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Investigation of Fibrinolytic Bacteria Ratios in Alveolitis Using Polymerase Chain Reaction: Cross-Sectional Study

Alveolit Vakalarında Fibrinolitik Bakteri Oranlarının Polimeraz Zincir Reaksiyonu Yöntemiyle Araştırılması: Kesitsel Araştırma

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ABSTRACT Objective: The objective of this research was to investigate the presence and abundance of fibrinolytic bacteria in alveolitis cases (dry socket) following tooth extraction. The study aims to elucidate microbial factors contributing to this common complication. **Material and Methods:** A cohort of 56 patients with alveolitis was included. Polymerase chain reaction (PCR) was used to detect specific fibrinolytic bacteria ratios associated with alveolitis. Pa-tient demographics, extraction details, and postoperative care practices were documented for possi-ble correlations. **Results:** This study included 56 patients with a total of 59 extraction sockets diag-nosed with alveolitis. Bacterial deoxyribose nucleic acid was successfully isolated and detected from 50 collected samples. PCR analysis revealed a high prevalence of specific fibrinolytic bacteria: *Treponema denticola* (*T. Denticola*) was identified in 76% (n=38/50) of the samples, and *Porphyromonas gingivalis* (*P. Gingivalis*) in 32% (n=16/50). Notably, *T. denticola* was consistently present in all samples where *P. gingivalis* was detected. Demographic analysis showed that most patients were female (62%) with an average age of 40.16 years. Alveolitis predominantly occurred following lower 3rd molar extractions (40.16% of cases). Postoperative care analysis indicated that 46% of patients received antibiotics and 51% used chlorhexidine (CHX) mouthwash, though adher-ence varied. Statistical analysis demonstrated a significant association between *T. denticola* preva-lence and female gender, while *P. gingivalis* was significantly correlated with lower rates of antibi-otic and CHX mouthwash usage. **Conclusion:** The high prevalence of *T. denticola* and *P. gingivalis* in alveolitis may be influenced by gender and postoperative care. These findings highlight the need for further research on their roles in disease pathogenesis and for developing targeted preventive strategies to improve postoperative outcomes.

Keywords: Dry socket; *Porphyromonas gingivalis; Treponema denticola*

ÖZET Amaç: Bu araştırmanın amacı, diş çekimi sonrası sıkça görülen bir komplikasyon olan alveolit vakalarında fibrinolitik bakterilerin varlığını ve yoğunluğunu incelemektir. Çalışma, bu durumun etiyolojisine katkıda bulunan mikrobiyal faktörlere ilişkin bilgiler sunmayı hedeflemektedir. **Gereç ve Yöntemler:** Çalışmaya, alveolit tanısı almış 56 hasta kohortu dâhil edilmiştir. Alveolitik durumlarla yaygın olarak ilişkilendirilen spesifik fibrinolitik bakterilerin oranlarını saptamak amacıyla polimeraz zincir reaksiyonu [polymerase chain reaction (PCR)] analizi uygulanmıştır. Olası korelasyonları değerlendirmek üzere hasta demografik verileri, çekim detayları ve postoperatif bakım uygulamaları da belgelenmiştir. **Bulgular:** Çalışmaya, alveolit tanısı konmuş toplam 59 çekim soketine sahip 56 hasta dâhil edilmiştir. Toplanan 50 örnekten başarılı bir şekilde bakteriyel deoksiribo nükleik asit izole ve tespit edilmiştir. PCR analizi, spesifik fibrinolitik bakterilerin yüksek prevalansını ortaya koymuştur: *Treponema denticola (T. denticola)* örneklerin %76'sında (n=38/50), *Porphyromonas gingivalis* ise %32'sinde (n=16/50) tanımlanmıştır. Dikkat çekici şekilde, *P. gingivalis*'in saptandığı tüm örneklerde *T. denticola*'nın da tutarlı bir şekilde bulunduğu gözlenmiştir. Demografik analiz, hastaların çoğunluğunun kadın (%62) olduğunu ve ortalama yaşın 40,16 yıl olduğunu göstermiştir. Alveolit vakaları ağırlıklı olarak alt 3. molar çekimlerini (%40,16) takiben meydana gelmiştir. Postoperatif bakım analizi, hastaların %46'sının antibiyotik kullandığını ve %51'inin klorheksidin [chlorhexidine (CHX)] gargarası kullandığını, ancak uyumun değişkenlik gösterdiğini belirtmiştir. İstatistiksel analiz, *T. denticola* prevalansı ile kadın cinsiyeti arasında anlamlı bir ilişki olduğunu, *P. gingivalis*'in ise daha düşük antibiyotik ve CHX gargara kullanım oranlarıyla anlamlı şekilde ilişkili olduğunu ortaya koymuştur. **Sonuç:** Bu çalışma, alveolit vakalarında *T. denticola* ve *P. gingivalis*'in önemli bir prevalansa sahip olduğunu ve cinsiyet ile postoperatif bakım uygulamalarından potansiyel olarak etkilenebileceğini düşündürmektedir. Bu bulgular, bu bakterilerin hastalık gelişimindeki spesifik rollerinin ve hedefe yönelik önleme stratejilerinin formülasyonunun daha fazla araştırılması gerekliliğini vurgulamaktadır. Bu mikrobiyal dinamiklerin anlaşılması, klinik sonuçların iyileştirilmesine ve postoperatif komplikasyon insidansının azaltılmasına katkıda bulunabilir.

