Risk Factors, Etiology and Treatment Modalities for Localized Alveolar Ischemia (The So-called Alveolar Osteitis): A Comprehensive Critical Review

Mosaad Abdaljawwad Khalifah
Oral and Maxillofacial Surgery Department, Kafr El-Sheikh University, Egypt

ABSTRACT
Dry socket is a typically common post-odontectomy complication. Although blood clot disintegration is known to be the cause of the condition due to fibrinolysis, the exact pathogenesis of the clot loss is still poorly understood, and agreement is lacking regarding the relative merits of various treatment methods. The aim of the current review therefore was to perform a comprehensive critical review after qualitatively analyzing a large body of the literature in order to provide the practitioners with a more thorough insight for pathogenicity, risk factors and treatment.

In the current review, and in regards with risk factors; age, surgical trauma, smoking, oral contraceptives and poor oral hygiene seemed to be a major risk factors. In the treatment domain, Ozone based therapies were considered the most effective curative treatments followed by curettage. With regard to palliation, the most effective treatments were local anaesthetics, Zinc oxide eugenol after saline irrigation and. Although healers group provided a better healing promotion, but that does not necessitate a relevance with pain relief.

To conclude, I hypothesize that ischemia causes the blood clot loss, and I propose renaming the condition “localized alveolar ischemia”.

Keywords: Alveolar, Ischemia, Osteitis, Treatment, Pathogenesis, Terminology

Introduction
Alveolar osteitis (AO) is one of the most common complications of dental extraction (1). Despite multiple attempts to introduce a term that is more suitable than “dry socket” (2), “dry socket” remains the most widely used term, along with “alveolar osteitis”(1). Although Birn’s suggestion(3) that OA results from blood clot disintegration has gained wide acceptance, the exact etiology is still poorly understood (4) (5). Pain is the most important aspect of OA according to Fazakerlev and Field (6), and although a variety of treatment methods have been attempted to treat or alleviate this pain, considerable controversy exists regarding their relative efficacies (4)(7)(8). The aim of the current review was to critically address the available literature concerned with risk factors and treatment methods in order to provide dentists with a comprehensive overview of that common complication particularly in regards with its treatment modalities.

1. Nomenclature
Since 1896 when Crawford has introduced the term “dry socket” (5), this term is still widely used. Other term that is also commonly used is “alveolar osteitis”. However, other terms including “localized osteitis”, “alveolitis”, “localized alveolar osteitis”, “alveolitis sicca dolorosa”, “alveolalgia”, “necrotic socket”, “septic socket” did not gain the same acceptance even the term “fibrinolytic alveolitis” that was proposed by Birn. (3,7–9)

2. Definition
A variety of definitions has been reported. Blum considered “postoperative pain inside and around the extraction site, which increases in severity at any time between the first and third day after the extraction, accompanied by a partial or total disintegrated blood clot within the alveolar socket with or without halitosis” as a definition for that condition(8). Other identifiers for defining the condition included greyish discharge (10), inflamed gingival margin (11), low grade fever and ipsilateral regional lymphadenopathy (12,13); however, did not gain the same acceptance such as pain and clot loss either complete or partial.

3. Pathophysiology
Birn hypothesized that blood clot disintegration due to increased local fibrinolysis is the cause of the condition (3,14,15). The direct or indirect activation of plasminogen pathway was supposed as the underlying mechanism for fibrinolysis. While direct activators are produced by alveolar bone cells due to trauma, indirect activators are produced by bacteria (16). However, the initial causative mechanism for initiation of plasminogen activation and in turn blood clot disintegration is still not understood.
4. Risk factors

4.1 Age: Since AO is associated with the age range from 20 to 40 years (17,18) with a peak of incidence at 30 to 34 years (3), various authors agree that age is a major risk factor for the development of AO. Lehner tried to correlate that age range to the period of third molar eruption (18), nevertheless, Fridrich and Olson refuted that concept relying on the fact that third molar concept does not provide explanation for the total period from 20 to 40 years (12). Almost no cases were reported before 18 or after 50 years of age (17,18).

