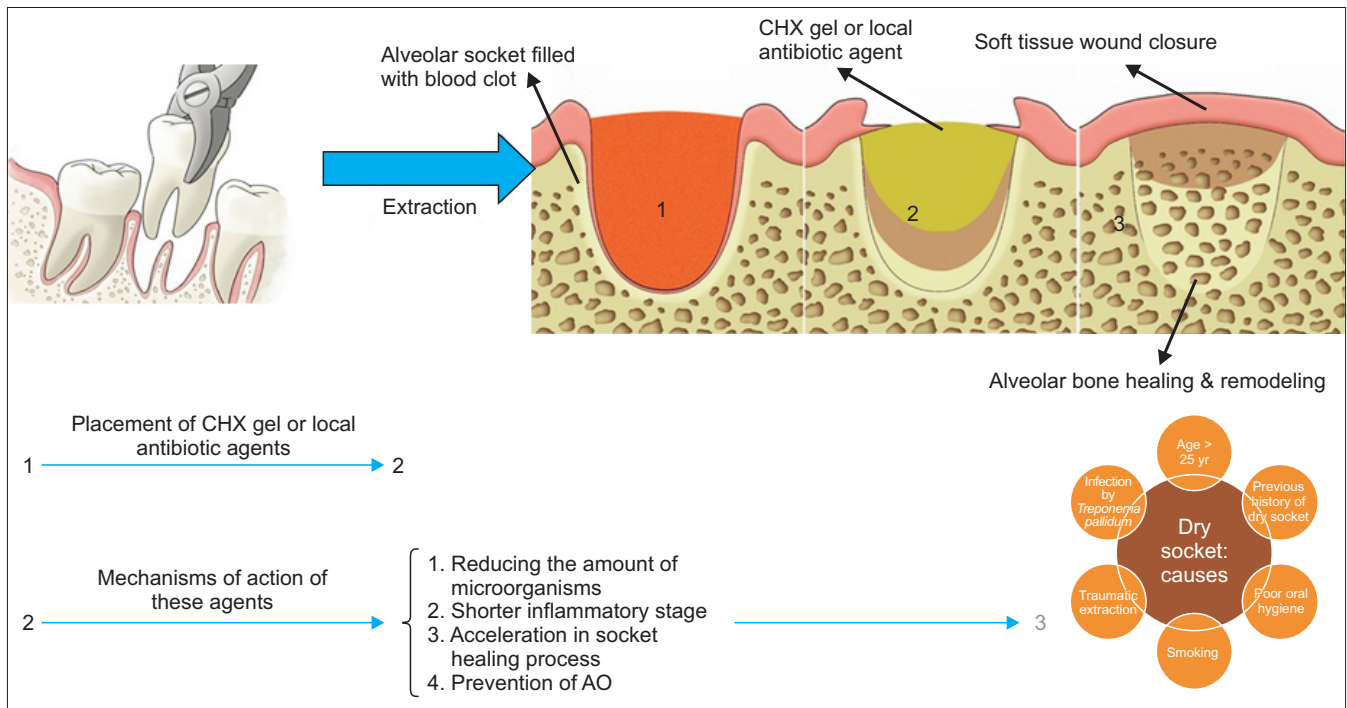
### 1) Tetracycline

Hedström and Sjögren<sup>55</sup>, 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.<sup>56</sup> used local tetracycline for the pre-

vention 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.<sup>57</sup>, 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<sup>58</sup>, 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.<sup>59</sup>, in a randomized study of 302 patients seen in three general dental practices by general dental prac-



**Fig. 1.** A schematic presentation of the mechanisms of action of chlorhexidine gluconate (CHX) gel and local antibiotic agents for the prevention of alveolar osteitis (AO).

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tioners 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.<sup>60</sup>, 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.<sup>61</sup>, 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.<sup>62</sup>, 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<sup>63</sup>, 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 Malmstrom<sup>64</sup>, 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.<sup>65</sup>, in a study of 80 patients, showed that lincomycin could significantly prevent the incidence of AO.

### 6) Amoxicillin

Olusanya et al.<sup>66</sup>, 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.<sup>67</sup>, in a systematic review of randomized controlled trials, reported that the consumption of a single oral dose of 2 g of amoxicillin could effectively reduce the risk of surgical site infection, while a single dose of 0.8 g of phenoxymethylpenicillin did significantly reduce the risk of AO. Arteagoitia et al.<sup>68</sup>, in a systematic review and meta-analysis of 10 papers, including extractions performed in 1997, showed 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.<sup>69</sup> showed that tetracycline can increase the expression of vascular endothelial growth factor and prompt better revascularization of the treated tissues. Rawal and Rawal<sup>70</sup> evaluated the nonantimicrobial properties of tetracycline and reported that it can regulate the angiogenesis processes, stimulate osteoblastic bone formation, and inhibit osteoclast function.

