# INHIBITION OF ALVEOLAR OSTEITIS IN MANDIBULAR TOOTH EXTRACTION SITES USING PLATELET-RICH PLASMA

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Alveolar osteitis (AO), also known as dry socket, continues to be a complication of tooth removal. Platelet-rich plasma (PRP) can be used to accelerate both soft and hard tissue healing. This paper is a retrospective review of the benefits of PRP in AO prevention. PRP was obtained from patients for use in the postremoval alveolar sockets of mandibular molar extraction sites. Statistical analysis of 904 extraction sites with and without PRP use was examined. PRP significantly reduced the incidence of AO by 62.1%, from 9.57% in patients not receiving PRP to 3.63% in patients who received PRP ($P = .00043$). PRP use had benefits in all subpopulations. The odds of AO occurring in patients not receiving PRP treatment following tooth extraction was 2.81 times greater than in patients receiving PRP treatment immediately following tooth extraction. Four statistically significant risk factors for AO were identified: complete impaction, oral contraceptive use, bruxism, and failure to administer PRP. The application of PRP can significantly reduce the incidence of AO even in patients with risk factors for AO, such as removal of impacted teeth, bruxism, and oral contraceptive use. PRP may be of benefit because it helps initiate clot formation, provides growth factors to facilitate the healing process, and contains concentrated white blood cells to inhibit infection. The use of PRP following tooth extraction is a simple, cost-effective technique that can be used to decrease the incidence of AO and therefore decrease postoperative pain.

**Key Words: platelet-rich plasma, PRP, alveolar osteitis, AO, dry socket**

## INTRODUCTION

Alveolar osteitis (AO) is a complication that occurs with variable frequency (0.5%–68.1%) following the removal of permanent teeth.[1–9] AO is characterized by severe throbbing pain that begins within 3 to 5 postoperative days and is usually refractory to NSAIDs and narcotic analgesics.[10,11] The clinical presentation of AO demonstrates a partial or total disintegration of the intra-alveolar sanguine clot, resulting in a denuded bony crypt with surrounding debris.[12,13] Suppuration is not evident but the patient usually complains of an acute throbbing pain emanating from the extraction site, frequently radiating to the ipsilateral ear and side of the head. Although rare, AO can affect the jugulodigastric lymph glands on the affected side as well.

A definitive etiology for AO has not been universally accepted but is commonly thought to include clot fibrinolysis as a result of bacterial invasion.[14,15] Smoking, female gender, oral contraceptive use, surgical trauma, operator experience level, poor oral hygiene, gingivitis, periodontitis, and pericornitis have all been reported in the literature to be associated with AO formation.[16–25] Increased age and systemic conditions, such as diabetes and

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immunosuppression, have also been associated with a greater incidence of AO.[26,27]

Treatment for AO is typically preventive in nature, and is based on two theories of etiology: (1) control of fibrinolysis at the time of extraction and during healing and (2) control of bacterial populations.[27] Due to potential adverse reactions to antifibrinolytic agents, most treatment has been directed towards control of bacterial colonization.

More recently, platelet-rich plasma (PRP) has been used to facilitate healing in various oral surgical procedures such as soft and hard tissue grafting.[28] PRP has been placed in the sockets of lower wisdom teeth to decrease the incidence of AO.[29] This paper examines the effect of PRP on AO incidence and its relationship with other patient factors.

Platelet-rich plasma has been employed either as a gelled autologous fibrin clot or as unaltered PRP to enhance postoperative healing in conjunction with the removal of teeth. Anecdotal clinical observations have suggested that with the application of PRP there is a decrease in the incidence and severity of AO, compared to other techniques used for tooth removal. The purpose of this study was to examine the effect of PRP on the incidence of AO following mandibular molar tooth removal. The study examined the incidence of AO formation and its association with immediate placement of platelet-rich plasma gel in the extraction alveolus socket. In addition to the efficacy of PRP in patients without potential risk factors for AO, the effectiveness of PRP in patients with potential risk factors was examined. Factors considered include:

• age,
• gender,
• smoking status,
• systemic antibiotic therapy,
• concurrent use of other oral medications,
• oral contraceptive use,
• presence of oral clenching/grinding habits (bruxism),
• tooth eruptive state,
• tooth position, and
• concurrent restorative treatments provided at the time of surgery.

