

# Effects of the topical hemostatic agent Ankaferd Blood Stopper on the incidence of alveolar osteitis after surgical removal of an impacted mandibular third molar

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## Abstract

**Background:** Alveolar osteitis (AO) is a commonly seen post-operative complication during the wound-healing period after permanent tooth extraction or surgical removal of impacted third molar teeth.

**Objectives:** The aim of this clinical study was to evaluate the effects of administration of the topical hemostatic agent Ankaferd Blood Stopper (ABS) into the socket on AO formation after impacted mandibular third molar extraction.

**Patients and Methods:** Bilaterally, 100 half-impacted mandibular third molars were extracted in 50 patients. Then, 1.0 mL ABS was administered to achieve hemostasis in one half of the sockets and as a control, the other half was irrigated with 1.0 mL physiological serum after surgery.

**Results:** There was no statistically significant difference in terms of AO formation ( $P > 0.05$ ) between the extraction sites. However, the postoperative pain in ABS administration sites was higher than in the other sites for the first 2 days after surgery ( $P < 0.05$ ).

**Conclusions:** The results showed that ABS administration did not increase the incidence of AO formation. Thus, ABS can be used safely for hemostasis after impacted mandibular third molar surgery.

**Key words:** Alveolar osteitis, Ankaferd Blood Stopper, hemostasis, third molar

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## Introduction

Alveolar osteitis (AO) is a commonly seen post-operative complication<sup>[1-4]</sup> during the wound-healing period after permanent tooth extraction or surgical removal of impacted third molar teeth. AO is also known as dry socket, alveolitis sicca dolorosa, fibrinolytic alveolitis, alveolitis, localized osteitis, localized AO, septic socket, necrotic socket, and alveolgia.<sup>[5-11]</sup> First, in the literature, AO was called as “dry socket” and defined by Crawford<sup>[12]</sup> in 1896. Although “dry socket” is a generic term, “AO” is used more commonly today.<sup>[2,11,13,14]</sup>

The incidence of AO has been reported to be between 0.5% and 5% for routine tooth extractions<sup>[2,11,13,15-18]</sup> and varies

from 1% to 45% after the extraction of mandibular third molars.<sup>[2,11,13,18-20]</sup> This rate can be approximately 10 times higher after surgical extractions when compared to normal tooth extractions.<sup>[13]</sup>

The exact etiology of AO is not well-understood. Many concepts about AO are still debated by researchers. Many causes have been suggested for AO formation, including bacterial infection,<sup>[2,21-23]</sup> and increased fibrinolytic activity.<sup>[11,23-25]</sup> Birn<sup>[7]</sup> suggested that increased local

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fibrinolysis caused the disintegration of the blood clot in the socket as the etiologic reason for AO. The fibrinolysis is the result of plasminogen pathway activation, which can be accomplished through direct (physiological) or indirect (non-physiological) activator substances. Direct activators are released after trauma to the alveolar bone cells. Indirect activators are produced by bacteria.

Many risk factors have been reported<sup>[10,11,13,14]</sup> to influence the formation of AO after surgical removal of impacted third molar teeth. In fact, AO can occur due to total loss, partial loss, or no formation of a blood clot in the bone socket in the early period after tooth extraction. Thus, the formation of a blood clot and prevention of blood clot disruption are important in preventing the development of AO in removed tooth sockets.

Ankaferd Blood Stopper (ABS; Ankaferd Health Products Ltd., Istanbul, Turkey) is a traditional folk medicinal plant extract product that has long been used in the traditional medicine as a topical hemostatic agent. In Turkey, ABS has been approved for the treatment of oral surgery bleeding and external source hemorrhages.<sup>[26-29]</sup> ABS is a standardized mixture of the plants *Thymus vulgaris* (dried leaf), *Glycyrrhiza glabra* (dried leaf), *Vitis vinifera* (dried leaf), *Alpinia officinarum* (dried leaf), and *Urtica dioica* (dried root). ABS is an effective hemostatic agent that has therapeutic potential for the management of hemorrhage. The basic mechanism of action of the hemostatic effects of ABS is currently unknown. However, ABS has been shown to promote the formation of an encapsulated protein mesh, which acts as an anchor for erythrocyte aggregation, without significantly interfering with individual coagulation factors.<sup>[30]</sup> Specifically, the blood clot forming mechanism of ABS varies from the normal blood clot mechanism. In addition, ABS has effects on new bone formation, bacteria, the endothelium, blood cells, angiogenesis, cellular proliferation, vascular dynamics, and/or cellular mediators.<sup>[30-35]</sup>

Clinical studies of hemostatic agents in terms of their effects on the incidence of AO after impacted mandibular third molar extraction have been reported.<sup>[36,37]</sup> Although ABS had some positive effects on new bone formation,<sup>[33]</sup> bacteria,<sup>[32]</sup> cytotoxicity,<sup>[38]</sup> and blood clot formation<sup>[30]</sup> during the wound-healing period, the effects of ABS in AO formation have not been studied previously in removed impacted mandibular third molar sockets. The purpose of this clinical study was to investigate the effects of ABS administration on the incidence of AO formation after impacted mandibular third molar surgery.