4.2 Gender: Gender as a risk factor was an area of debate. Although Cohen and Simecek (19); and MacGregor(17) associated AO increased incidence with female gender even if were not on contraceptives, Larsen (20) and Colby (21) denied that correlation. Reports before the 1960s shows no gender predilection (18,22). Schow reported that no difference in incidence between males and females who were not on contraceptives (23). Catellani showed similar results as Schow (24). The author reanalyzed data offered by Almeida et al (25) using Chi square with Yates correction and Fisher’s exact tests and found out a statistically insignificant difference between males and females not taking oral contraceptives ( Chi square = 2.261, the two-tailed P value = 0.1327, the two-tailed P value of Fisher’s exact test = 0.1235).

4.3 Surgical Trauma: The greater the surgical trauma, the higher the incidence of AO (3,7,9,21,26–29). That might be the reason behind the higher incidence of AO in cases of surgical extraction, third molar extraction (30,31) and lack of experience in extraction or oral surgery (7,20,32,33).

4.4 Oral Contraceptives: Despite the fact that Larsen did not consider oral contraceptives as a risk factor for higher incidence of AO (20), oral contraceptives use have been associated with the occurrence of AO (23,25,34–37) and in a dose dependent manner (38). Various authors agree that the fibrinolytic effect of oral contraceptives is responsible for the increased incidence of AO (24,35,39,40).

4.5 Smoking: Smoking is a well-accepted risk factor by several authors (8,28,36,41,42). Sweet and Butler noticed a dose dependent risk of increased AO incidence (35).

4.6 Oral Hygiene: Bacterial infection could lead to indirect activation of fibrinolysis and hence could be a risk factor that gained some acceptance (38,43,44). Other risk factors such as systemic diseases (26), local anaesthetics with vasoconstrictors (18), remaining bone fragments (3) and saliva (45) have been suggested, but no scientific evidence to support these claims.

5. Treatment:

5.1 Alvogyl (alv): It is a combination of eugenol which serves as an obtundent, iodoform as an antimicrobial and butamen as an anesthetic. Although alvogyl was an accepted treatment modality by several authors (7,46–48), other authors opposed its use (49,50).

5.2 Zinc oxide eugenol pack of freshly prepared mix (ZOE) Zinc oxide eugenol is a commonly used treatment agent (4,8,46,47,51–55). It is almost always applied after irrigating extraction socket with a normal saline.

5.3 Saline irrigation: Irrigating extraction socket with normal saline as a sole agent was scarcely recorded in the literature as a treatment for the condition. Up to the best of my knowledge, only two papers could be addressed in this regard (51,55).

5.4 G.E.C.B. Pastille: These pastilles are composed of 3% eugenol, 3% guaiacol (a precursor to eugenol) and 1.6% chlorobutanol (a weak local anaesthetic) as effective ingredients, and Balsam Peru as a base, and hence was its name. Haghighat et al advocated its use (54).

5.5 SalicCept Patch: Since consisting of Acemannnan hydrogel which is obtained from the clear inner gel of Aloe Vera, it functions as a healing promotor, immune-stimulant, reticuloendothelial function enhancer, antiviral, antibacterial and anti-inflammatory. Kaya et al recommended it (48).

5.6 Plasma rich in growth factors (PRGF): PRGF contains fibrinogen and platelets, so it promotes wound healing and osteogenesis as well. Of the growth factors found in PRGF are Platelet-derived Growth Factor (PDGF) and Tissue Growth Factor (TGF). It was described as a treatment by Pal et al (55) and as a preventive measure by Haraji et al (56).

5.7 Topical anesthetics: Burgoyne et used an antiseptic and anesthetic gel containing 2.5% prilocaine and 2.5% lidocaine and supported its use over zinc oxide eugenol (53).

5.8 Neocone : It is a mixture of the topical antibiotics polymyxin B sulfate (for Gram negative bacterial infection), tyrothricin (for Gram positive bacterial infection) and neomycin sulfate (for streptomycin-resistant bacteria); in addition to tetracaine hydrochloride (anaesthetic). It was used by Faizel et al as a recommended treatment (4).
5.9 **Vitamin C**: It is a well-known antioxidant and wound healing promoter which reduces infection and inflammation. It was proposed by Halberstein et al in the tablet form after performing curettage and irrigation of the socket. They reported a more than 50% remission by 2 days of treatment and a 100% remission by the fourth day (57).