Anahtar Kelimeler: Kuru soket; *Porphyromonas gingivalis; Treponema denticola*

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Alveolar osteitis, commonly known as dry socket, is a prevalent postoperative complication following tooth extraction, as originally described by Crawford.[1] This condition occurs when the formation of a blood clot is disrupted or displaced from the extraction socket, resulting in inflammation and severe pain. Although some authors consider alveolar osteitis to be related to an alteration of the blood clot, the underlying etiology remains unclear, and recent reports suggest that bacteria might play an important role.[2] Various factors are implicated in the development of alveolitis, including the presence of oral bacteria, particularly *Treponema denticola (T. denticola)*, inadequate oral hygiene practices, traumatic extraction procedures, pericoronitis, retention of foreign bodies in the extraction site, clot displacement, and risk factors such as smoking or oral contraceptive use.[2-6] Blood clot lysis is mostly dependent on microorganism fibrinolytic activity.[7]

The aim of this study was to determine the presence and abundance of fibrinolytic bacteria in cases of alveolitis after tooth extraction. These bacteria have been shown to impede or modulate periodontal protective mechanisms, leading to dysbiosis between the host and dental plaque. This dysbiosis can trigger an inflammatory response and contribute to the development of alveolitis.[8] Polymerase chain reaction (PCR) analysis will be used to detect and quantify the specific fibrinolytic bacteria present in the alveolitic cases. This powerful molecular technique allows for amplification of deoxyribose nucleic acid (DNA) sequences, facilitating identification and quantification of target bacteria.

The findings from this study on identifying specific ratios of fibrinolytic bacteria associated with alveolitis could potentially lead to novel therapeutic strategies targeting these microbial culprits.

MATERIAL AND METHODS

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki for medical protocols and ethics. Approval for the study was obtained from the Ethical Review Board of Ankara University Faculty of Dentistry Ethics Committee (date: October 31, 2018; no: 36290600/87). Informed consent was obtained from all participating patients after providing them with the "informed volunteer consent form".

This research was designed as a cross-sectional study. It included all patients who presented with pain complaints following tooth extraction and were diagnosed with alveolitis within a 2-month period, provided they consented to participate in the study. The focus was on patients diagnosed with alveolitis who were prescribed a combination of amoxicillin and clavulanic acid as an antibiotic, along with chlorhexidine (CHX) mouthwash for oral hygiene. Only patients who had undergone dental extraction at the same hospital and subsequently reported symptoms of alveolitis were included in the study. All patients included in the study underwent standard tooth extractions, while open surgical extractions were excluded from the study.