## Patients and Methods

This study followed the Declaration of Helsinki on medical protocols and ethics and the regional Ethical Review Board of Abant İzzet Baysal University approved the study. All patients were informed that they were to be included in

the study before surgical treatment. The purpose, plan, procedure, and treatment were included in this information. All patients provided written informed consent before being included in the study.

In this prospective, randomized, blinded study, bilateral mandibular half-impacted third molars of 50 patients, which were only partially covered with soft-tissue, were in a vertical position, and posed similar difficulties for operation were removed. 35 of the patients were females and 15 were males. There were no symptoms of acute inflammation or infection in the surgical sites in any patient at the time of surgery. Some patients were smokers. None of the patients that were included in the sample was using antibiotics for any medical condition.

Conventional impacted third molar surgery procedures were performed in all patients. Surgical treatments were performed by the same experienced oral and maxillofacial surgeons in all 50 patients. Bilateral mandibular impacted third molars were removed at the same time and under local anesthesia, obtained by inferior alveolar, lingual, and long buccal nerve block, using 2 mL Maxicaine (Vem İlaç Sanayi ve Ticaret Ltd. ŞTİ., Ankara, Turkey; 80.0 mg articain with 1:200 000 epinephrine) via a dental injector. The incision was performed with a #15 blade for the envelope flap. After a mucoperiosteal flap was raised, bilateral mandibular impacted third molars were removed during the same procedure. Then, in a consecutive manner, one of the bilateral mandibular impacted third molar sockets was irrigated with 1.0 mL of physiological serum using a dental injector and 1.0 mL of ABS was administered to achieve hemostasis in the other socket, also using a dental injector. The intra-oral region was cleaned using a sterile suction tip. Within a few seconds, a blackish-brown blood clot was formed in the socket that received ABS. Subsequently, these wounds were closed with 3.0 silk sutures, maintaining the blood clot in both sockets. No antibiotic was prescribed after surgery.

A visual analog scale (VAS) form was used daily to determine the degree of pain in the bilateral extraction sites in all patients. All patients were instructed to fill out the VAS form for 7 days and to return 1 week later for the removal of sutures and a follow-up evaluation. If there was severe pain or discomfort in the wound area, or a bad taste or smell in the mouth, patients were encouraged to return sooner for their appointment.

The evaluation of all patients for AO was performed by the same surgeon who was not one of the operating surgeons. If the patient complained of severe pain in the wound area and if there was a loss of blood clot, necrotic debris, or exposed bone, clinically, AO was diagnosed. In addition, if there were signs of bacterial infection, such as swelling, pain, purulent drainage from the extraction site, and high body

temperature, a bacterial infection was diagnosed, clinically. In case, AO or bacterial infection, necessary therapy was made available.

Post-operative AO formation in the physiological serum-irrigated sites and ABS administration sites was compared statistically with the Chi-squared test. Statistical analysis of the VAS values was conducted using the Mann-Whitney U-test.

## Results

In this clinical study, bilateral mandibular impacted third molars were removed in 50 patients. The average age of the patients was 22.8 (range, 17-41) years. Of the patients, 70% were female, and 30% were male. Furthermore, 24% were smokers, and 8% were in their menstrual period. The overall average AO rate was 15/100 (15%). AO occurred in 8/50 ABS administration sites (16%) and in 7/50 sites irrigated with the physiological serum (14%). There was no statistically significant difference between the sites ( $P > 0.05$ ). VAS scores demonstrated that post-operative pain was statistically significantly higher in the ABS administration socket sites than in the sites irrigated with physiological serum during the first 2 days after surgery ( $P < 0.05$ ).

## Discussion

ABS has positive effects on new bone formation,<sup>[33]</sup> bacteria,<sup>[32]</sup> cytotoxicity,<sup>[38]</sup> and blood clot formation<sup>[30,35]</sup> in the wound-healing period. Based on this, we first determined the effects of ABS on AO formation in removed impacted mandibular third molar sockets in this clinical study.