## MATERIALS AND METHODS

This study was reviewed and approved by the Investigational Review Board for the Protection of Human Subjects in research of Duquesne University. Data was obtained by retrospective chart reviews of 904 mandibular molar extraction sites from 499

patients. A total of 506 patients had been treated, but 7 patients (all no-PRP treatment) were excluded because of missing data on one or more variables. All molar tooth positions and eruptive states (erupted, partially erupted, and complete bone impaction) were included in the study. All surgeries were performed by the same general dentist in private practice. Tooth removals done without PRP were performed between June 1996 and December 2000. Tooth removals done with PRP were performed between January 2001 and August 2003. Demographics for the data collection set are presented in Table 1.

### Protocol for obtaining PRP in an autologous fibrin clot

Intravenous access was achieved utilizing a 22-gauge, 1-inch Terumo Surflo intravenous catheter (Terumo Medical Corporation, Elkton, Md). The catheter was then used to administer intravenous sedation to the patient. Aseptic technique was used.

Two blood samples of approximately 4 mL each were aspirated and placed in 2 sterile 4.5-mL BD Vacutainer blood collection tubes (Becton Dickinson & Co., Franklin Lakes, NJ) that contained 0.5 mL of 10% trisodium citrate as the anticoagulant. The tubes are referred to as tubes No. 1.

Tubes No.1 were labeled with a patient identification mark and centrifuged for 10 minutes using a Clinaseal laboratory centrifuge (Salvin Dental Specialties, Charlotte, NC). Centrifugation separated the whole blood into 3 layers: red blood cells (RBCs) on the bottom, platelet-poor plasma (PPP) on the top, and between these two layers, a small band of PRP.

TABLE 1

Demographic profile of database by race and age*

| Demographic | Treatment | | Total n = 499 |
|---|---|---|---|
| | No-PRP n = 272 | PRP n = 227 | |
| Race | | | |
| African-American | 7 (2.6%) | 4 (1.8%) | |
| Asian | 0 (0%) | 1 (0.4%) | |
| White | 265 (97.4%) | 222 (97.8%) | |
| Age groups | | | |
| 15–20 years | 161 (59.2%) | 146 (64.3%) | 307 |
| 21–30 years | 47 (17.3%) | 47 (20.7%) | 94 |
| 31–40 years | 22 (8.0%) | 9 (4.0%) | 31 |
| 41–50 years | 18 (6.6%) | 10 (4.4%) | 28 |
| 51–60 years | 12 (4.4%) | 10 (4.4%) | 22 |
| 61–70 years | 7 (2.6%) | 4 (1.8%) | 11 |
| 71–80 years | 4 (1.5%) | 1 (0.4%) | 5 |
| 80+ years | 1 (0.4%) | 0 (0.0%) | 1 |

*PRP indicates platelet-rich plasma.

This PRP layer is made up of concentrated platelets and concentrated white blood cells.

With a 21-gauge, 1.5-inch needle attached to a 3-mL syringe (Becton Dickinson & Co.), the top half of the plasma layer (approximately 1 mL) was aspirated, labeled with the patient identification mark, and set aside for later use. This syringe is referred to as the PPP syringe.

Using a new 3-mL syringe with needle (21-gauge, 1.5-inch) the remaining PPP and PRP layers were removed. The top 1 to 2 mm of RBCs may also be removed. The contents of the syringe were then placed into an empty Vacutainer tube (not containing trisodium citrate). This tube is referred to as tube No. 2.

The next step was to coagulate, or gel, the PRP. Using a 0.5-mL, 29-gauge, 0.5-inch insulin syringe (Sherwood Medical, St. Louis, Mo), 0.05 mL (5 units) of 10% calcium chloride were added to the contents of tube No. 2. This step provides the necessary calcium to re-establish the coagulation cascade, thus leading to the formation of an autologous fibrin clot that is rich in platelets. This gelling process usually takes between 10 and 20 minutes.

The final product was a pink-to-light red, ovoid-shaped gel with enough integrity to be easily removed from the test tube by tapping at the closed end while holding the test tube upside down. The PRP was dropped into a sterile surgical stainless steel cup. The extraction socket was prepared by curetting and irrigating with 10 to 20 mL of sterile saline.

The gelled autologous PRP fibrin clot was removed from the sterile surgical cup with sterile college pliers and placed into the prepared extraction socket. Sutures were then placed to achieve primary closure and to help retain the PRP clot.