Samples were collected from a total of 56 patients and 59 extraction sockets. Nine socket samples were excluded from the study due to degradation under storage conditions, resulting in a total of 50 extraction socket samples being analyzed in the study results. In the extraction of lower 3rd molars included in the study, the criteria for routine dental extraction were applied. Patients who underwent surgical extraction of impacted teeth were excluded from the study. Samples were collected from the alveolar sockets of enrolled patients for PCR analysis. Patients whose socket area isolation was compromised were excluded from PCR examination but included in other aspects related to determining alveolitis etiology. A "patient anamnesis form" was used to assess potential factors contributing to alveolitis. Demographic data was collected through patient interviews, while variables related to *T. denticola* and *P. gingivalis* were analyzed based on both demographic and clinical characteristics of each case.

POLYMERASE CHAIN REACTION ANALYSIS OF SAMPLES

After isolating the extraction socket area with cotton pellets, a sample was obtained from the dry socket using a surgical curette. These samples were then placed in Eppendorf tubes containing 0.5 ml of 0.09% NaCl solution and stored at -24 ˚C, followed by further storage at -70 ˚C until analysis. Each tissue

sample underwent boiling at 100 °C for 15 minutes to release bacterial DNA.[9] PCR analysis was performed using a Thermocycler device (Whatman, Biometra, Goettingen, Germany), and the resulting PCR products were examined on agarose gels were prepared separately for all 50 samples with Tris-ethylenediaminetetraacetic acid-Buffer. To evaluate the PCR products and to confirm that the reaction amplified the desired regions of the correct length, a DNA marker (MassRuler, Fermentas, USA) was loaded onto the gel alongside the PCR products. After running the gel at 100 volts for 20 minutes, it was visualized using a transilluminator (Vilber Lourmat, France). The bands observed on the gel (*P. gingivalis*: 404 base pairs, *T. denticola*: 316 base pairs) indicated the presence of bacteria in the tissue samples collected. To ensure the reliability of the results, the samples were repeated 3 times under the same conditions. Specific oligonucleotide primers targeting the 16S ribosomal ribonucleic acid sequences of *P. gingivalis* and *T. denticola* were used to investigate their respective DNA presence (Table 1).

The samples were visualized using a transilluminator (Vilber Lourmat, France) after running for 20 minutes at 100 volts. The bands observed on the gel indicated presence of bacteria in tissue samples. To confirm findings each sample replicated 3 times under identical conditions yielding consistent results. Due to degradation or loss during isolation procedure 9 sockets couldn't be processed therefore there is no isolate. However there are totally 50 positive results gained by processing.

STATISTICAL ANALYSIS

The data analysis was conducted using IBM SPSS Statistics 17.0 (IBM Corporation, Armonk, NY, USA). The Shapiro-Wilk test was employed to assess the normality of the distribution of discrete numerical variables. The Mann-Whitney U test was utilized to determine whether there was a significant age difference between the groups that tested negative for *T. denticola* and *P. gingivalis* compared to those that tested positive. Results with $p<0.05$ were deemed statistically significant.

RESULTS

During the 2-month study period, 56 patients presenting with pain complaints following tooth extraction were diagnosed with alveolitis, encompassing a total of 59 extraction sockets. Of these, 50 samples were successfully analyzed via PCR; 9 samples were excluded from evaluation due to degradation during storage.

PCR analysis revealed the presence of bacterial DNA in all 50 examined samples. Specifically, *T. denticola* was detected in 76% (n=38) of the sample sockets, while *P. gingivalis* was identified in 32% (n=16). Notably, *T. denticola* was consistently found in all samples were *P. gingivalis* was present, indicating that *P. gingivalis* was never isolated alone. The presence of these bacteria in the tissue samples was confirmed by bands displayed on the gel electrophoresis (Figure 1, Figure 2).

