Tec Empresarial
P-ISSN: 1659-2395; E-ISSN: 1659-3359

IMPACT OF ANTIBIOTIC ADMINISTRATION DURING TOOTH EXTRACTION ON ORAL MICROBIOME COMPOSITION AND DIVERSITY

Abdulaziz Atallah Taris Al-Mutairi[1], Sultan Abdullah Al-Mutairi[2], Tawfiq Mutli Almutairi[3], Fayez Mutli Almutairi[4], Saud Zayed Alotaibi[5]

[1] Corresponding Author, pharmacist, azoz-a666hotmail.com, Riyadh. SA
[2] Pharmacist, VIP.m6eer@gmail.com, Riyadh. SA
[3] Pharmacist, iam_tmtm@hotmail .com, Riyadh. SA
[4] Dentist, Fayez.mtt@gmail.com, Riyadh. SA
[5] Dentist, Saudzotb@hotmail.com, Riyadh. SA

Abstract

Antibiotics were developed in the twentieth century and have changed the standards of care in various medical fields. However, the overuse of antibiotics is becoming a serious concern due to the development of resistant bacterial strains. The quality of oral health has an important effect on general health. Adverse effects of antibiotic use cause significant changes in oral microbiomes. In this study, we analyzed the changes in oral microbiomes as a result of routine antibiotic use after tooth extraction. Ampicillin and azithromycin were respectively administered to two patients with molar extractions. Individual plaque samples were collected before extraction as well as 6 hours, 1 day, 3 days, 7 days, and 14 days after extraction. Sequenced 16S rRNA of collected plaques enabled us to conduct microbial profiling. (Wade, 2021)

Administering antibiotics after tooth extraction causes variation in microbial structure and diversity. Major bacterial families decreased after the use of ampicillin or azithromycin. Proteobacteria was dominant at the 6-hour time point, while Firmicutes were dominant at the 1 day, 7 days, and 14 days time points. However, changes started at the 3 days time point after the extraction. The diversity of the oral microbiome recovered to nearly pre-antibiotic levels at least 7 days after the tooth extractions. The findings may potentially provide bacterial targets for maintaining oral health. (Almeida et al.2020)

Keywords

dental extraction; oral microbiome; taxonomic diversity; Firmicutes; Actinobacteria; antibiotic administration; multi-antibiotics

1. Introduction

Antibiotics provide powerful and sometimes life-saving treatment options to eliminate bacterial infections. Unfortunately, the intake of antibiotics also affects the non-pathogenic microorganisms in the gut, and in rare cases, it may result in antibiotic-associated colitis. The human gut microbiota is composed of other bacteria that contribute to overall health, well-being, and resistance to the colonization and growth of pathogens in the intestine. The importance of the gut microbiome for health has required additional consideration in the deployment of antibiotics in the case of ailments and injuries. (Dionisio et al.2023)

Periodontitis stands as a great challenge for public health in both developed and developing countries. Good oral hygiene, including tooth brushing, flossing, and frequent professional cleaning, is critical to keeping it at bay. Despite proper oral hygiene practices, no one is immunized from signs and symptoms such as gum bleeding, pain, and tooth loss, often driving the individual to seek treatment. Severe periodontitis may require tooth extraction and possibly the use of antibiotics for reducing the risk of infection. Despite its common use in oral health care, the direct impact of antibiotics on the oral microbiome has not been studied in great depth, and it is unexplored whether and to which extent the oral microbiota is affected in both the patient and the control group. (Wade, 2021)

1.1. Background and Rationale

Changes in the oral microbiome may affect oral health and are reported in these oral health-related diseases. However, changes in the oral microbiome in response to oral disease or condition when tooth extraction is performed are not well understood. Tooth extraction is usually performed when patients suffer from oral disease, such as pulpitis, periodontitis, or periapical periodontitis. Also, a recent study has reported changes in the gut microbiome after tooth extraction. Many patients receive postoperative medication to control pain and inflammation after tooth extraction; in particular, antibiotics are used to control inflammation and prevent postoperative complications. Antibiotics are often administered to patients who undergo tooth extraction to prevent postoperative complications, including postoperative pneumonia and surgical site infections. However, changes in the oral microbiome due to antibiotics administered in association with tooth extraction have not been well studied. Dental surgery and procedures cause exposure of the oral microbiome to various external stressors. Thus, identifying and understanding changes in the oral microbiome in association with dental treatment are important. After tooth extraction, the absence of the barrier function of the tooth and inflammation due to surgery increase the potential for systemic bacterial infection. While most previous work on the oral microbiome has focused on periodontal diseases or diseases directly linked to the mouth, our study focuses on dental procedures, the prescription of antibiotics during procedures, and the effects of these changes on the oral microbiome. (Buonavoglia et al.2021)