5.10 **Low level laser therapy (LLLT)**: A 808 nm, 100-mW, 60 seconds and 7.64 J/cm² continuous mode Gallium-Aluminum arsenide diode laser has an antimicrobial potential and wound healing promotion capabilities; and thus, it was recommended by Kaya et al (48).

5.11 **Curettage (Cur)**: Although socket curettage and irrigation was an accepted maneuver by several authors (48,57–60), it was contraindicated by others (61–63). Khalifah MA (64) conducted a large prospective study in order to assess whether curettage is indicated or contraindicated and concluded that curettage is an accepted modality.

5.12 **Ozone gas (O₃)**: Medical grade Ozone is one treatment method that was advocated by Khalifah MA. Ozone has a potent germicidal action by both direct attack to the micro-organisms and by increasing the phagocytic capacity (65,66). Ozone increases Oxygen delivery to ischaemic tissues (67). Ozone is a powerful healer (68,69). O₃ is a recommended treatment by Khalifah MA (70).

5.13 **Ozonized water (OW)**: Mazánek et al (71) and Khalifah MA (70) supported OW as a treatment method.

5.14 **Ozonized oil (Oleozon) (Ole)**: Ole is an ozonized olive oil. Ole is recommended by Martinez-Abreu et al and by Khalifah MA (70).

Comparisons between two or more agents are scare in oral surgery literature (4). Nevertheless, Faizel et al recommended Neocone over alv and ZOE for a rapid and complete healing where they considered alv to be superior to ZOE and Neocone for initial pain relief (4). On contraire, Khalifah MA supported ZOE over alv (47). Although Pal et al advocated PRGF over ZOE with regards to healing, their study showed that ZOE was superior to PRGF in alleviating pain (55). Despite the fact that Kaya et al recorder better results for LLLT rather than those for alv, SalicCept and curettage, they considered alv and SalicCept to have the same results. It is worth noting that they performed curettage and irrigation for all patients (48).

On the other hand, Burgoyne et al recommended topical anaesthetic gel over ZOE (53). G.E.C.B. Pastilles were the treatment modality recommended by Haghighat over ZOE (54). Mazánek et al (71) supported Ole over alv. Khalifah MA concluded that Ozone in the gaseous form is the most potent form of ozone therapy. Although ozonized oil shows the weakest form, ozonized water had an intermediate potency (70).

**Discussion**

Since AO is by far one of the most common complication of odontectomy (3), a plethora of treatment protocols have been suggested to prevent and to treat this condition. However, results are quite controversial (46). Therefore, the author conducted the current review in order to provide a comprehensive critical qualitative analysis for a considered body from the literature for better understanding of the condition.

In regards with risk factors; age, oral contraceptives, surgical trauma, smoking and poor oral hygiene seemed to be major risk factors. AO is restricted with an age range of 18-50 years with a high incidence between 20 and 40 years and a peak of incidence at 30 to 34 years (3). This relationship could qualitatively be described as a somewhat steady increase of the incidence of AO between the age of 20 to 30 years, followed by a peak between 30 and 34 years before it steeply decreases between 34 to 40 years to end with a steady decrease to the age of 50 years. In more summarized description, it is an increase to reach a peak at thirties to decrease again. This scheme readily correlates with the that described by several authors (72) for the changes in Young’s modulus of elasticity with age. That means bone yields well at newborn and childhood period, followed by an adulthood period when it shows marked resistance to stresses to end again with somewhat yielding period as age increases.

Since extraction depends on socket dilatation, forces delivered to the bone should be well-withstood otherwise, undue compression of bone could result in ischemia. Resilient bone would readily yield and regain its previous condition as stress is removed. Age range related to the incidence of AO is that age range associated with marked bone stiffness (increased Young’s modulus of elasticity). The same principle could apply for surgical trauma as a risk factor. Fibrinolysis could account for considering oral contraceptives, poor oral hygiene as risk factors. Smoking might lead to poor circulation due to nicotine effect; and so, ischemia could issue.

Aging leads to increased bone porosity (73) and a decrease in bone toughness after the age of 35 years (74). As a result, porosity and increased microfractures on extraction are two factors to allow for channels through which circulation could have an access the blood clot and thus can maintain it. This could give reasons for the decreased incidence of
AO after the thirties. Moreover, Ritchie et al mentioned that by reviewing the national survey in their country, there is “one in two women and one in four men over the age of 50 suffers osteoporosis” (75). This might give account for the absence of AO cases over the age of 50 years.