Regarding patient demographics, the study included 35 female participants (62%) and 21 male participants (38%), with an average age of 40.16 years. Alveolitis predominantly occurred following lower 3rd molar extractions (40.16% of cases). No cases were observed in pediatric patients or after central, lateral, and canine tooth extractions. Most affected extraction sockets (76.3%) were located in the lower

TABLE 1: Oligonucleotide primer sequences used in PCR experiments (Sentegen, Türkiye)

Target organism	Primer/prob name	Nucleotide sequence
Porphyromonas gingivalis	Pg16SF (forward)	5'-AAG CAG CTT GCC ATA CTG CG-3'
Porphyromonas gingivalis	Pg16SR (reverse)	5'-ACT GTT AGC AAC TAC CGA TGT-3'
Treponema denticola	Td16SF (forward)	5'-TAA TAC CGA ATG TGC TCA TTT ACA T-3'
Treponema denticola	Td16SR (reverse)	5'-TCA AAG AAG CAT TCC CTC TTC TTC TTA-3'

PCR: Polymerase chain reaction

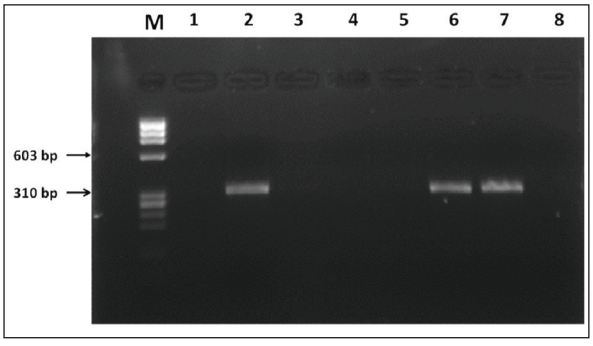

FIGURE 1: Agarose gel image of *Treponema denticola*
bp: Base pair; M: Marker; 1, 3, 4, 5, 8: Patients without *Treponema denticola*; 2, 6, 7: patients with Treponema denticola (316 base pairs)

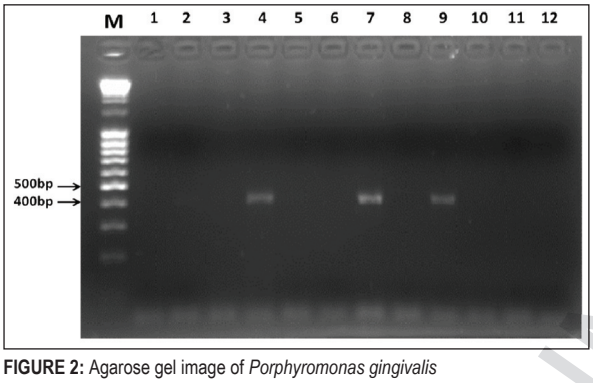

FIGURE 2: Agarose gel image of *Porphyromonas gingivalis*
bp: Base pair; M: marker. 1, 2, 3, 5, 6, 8, 10, 11, 12: Patients without *Porphyromonas gingivalis*; 4, 7, 9: Patients with *Porphyromonas gingivalis* (404 base pairs)

jaw, with no cases reported after primary tooth extraction.

In terms of postoperative care, 46% of alveolitis patients reported using postoperative antibiotics, while 51% utilized CHX mouthwash after tooth extraction.

Analysis of the demographic and clinical characteristics in relation to bacterial presence showed a statistically significant higher incidence of *T. denticola* in female patients. No other significant demographic differences were observed for *T. denticola*. Conversely, the isolation of *P. gingivalis* was found to be statistically significantly lower in the group of patients who used both antibiotics and CHX mouthwash after tooth extraction.