AO consists of a breakdown in the normal healing mechanism in the sockets. The incidence of AO has been previously reported in the range 1-45% after the extraction of mandibular third molars.<sup>[2,11,13,18-20]</sup> In this study, the overall incidence of AO was 15% in 100 impacted mandibular third molar sites. The incidence of AO was 16% in the ABS administration sockets and 14% in the control sockets. Results in both sites were almost equal. Our findings are similar to an other reports<sup>[2,11,13]</sup> in terms of the incidence of AO formation in both sites.

True AO is characterized by the partial or total premature loss of the blood clot that forms in the interior of the alveolus after extraction. This must be distinguished from other conditions, such as hypovascularization of the alveolar bone, caused by vascular and hematological impairment, osteonecrosis induced by radiotherapy, osteopetrosis,<sup>[39]</sup> Paget's disease, and cement-osseous dysplasia, in which the clot forms in the interior of the alveolus.<sup>[13,39,40]</sup> In our study, in order to increase the reliability of the outcomes, in

the selection of the sample, it was ensured that none of the above mentioned conditions existed in any of our patients.

Many techniques and methods that can assist in the prevention of AO formation have been proposed.<sup>[11,13]</sup> These include use of chlorhexidine mouthwash,<sup>[22,41,42]</sup> the placement of medicated packing into the extraction sockets,<sup>[43]</sup> the use of different patterns of antibiotics<sup>[44-46]</sup> (systemic antibiotic, topical antibiotic), use of para-hydroxybenzoic acid,<sup>[47]</sup> and the use of polylactic acid.<sup>[37,48,49]</sup> Further, for the reliability of outcomes, in this study no other method or technique was used to prevent the formation of AO.

Treatment of patients with AO is palliative. Specialists first think of prompt relief from the severe pain until normal healing begins in removed tooth sockets for AO treatment. In general, AO healing occurs within 1-4 weeks after the initial surgery.<sup>[11,13,14,43,50-52]</sup> Many treatment modalities have been presented in the literature such as using the low-level laser therapy,<sup>[52]</sup> placing SaliCept patches,<sup>[50,52]</sup> Alvogyl,<sup>[52,53]</sup> medicated packing,<sup>[43]</sup> or lidocaine jelly.<sup>[51]</sup> Other than these, cleaning and irrigation of the tooth socket are important to remove any debris and bacteria from the extraction site in AO treatment.<sup>[51,52]</sup> In our study, the post-operative treatment of the formation of AO was carried out using the proper medical treatment.

There are many risk factors associated with an increased incidence of AO, which include frequent changing of pressure-dressing gauze and frequent mouth rinsing,<sup>[54]</sup> surgical trauma and difficulty in surgery,<sup>[7,8,11,37,55]</sup> bacterial involvement,<sup>[11,56-58]</sup> smoking,<sup>[11,59,60]</sup> inadequate wound irrigation,<sup>[61]</sup> an inexperienced surgeon,<sup>[9,24,62]</sup> gender (female),<sup>[8,11,63]</sup> increased age,<sup>[8,11,63]</sup> use of oral contraceptives<sup>[11,41,64]</sup> and timing in the menstrual cycle,<sup>[64]</sup> flap design/suturing,<sup>[11,65]</sup> vasoconstrictors in local anesthetics,<sup>[11]</sup> saliva,<sup>[11,66]</sup> single extraction (*versus* multiple),<sup>[14]</sup> and bone/root fragments.<sup>[7,11,13]</sup> Thus, to eliminate these risk factors and to increase the reliability of the results, the procedures presented below were taken into consideration in the planning stage of this research as standard and were applied to all patients:

1. Conventional impacted third molar surgery procedures were performed in all 50 patients by four oral and maxillofacial surgeons who had similar professional experience in order to minimize any possible after surgery complications that would otherwise have been caused by surgeons with different professional experience
2. Both bilateral mandibular half-impacted third molars of the patients were removed on the same day at the same time
3. There were no symptoms such as acute inflammation or acute infection in any of the surgical sites.
4. No patient was using antibiotics for any medical condition prior to the surgery and no patient was prescribed antibiotics after surgery as the use of

- antibiotics affect the outcome of the treatment.
5. All bilateral mandibular half-impacted third molars of the patients were only partially covered with soft-tissue, were in a vertical position, and posed similar difficulties for operation.
  6. To increase the reliability of the study, the evaluation of all patients for AO and wound healing after surgery was performed by one surgeon who was not one of the operating surgeons.