Other risk factors are not supported by sufficient scientific evidence. Gender in particular should be precisely addresses away from the effect of oral contraceptives; and hence; the author does not consider gender to have a sufficient advocating scientific evidence as a risk factor.

Within the domain of treatment, the author grouped and categorized the reviewed treatment methods into seven categories. Obtundents are the first category where eugenol is the “main player “ in that group. Alv, ZOE and GECB are the members of that category. The second group is the group of the anaesthetic agents which include butamen, chlorobutanol, tetracaine and the alike drugs. The third group is the healers group and includes acemannan (Salicept), Vit C, LLLT and PRGF. This group promotes healing and could act as antimicrobial and anti-inflammatory. Antimicrobials are the fourth group and could have their effect by rehabilitating the extraction socket environment for better and faster healing by diminishing the bioburden. Normal saline acts as an osmolar that raises the saline content of the outermost layer of ES, and hence raising osmolarity at that side of ES which could ultimately lead to “recruiting” more blood through the ES walls. Enhanced circulation through the ES wall might have some role in eliminating the noxious substances and in providing that layer with nourishment and Oxygen. The sixth group consists of surgical curettage modality which depends on the removal of the existing socket walls to provoke bleeding in order to re-establish a new blood clot that would be capable of maintaining a more secure anatomical and physiological contact with the newly formed ES. The physiologic contact might be in the form of providing the clot with the necessary circulation which was previously prohibited in the case of the presence of the removed layer. The last group is Ozone dependent group which might rely on reversing the ischemic state that affected the bone of the socket. Members of this group are OW, Ole and O₂. The first two categories act on the free nerve endings within the bone by either denaturation or anaesthesia mechanisms respectively, thus it proceeds to eliminate pain and not to treat the pain source. The third and the fourth groups might have their effects by promoting healing. The fifth and the sixths categories depend on considering the outermost layer of the existing extraction socket wall as a barrier layer between the old blood clot and the inner layers of the extraction socket bone due to ischemia occurred in that layer as a result of failure to withstand the extraction forces. Therefore, saline was used in an attempt to reinvade that barrier layer with sufficient circulation in addition to removing the noxious and fibrinolytic substances liberated by the ischemic process. The last group is the direct anti-ischaemics in addition of possessing a potent germicidal and potent healing effects.

To re-summarize, there are three strategies where all reviewed treatments could accordingly be categorized under. The first strategy depends on direct addressing of the nerve and could be named as “the local analgesic strategy” and includes the first two categories mentioned here-above in the previous paragraph. The second strategy is “the healer strategy” and comprises the third and the fourth groups. The third strategy is “the anti-ischemic strategy” which consists of the fifth, the sixth and the seventh groups since saline osmolarity could help in enhancing perfusion and curettage removes the ischemic layer and on the other hand; OW, Ole and O₂ acts as reoxygenating agents. In the light of the current review, the recommendation of Neocone over ZOE in promoting healing made by Faizel et al (4) seems logic since Neocone contains multiple antimicrobials which promotes healing and anaesthetic, where ZOE acts only as a nerve obtundent. An outstanding finding in that study of Faizel et al (4) is that Neocone was superior to Neocone and ZOE for initial pain relief. In a study by Khalifah MA (47), he supported ZOE over alv after briefly irrigating the socket with 2mL of normal saline for only removing the debris and mentioned that Faizel et al used alv after irrigating the socket with warm normal saline in both alv and ZOE groups, but they did not record the amount of saline they used. In a similar manner, Pal et al (55) advocated PRGF over ZOE for healing promotion and the vice versa for pain relief and that could be logic from my point of view. Kaya et al (48) performed curettage and irrigation for all patients followed by applying different protocols for three groups all of which were healing promotion protocols and found out that Salicept was equivalent to alv where LLLT was better than alv and Salicept and curettage in healing promotion. The findings of Burgoyne et al (53) that a mixture of prilocaine and lidocaine topical anaesthetic performed better than ZOE which is only obtundent; and that findings of and Haghhighat et al (54) that GECB (which contains Eugenol and Eugenol precursor among other constituents) was superior than ZOE alone is accepted in the context of the current review as well. A worth noting hint is that healing promotion was independent of initial pain relief in two studies (4,55).