DISCUSSION

The role of microorganisms in the oral flora in the development of alveolitis, one of the most common complications following tooth extraction, is a topic of debate. *T. denticola* and *P. gingivalis* are significant microorganisms in this context. Detecting the presence of *T. denticola* and *P. gingivalis* using traditional culture methods can be challenging. However, the PCR method has revealed these bacteria as active microorganisms in various oral infections, ranging from root canal infections to osteomyelitis and alveolitis.[10,11] In this study, PCR was chosen as the method of analysis due to the difficulties in culturing these bacterial species in a laboratory setting. The superiority of the PCR method in this context lies in its high sensitivity and specificity, allowing for the accurate detection of bacterial DNA even in samples where the bacteria may not be viable. This capability ensures that the presence of *T. denticola* and *P. gingivalis* can be identified regardless of their metabolic state, providing a more comprehensive understanding of their role in alveolitis and other oral infections.

The reported incidence of alveolitis following tooth extraction varies, with rates ranging from 0.5% to 5% for normal extractions and increasing to 3% to 20-30% for lower 3rd molar extractions.[12,13] In mandibular 3rd molar extractions, the rate of alveolitis may go up to 30%.[14] In our study, consistent with the literature indicating higher rates of alveolitis following the extraction of lower 3rd molars, alveolitis occurred in 40.67% of cases.[15] However, contrary to the existing literature, all lower 3rd molars in our study were extracted as normal tooth extractions. Interestingly, no cases of alveolitis were observed in central-lateral and canine tooth extractions in our study. This could be due to factors such as reduced food retention in the anterior region and the cleansing effect of the tongue, which may contribute to a lower incidence of alveolitis in these areas.

The fibrinolytic activity of *P. gingivalis* and *T. denticola*, believed to contribute to the development of alveolitis, has been studied extensively. Studies have identified that *T. denticola* is among fibrinolytic bacteria and leads to the lysis of blood clots.[2] Interestingly, *T. denticola* was not detected in the oral cavity of children, potentially explaining the absence of alveolitis in childhood.[6] On the other hand, *P. gingivalis*, known to act synergistically with *T. denticola*, possesses fibrinolytic properties and is associated

with destructive periodontal diseases, pericoronitis, and alveolitis.[10]

Research investigating the periodontal pockets of 3rd molar teeth found *P. gingivalis* in 20% of cases using PCR analysis.[10] Similarly, in a study examining microorganisms in the apical region of infected tooth root canals, *T. denticola* was detected at a rate of 26% and *P. gingivalis* at 4%.[16] This suggests that existing infections in extracted teeth can impact the socket area upon reaching the apical region. In our study, PCR analysis revealed that *P. gingivalis* was present in 32% of samples, while *T. denticola* was detected in 76% of samples.

Synergy refers to the phenomenon where microorganisms in the same environment enhance each other's effects. The synergy between *P. gingivalis* and *T. denticola*, both members of the "Red Complex", has been documented in numerous studies.[17,18] In our study, both bacteria were identified in 16 (32%) of the 50 samples examined using PCR, with *T. denticola* present in all samples containing *P. gingivalis*. This finding suggests a potential synergy between these 2 bacteria.

Many studies have explored strategies to prevent alveolitis by targeting the reduction of oral bacteria. Common approaches to reducing oral bacteria include the use of broad-spectrum antibiotics and antibacterial mouthwashes.

Chlorhexidine mouthwash is extensively recognized as an effective antibacterial agent in the field of dentistry. It is believed that the application of chlorhexidine mouthwash after tooth extraction may be effective in preventing alveolitis formation.[19,20] The meta-analysis, which included 18 studies, concluded that the use of chlorhexidine in any formulation, concentration, or regimen is effective and efficient in preventing dry socket in patients undergoing 3rd molar extraction.[21] However, Delilbasi et al. reported that chlorhexidine did not significantly reduce the prevalence of alveolitis after mandibular third molar extraction.[22] In our study, patients were instructed to use CHX mouthwash following the surgical procedure. Nevertheless, despite 51% adherence to this guideline, instances of alveolitis still arose. While there was no significant difference in the presence of *T. denticola* between patients who used chlorhexidine mouthwash and those who did not, a statistically lower prevalence of alveolitis was observed in patients positive for *P. gingivalis* who used the mouthwash. This suggests that CHX mouthwash may be more effective against *P. gingivalis* compared to *T. denticola* in preventing alveolitis.