### Statistics

Statistical analysis used both bivariate tests for independence of categorical data and multiple logistic regressions. Bivariate analysis was performed using the Fathom Dynamic Statistics software and multivariate analysis was performed using SPSS software (SPSS, Inc., Chicago, Ill). $P$ values of less than .05 were considered significant. The Mantel-Haenszel test for equality of population odds ratios was used to investigate interaction effects among factors.

### RESULTS

The 904 extraction sites were assumed to be independent from one another. The test for equality of proportions revealed a significantly greater proportion of AO cases occurred among the nontreated sites
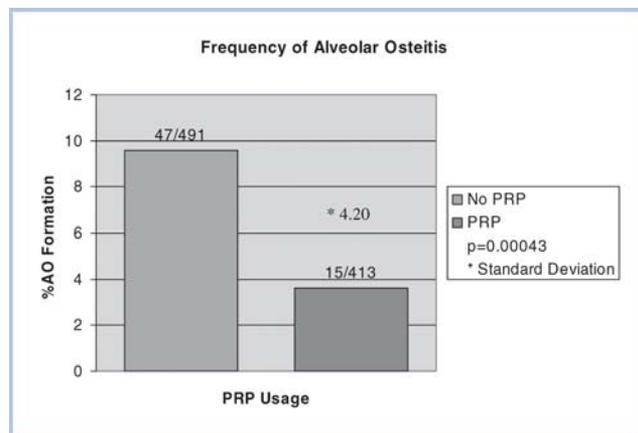


FIGURE 1. Alveolar osteitis (AO) formation in extraction sites with or without platelet-rich plasma (PRP) treatment.

(n = 491) compared with sites in the PRP treatment group (n = 413); ($P$ = .00043). The odds ratio (OR) was 2.81 (95% CI, 1.54 to 5.10), indicating an almost threefold increase in the odds of AO occurring in the control sites compared to the PRP-treatment group. Figure 1 illustrates the difference in AO formation for non-PRP treatment sites and sites receiving PRP treatment at the time of surgery.

Table 2 lists all 10 patient factors considered in this study along with the corresponding proportions experiencing AO for both PRP and non-PRP treated sites. PRP treatment decreased AO incidence for all subpopulations in which AO occurred. AO formation was not observed with first molar extraction sites and was seen in only one second molar extraction site (which did not receive PRP treatment). The remaining 61 sites that developed AO formation were all third molar extraction sites. Note that bruxism and oral contraceptive use display the greatest likelihood of AO formation for both PRP and non-PRP groups.

Multiple logistic regression (multivariate) analysis revealed exactly four significant risk factors for AO: complete impaction, oral contraceptive use, bruxism, and failure to use PRP. Figure 2 lists the expected probability of AO formation for each of these significant risk factors alone and in combination. The individuals most at risk for AO were those presenting with a combination of complete impaction, use of oral contraceptives, bruxism, and no treatment with PRP. With each risk factor combination, the use of PRP significantly reduced the probability of AO by approximately one half. Multiple logistic regression analysis revealed that other examined factors (gender, age, tooth position, smoking, prophylactic antibiotic use, other operative procedures performed at the same appointment, and concurrent use of other