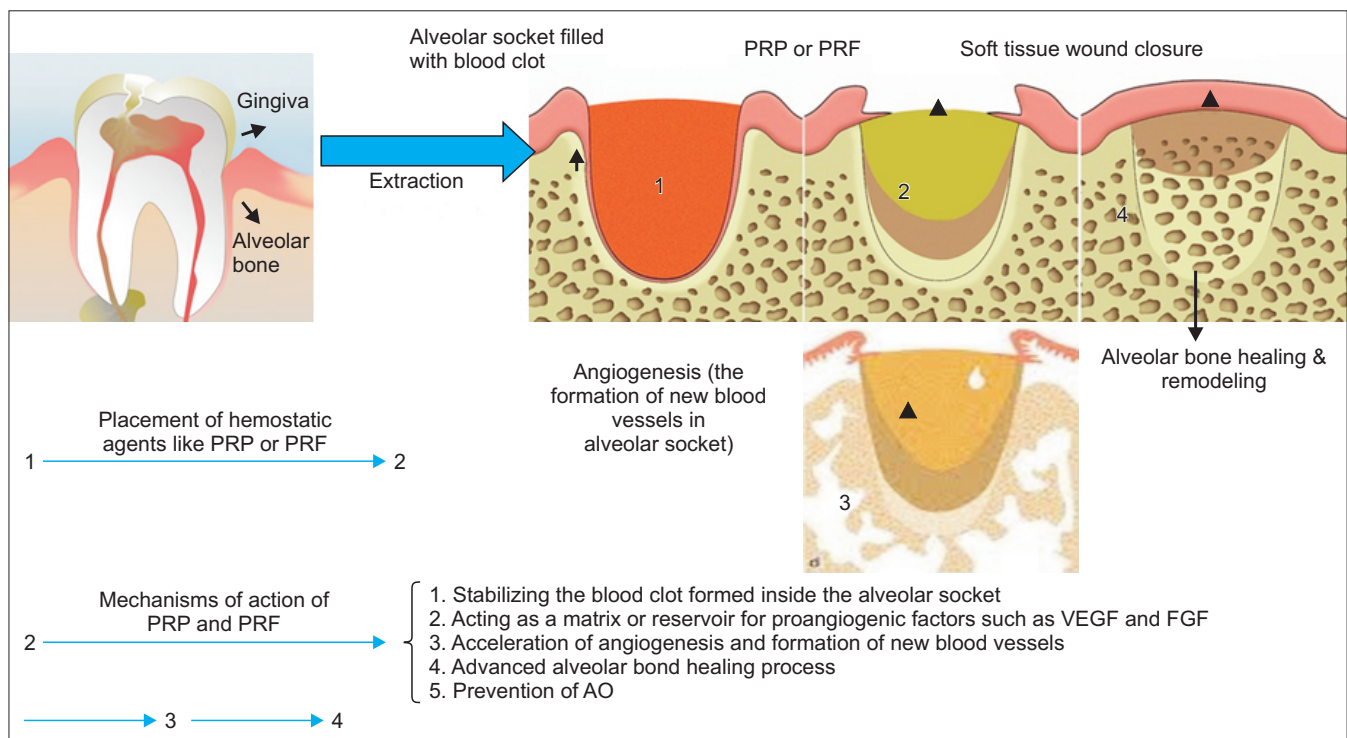
3. Other materials

Bloomer<sup>71</sup>, 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.<sup>25</sup>, 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.<sup>72</sup>, 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.<sup>73</sup>, 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.<sup>74</sup>, in their study of 100 extraction cases, found that the application of Ankaferd BloodStopper (Ankaferd Health Products, Istanbul, Turkey) as a hemostatic agent did not significantly decrease the risk of AO. Eshghpour et al.<sup>75</sup>, in a randomized clinical trial of 78 patients, showed that 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.<sup>76</sup> 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-



**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.<sup>77</sup> 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.

## ORCID

Mohammad Ali Saghiri, <https://orcid.org/0000-0002-5064-7828>

Armen Asatourian, <https://orcid.org/0000-0002-5948-1465>

Nader Sheibani, <https://orcid.org/0000-0003-2723-9217>

## 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.

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