The use of antibiotics is another effective method for reducing oral bacteria levels. In a meta-analysis involving 3,206 participants, it was determined that antibiotics could reduce the risk of dry socket by 34% in patients undergoing 3rd molar extractions when compared to a placebo.[23] In a study evaluating the impact of antibiotics on "Red Complex" member bacteria, the combination of amoxicillin and metronidazole was found to be more effective than other antibiotics.[24] In our study, 46% of patients who developed alveolitis reported using amoxicillin-clavulanic acid combination antibiotics after tooth extraction. There was no significant difference in the use of amoxicillin antibiotics between the *T. denticola* negative and positive groups. However, the rate of antibiotic use after tooth extraction was significantly lower in the *P. gingivalis* positive group. Our study results suggest that while the amoxicillin-clavulanic acid combination is effective against *P. gingivalis*, it may be insufficient against *T. denticola*. Considering that more patients in our study were positive for *T. denticola* compared to *P. gingivalis*, using antibiotic combinations that are more effective against *T. denticola* may be crucial in preventing alveolitis formation. This highlights the importance of tailored antibiotic therapy to target specific oral bacteria involved in alveolitis development.

This study, while providing valuable insights, has certain limitations that should be considered. Firstly, the cross-sectional design limits the ability to establish causality between the detected bacterial species and the development of alveolitis. A longitudinal study design would provide more robust evidence of the temporal relationship. Secondly, the sample size, though adequate for detecting the reported prevalences, might not be sufficiently large to identify more subtle associations or rare bacterial patterns. Thirdly, the study relied on patient-reported adherence to postoperative care (antibiotics and CHX

mouthwash usage), which may be subject to recall bias. Objective measures of adherence, if feasible, would strengthen these findings. Lastly, the study focused on specific fibrinolytic bacteria; future research could expand to investigate a broader spectrum of oral microorganisms and their complex interactions in alveolitis.

CONCLUSION

This research provides valuable insights into the prevalence and characteristics of *T. denticola* and *P. gingivalis* in alveolitis cases following tooth extraction. The presence of these bacteria suggests that existing infections in extracted teeth may contribute to alveolitis development.

The synergy between *T. denticola* and *P. gingivalis*, both members of the "Red Complex", has been documented and this study supports the notion that their combined presence may enhance their effects on alveolitis development.

Preventive strategies such as antibacterial mouthwashes and antibiotics are effective in reducing oral bacteria levels. Chlorhexidine mouthwash showed a lower prevalence of alveolitis in patients positive for *P. gingivalis* who used the mouthwash.

Similarly, tailored antibiotic therapy targeting specific oral bacteria may be crucial for preventing alveolitis formation, especially considering the higher prevalence of *T. denticola* compared to *P. gingivalis*. Further research is needed to better understand the interactions between different bacterial species and their role in alveolitis development following tooth extraction.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Cahit Üçok, Funda Gökçe Akbulut;* ***Design:*** *Ayça Dilara Yılmaz, Funda Gökçe Akbulut;* ***Control/Supervision:*** *Funda Gökçe Akbulut, Ayça Dilara Yılmaz;* ***Data Collection and/or Processing:*** *Funda Gökçe Akbulut, Ayça Dilara Yılmaz;* ***Analysis and/or Interpretation:*** *Mehmet Emre Yurttutan, Funda Gökçe Akbulut;* ***Literature Review:*** *Funda Gökçe Akbulut;* ***Writing the Article:*** *Funda Gökçe Akbulut, Mehmet Emre Yurttutan;* ***Critical Review:*** *Mehmet Emre Yurttutan, Ayça Dilara Yılmaz, Cahit Üçok;* ***References and Fundings:*** *Funda Gökçe Akbulut, Ayça Dilara Yılmaz;* ***Materials:*** *Funda Gökçe Akbulut, Ayça Dilara Yılmaz.*

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