The above mentioned cautions were taken to minimize standard post-operative pain on both sides where teeth are located. Although it was expected for patients to have similar levels of post-operative pain because of these measures, for the 2 days that followed surgery some patients whose mandibular teeth were treated with ABS reported more pain in the wound healing site. VAS values also showed pain in those patients at a statistically significant level. As ABS is relatively new and no study was conducted on the same issue, it was not possible to find any relevant clinical study to consult or utilize. Thus, based on the evidence since the occurrence of pain took place only in the surgical site that was treated with ABS in some patients, it would be safe to deduce that minor excess pain may have stemmed from the effect of ABS on the live tissues in the wound areas. Further, studies should be conducted on this minor discomfort for patients.

There are several discomfiting symptoms, such as severe pain in the wound site, added cost, extra time, and repeated hospital/clinic visits for patients with AO.<sup>[2,11,13,22,52,67]</sup> In the literature, AO is considered to begin within 2-3 days after tooth extractions,<sup>[58,68,69]</sup> and 95-100% of AO cases have been reported within 1 week.<sup>[16]</sup> Pain caused by the occurrence of AO should not be confused with the pain that occurs in the surgical site that was treated with ABS we used in our study because the pain caused by AO occurs as a strong pain in the second or third day after the operation.

High-volume surgical irrigation with the physiological serum solution may be of benefit in lowering the overall AO rate.<sup>[61]</sup> In our study, control sockets were irrigated with only 1.0 mL of physiological serum, the same as the volume of ABS used.

In previous studies, although some materials, such as medicated packing,<sup>[43]</sup> tetracycline-treated polylactic acid,<sup>[49]</sup> and zinc oxide-eugenol packing,<sup>[70]</sup> have been placed in removed tooth sockets to reduce the AO incidence, there is also evidence of foreign body reactions and unwanted side-effects during the wound-healing period.<sup>[43,49,70]</sup> ABS administration into the sockets did not induce any foreign body reaction or any unwanted side-effect during the wound healing period, apart from post-operative pain in the first 2 days after surgery.

Medicated packing material that is placed immediately to reduce AO formation in a post-operative extraction socket

has some disadvantages in that the medicated packing should be removed from the tooth socket and a delay in wound closure can occur.<sup>[43]</sup> ABS administration into the sockets does not have these disadvantages.

There are many known hemostatic materials, such as medicinal plant extracts (e.g., ABS), oxidized regenerated cellulose (Surgicel), polylactic acid granules or mesh, fibrin sealants, microfibrillar collagen, gelatin hemostatic agents, and cyanoacrylate adhesives.<sup>[30,37,48,71,72]</sup>

Surgicel is a known biodegradable hemostatic material that has been used to provide hemostasis and to control bleeding. This material causes hemostasis by a physical mechanism at the hemorrhage site.<sup>[71]</sup> If it is used for hemostasis, the removal of Surgicel is advised to prevent complications due to a mass effect or a reaction after hemostasis has been achieved.<sup>[36,73]</sup> In a previous clinical study, Suleiman<sup>[36]</sup> reported that the application of Surgicel into extraction sockets after removal of mandibular impacted third molars *increased* the incidence of AO. However, our data demonstrated that ABS administration into sockets for hemostasis after removal of mandibular impacted third molars did not increase the incidence of AO. In addition, it is not necessary to remove ABS from the hemorrhage site, unlike Surgicel.

In another study, Brekke *et al.*<sup>[72]</sup> reported that the use of polylactic acid mesh as a biodegradable surgical implant reduced the incidence of AO following mandibular third molar extraction. However, in a later prospective randomized clinical study, Hooley and Golden<sup>[48]</sup> found that polylactic acid granules did not reduce the incidence of AO; indeed, their use may actually have increased the incidence. In this present study, we showed that ABS administration into sockets for hemostasis after removal of mandibular impacted third molars did not increase the incidence of AO.

In summary, the results of this randomized clinical study demonstrated that ABS administration into sockets for hemostasis after impacted mandibular third molar surgery did not increase the incidence of AO. This offers advantages for both the surgeon and patient, such as decreasing the number of post-operative visits for AO management. Furthermore, ABS administration into sockets for hemostasis may increase post-operative pain, but that is a minor discomfort, for the first 2 days after surgery. No other discomfort due to its use was reported by these patients. Thus, ABS can be used safely for hemostasis after impacted mandibular third molar surgery.

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