TABLE 2

Comparison of Non-PRP treatment and PRP treatment for each patient factor*

| Patient Factor | Non-PRP Treated Sites | | PRP Treated Sites | | Difference in % Occurrence of AO with PRP | % Decrease in AO with PRP |
| --- | --- | --- | --- | --- | --- | --- |
| | (n/N) | (%) | (n/N) | (%) | (%) | (%) |
| Sex | | | | | | |
| Male | 21/231 | 9.10 | 4/191 | 2.10 | 7.00 | 76.90 |
| Female | 26/260 | 10.00 | 11/222 | 4.95 | 5.05 | 50.50 |
| Age | | | | | | |
| <40 years | 42/436 | 9.63 | 14/380 | 3.68 | 5.95 | 61.79 |
| ≥40 years | 5/55 | 9.09 | 1/33 | 3.03 | 6.06 | 66.67 |
| First molar | 0/23 | 0.00 | 0/8 | 0.00 | No change | No change |
| Second molar | 1/22 | 4.55 | 0/12 | 0.00 | 4.55 | 100.00 |
| Third molar | 46/446 | 10.31 | 15/393 | 3.82 | 6.49 | 62.95 |
| Erupted | 6/93 | 6.45 | 1/55 | 1.82 | 4.63 | 71.78 |
| Partially impacted | 6/130 | 4.62 | 4/100 | 4.00 | 0.62 | 13.42 |
| Full impaction | 35/268 | 13.06 | 10/258 | 3.88 | 9.18 | 70.29 |
| Bruxism | 24/105 | 22.86 | 6/41 | 14.63 | 8.23 | 36.00 |
| Prophylactic antibiotics | 6/60 | 10.00 | 1/40 | 2.50 | 7.50 | 75.00 |
| Oral contraceptives | 8/45 | 17.78 | 5/49 | 10.20 | 7.58 | 42.63 |
| Other medications | 7/88 | 7.95 | 3/95 | 3.16 | 4.79 | 60.25 |
| Tobacco smoking | 10/59 | 16.95 | 0/37 | 0.00 | 16.95 | 100.00 |
| Other operative procedures | 7/48 | 14.58 | 1/12 | 8.33 | 6.25 | 42.87 |

*PRP indicates platelet-rich plasma and AO, alveolar osteitis.

medications) were not associated with an increase (or decrease) in the probability of AO.

Analysis of potential interactions between the use of PRP and identified risk factors were examined using the Mantel-Haenzel test for OR equality. The results revealed no significant interactions between PRP and other risk factors for AO. Thus, the effectiveness of PRP in reducing the incidence of AO is not dependent upon the presence or absence of other risk factors for this complication.

## Discussion

The beneficial effects of PRP for decreasing the incidence of AO may be related to a number of signaling proteins found in the platelets, including multiple growth factors such as insulin-like growth factor, vascular endothelial growth factor, epidermal growth factor, nerve growth factor, transforming growth factors β1 and β2 (TGF-β1), platelet-derived growth factors, and cytokines such as angiopoietin-2, and interleukin-1.[30,31] These factors stimulate cell mitosis and differentiation,[32] increase collagen production, recruit leukocytes and other cells to the surgical site, and initiate vascular in-growth. Growth factors promote both soft and hard tissue healing and angiogenesis. In addition, platelets promote clot formation, which is beneficial in healing. Aside from

platelets, PRP also contains white blood cells that can inhibit bacterial growth. Therefore, PRP application mitigates the currently accepted causes of AO by facilitation of clot and soft tissue formation and inhibition of bacterial colonization.

When trying to determine whether any one of the aforementioned 11 factors are significant in predicting AO, individual bivariate analyses are inappropriate since they do not incorporate the impact of a given factor on AO in the presence of the remaining factors. Multivariate logistic regression, however, takes into account the impact of all factors on AO simultaneously, and therefore can determine significant AO predictors without multiple- and/or cross-factor confounding.

Multivariate analyses revealed that PRP significantly reduces the incidence of AO, with the odds of AO formation 2.37 times higher for extraction sites without PRP treatment (95% CI, 1.3 to 4.4). In addition to the absence of PRP administration, this multivariate analysis revealed exactly three other significant risk factors for AO: bruxism, oral contraceptive use, and complete impaction. Figure 2 shows the expected AO probabilities for patients presenting with any combination of these four significant risk factors. Notice that when PRP is administered, the AO probability is reduced by roughly half for patients in any partition.

Furthermore, this analysis did not find an association between smoking status and the occurrence of AO ($P = .3$). However, this study did not take into