Khalifah MA conducted a series of studies structured on the same scheme, and so their results are quite comparable (47,51,64,70). Khalifah MA considered that patients of AO are a heterogenous group and should not be dealt with

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as one population and hence he divided AO patients into four populations (four groups) according a pain scale he introduced as group I for patients had KPS1 pain (mild pain group), group II for patients had KPS2 (moderate pain), group III for patients had KPS 3 (severe pain group) and group IV for patients had KPS 4 (agonizing pain group). Each group was then randomly divided into subgroups according to the treatment modality they received (47,51,64,70).

In addition, Khalifah MA set definitive criteria of for assessing treatment effectiveness to be curative, palliative or ineffective. On qualitatively comparing the results, we can conclude that the most effective curative treatments were as follows: ZOE after saline irrigation, Ole, I+O, O₃, and curettage for group I patients; Ole, O₃, and curettage for group II patients; and O₃ and curettage for group III and group IV patients. He recommended O₃ as a definitive therapy for AO. With regard to palliation, the most effective treatments were Alv for group I patients, ZOE after saline irrigation for group II patients, and I+O for group III and IV patients (47,51,64,70).

The wide controversy alleged to AO treatment could now be alleviated or even refuted as it could be a result of addressing heterogenous groups of patients according to Khalifah MA or an attempt to use one treatment out of the capabilities of its category or its strategy as depicted in the current review.

Although AO is accepted to be a result of interrupted healing (3) and its treatment is principally pain relief-based till healing resumed (6), the cause of healing interruption is still unknown (4,5). In the light of the current comprehensive review, and despite the fact that healers helped well in the attempt of reinitiating the healing process, some results showed that was irrelevant with pain relief. Moreover, local analgesics strategy could have a considered effect in alleviating pain, but that was a palliative role rather than a definitive curative task. Anti-ischemic strategy was the most effective in treating AO and it might be the only strategy targeted the core cause of AO development.

Analysis of risk factors and treatment modalities in addition to the above-mentioned deductions suggest that AO is a condition caused by ischemia in extraction socket walls and probably in particular, the outer most layer. The mechanism may well relate to the role of the ES walls in maintaining the blood clot “in-situ” and providing the necessary blood supply for it. If ES walls lacks the resiliency to withstand compressive forces applied during dental extraction, ischemia would be inevitable, leading to formation of some sort of barrier layer between the alveolar cancellous bone and the newly-formed blood clot, and in turn ultimately leading to clot disintegration and loss. In addition, release of chemicals because of ischemia might contribute to fibrinolysis blood clot disintegration. Thus, dry socket could be a condition of “Localized Alveolar Ischemia” (LAI) [the term I suggest for the condition] that results in fibrinolysis and blood clot loss and subsequent pain and delayed, slow-paced healing. This hypothesis seems to merit testing.

**Conclusion**

Dry socket (alveolar osteitis) results from blood clot disintegration. Until now, there has been no generally agreed on treatment of choice. In the current review, and in regards with risk factors; age, surgical trauma, smoking, oral contraceptives and poor oral hygiene seemed to be major risk factors. The former three factors could directly be related with ischemia development. However, the latter two factors could have a direct fibrinolytic effect. In the treatment domain, the most effective curative treatments were as follows: I+Z, Ole, I+O, O₃, and Cur for KPS1 patients; Ole, O₃, and Cur for group KPS2 patients; and O₃ and Cur for KPS3 and KPS4 patients. O₃ was the definitive therapy for “dry socket”. With regard to palliation, the most effective treatments were local anaesthetics and Alv for KPS1 patients, I+Z for KPS2 patients, and I+O for KPS3 and KPS4 patients. The findings suggest that ischemia is the pathogenic mechanism for “dry socket”; hence I propose renaming the condition “localized alveolar ischemia” (LAI).

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*Corresponding author: Mosaad Abdaljawwad Khalifah, Kafr El-Sheikh University, Al-Geish St., Kafr El-Sheikh, Kafr El-Sheikh, Egypt. Postal code: 33516. Phone: +21008603084 Email: mosaad_khalifa@den.kfs.edu.eg, mosaad78@hotmail.com

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