**AO Formation for Combinations of Variables Found to be Significant Risk Factors**

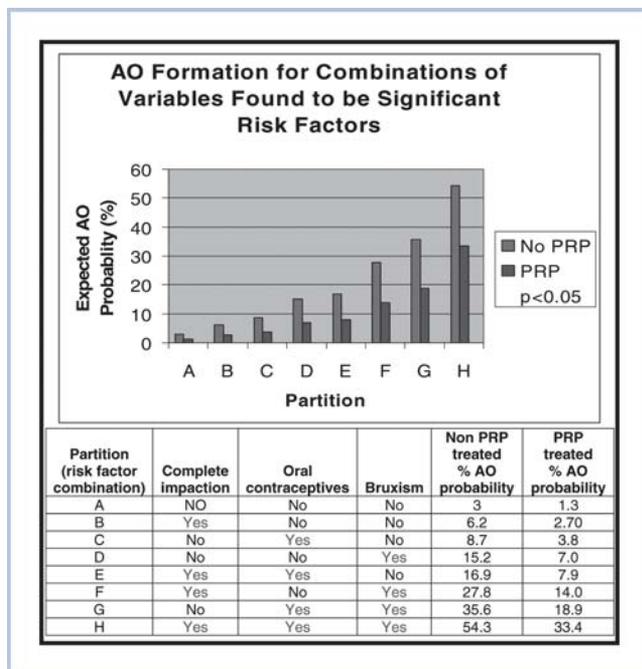| Partition (risk factor combination) | Complete impaction | Oral contraceptives | Bruxism | Non PRP treated % AO probability | PRP treated % AO probability |
|---|---|---|---|---|---|
| A | NO | No | No | 3 | 1.3 |
| B | Yes | No | No | 6.2 | 2.70 |
| C | No | Yes | No | 8.7 | 3.8 |
| D | No | No | Yes | 15.2 | 7.0 |
| E | Yes | Yes | No | 16.9 | 7.9 |
| F | Yes | No | Yes | 27.8 | 14.0 |
| G | No | Yes | Yes | 35.6 | 18.9 |
| H | Yes | Yes | Yes | 54.3 | 33.4 |

Figure 2. Alveolar osteitis (AO) formation for various partitions found to be significant risk factors (multivariate analysis). Statistical significance $P < .05$ for all of the above combination of variables. PRP indicates platelet-rich plasma.

account smoking quantity. Moreover, smoking status is subject to a possible response bias. It was interesting that none of the smoking PRP-treated patients (n = 37) experienced AO.

The participants in this study were, overall, young (15 to $\leq$ 30 years of age, 80.5%) and white. However, statistical analysis did reveal that the effectiveness of PRP in reducing the occurrence of AO was significant and independent of all confounding factors, including age. Patients younger than 40 years of age and those older than 40 years of age both had AO formation reduced by approximately two thirds. Race was not considered a variable in the study because of the small number of nonwhite participants.

Placing PRP in surgical sites, particularly in the elderly and/or medically compromised patient, is a rational approach to treatment. This is supported by the in vitro work of Cei et al, who found that, irrespective of age, bone marrow stromal cells responded similarly to platelet-released supernatant and bone morphogenetic protein 6, both of which are found within PRP.[33] Furthermore, in animals, osteo-progenitor cells were reduced in quantity in adult rats, but preserved their juvenile potential to respond to growth and differentiation factors.[33] Moreover, it is known that TGF-$\beta$1 enhances mineralization on dental

implant materials in osteoblast cultures from elderly human subjects.[34]

Mesenchymal stem cells decrease in number early during aging in humans.[35] These stem cells can differentiate into osteoblasts when stimulated by the proper growth factors contained within platelets. However, the physiologic bone marrow microenvironment changes with maturity and may possibly be unfavorable for mesenchymal stem cells (MSC) proliferation or may favor MSC maturation toward a different cell lineage such as adipocytes.[36–38] Adipogenesis can be inhibited by TGF-$\beta$, which again is contained in PRP.[39] Ultimately, since stem cell numbers decrease with age but still retain their juvenile potential, it is reasonable to suggest that PRP, with increased concentrations of growth factors, would be beneficial in treating elderly patients.

Many practitioners prescribe systemic antibiotics to prevent dry socket, but this study found no significant effect of prophylactic antibiotics on the incidence of AO. This result supports the position that using prophylactic antibiotics to prevent AO is without benefit, unless the patient has a systemic pathology that indicates the need for pre-medication with antibiotics. This study did not examine the effect of localized intra-alveolar post-extraction antibiotic administration. Sanchis et al found that intra-alveolar placement of tetracycline did not affect the incidence of dry socket.[40]

## Conclusion

The results of this study demonstrated that complete impaction, oral contraceptive use, and especially bruxism are associated with significant increases in AO incidence. This study also found a substantial reduction in the incidence of AO following treatment of the extraction site with PRP. This simple and cost-effective technique appears to be a viable methodology by which dental practitioners can decrease the incidence of AO formation in patients. This study supports the use of PRP in mandibular extraction sites as a method for reducing patient postoperative discomfort and the need for multiple postoperative visits that can be associated with AO.

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