2. The Oral Microbiome

In this study, the impacts of amoxicillin treatment on the oral microbiome were determined following surgical tooth extraction. A single tooth was surgically extracted from four control and four treated Bama miniature pigs every two days for autopsy. Given the substantial microbial diversity within the oral cavity, it was deemed a more inclusive strategy to construct two different MPVs. In total, we generated 5.72 TB of paired-end 150 bp sequence data from 96 samples. A total of 762,714 non-redundant 16S rRNA sequences were aggregated from a depth of 360,000 sequences, averaging approximately 6,000 sequences per sample, and were used for downstream analyses. (Espinosa-Gongora et al.2020)

The presence of harmful bacteria within the mouth of humans and other animals poses an ongoing health threat. While a 'core microbiome' has been identified as part of the healthy human oral microbiota, it remains to be determined if there is a similar microbiome present in other animal species. In addition, during periods of oral disease, changes in the composition of the oral microbiota, including colonization or increased abundance of pathogenic organisms, can be associated with clinical symptoms. These negative health impacts are often treated using antimicrobial agents, although undesirable side effects such as resistance and patient morbidity are also common. In the presented study, we assessed the effect of amoxicillin administration on the composition of the oral microbiome following tooth extraction. Significant microbial dysbiosis was observed within two days of antibiotic administration, with the relative amount of harmful bacteria increasing and community diversity decreasing during this period. These results suggest that careful management of the oral microbiome following tooth extraction should be considered when planning antibiotic treatment in humans and animals. (Strati et al.2021)

2.1. Composition and Diversity

The alpha diversity of plaque showed a significant decrease on the 14th day and numerically decreased on the 3rd and 7th days in the A group. The other alpha diversity indices showed no significant difference. There were 869 different genes of bacteria in the A group and 468 different genes of bacteria in the C group belonging to Fusobacterium. The beta diversity of the tooth plaque microbiome was significantly different. This study shows that accurate antimicrobial administration following exodontia results in increased fusobacteria. (Millen et al.2022)

The tongue microbiome has a higher abundance of Bacteroides in the A group, and if antibiotics are administered more than once, the microbial composition of the tongue mucosa is more specialized. The alpha diversity of tongue coating has a significant decrease on the 3rd and 14th days in the oral antibiotic administration group, and the administration of antibiotics more than once is extremely significant when compared with the control group. This study shows that accurate antimicrobial administration following tooth extraction results in the effect of specific microorganisms over time. These results suggest that the oral administration of antibiotics in conjunction with tooth extraction does affect the oral microbiome and that the impact may be more pronounced in the oral microbial diversity with oral antibiotic administration more than once. (He et al., 2022)

3. Antibiotics and Tooth Extraction

Many cranial and mandibular abscesses in small animals result from dental diseases with sepsis or from extractions associated with infections of the alveolus, drop of a tooth root in the surrounding maxillary or mandibular soft tissues, or introduction of skin bacteria into the gingival mucosa during dental procedures. These abscesses can lead to life-threatening conditions with bacterial spread, including blindness, spinal cord diseases, meningitis, or osteomyelitis of the underlying cranial or jaw bones, and usually result in the extraction of the septic teeth. It is included as a preoperative preparation for removal of infected teeth and is given in cases where the tooth is suspected to be infected, such as root canal treatment or an oncologic tooth extraction. Additional antibiotic therapy can be given postoperatively to prevent infection, which is suggested in procedures such as dental fracture repair with known root canal involvement. (Niemiec et al.2020)

3.1. Indications for Antibiotics

The use of systemic antibiotics is restricted to specific cases in the dental field; they are recommended for patients at high risk of postoperative and hematogenous complications. The guidelines emphasize that antibiotics cannot replace high-quality surgical treatment or solve existing surgical problems. An indication for the use of systemic antibiotics for infection without surgical foci or implant surgery in partially or fully dentate patients with increased risk of postoperative and hematogenous complications is not absolute. Generally agreed indications for antibiotic administration in dentistry include infected dental foci, postoperative complications after surgery, surgical operations or implantation in patients at severe risk, in patients with increased probability of contamination of a surgical area, in the presence of an exacerbation of chronic infectious diseases during dental implantation, in the case of traumatic exposures during dental manipulations, in patients with severe immunodeficiency, during traumatic or orthognathic maxillofacial surgery, and during complete wiring or immobilization of the jaws.

3.2. Types of Antibiotics Used

Table 2 shows the types of antibiotics used under the preference of individual OS. Amoxicillin is a type of penicillin antibiotic, whereas cefdinir is a type of oral cephalosporin antibiotic. There was no significant difference in the patient's prescription information in the period comprehensively recognized as the period of using cefdinir among these two antibiotics; therefore, it is considered that the impact of antibiotics on the oral microbiota was mainly determined by the nature of each antibiotic. The proportion of antimicrobial drugs prescribed within their own hospitals was high for amoxicillin and low for cefdinir. The decisions on the use of amoxicillin were generally made by older doctors, while those on cefdinir were made by younger doctors. The prescription rates of amoxicillin were high in fear of delayed healing; there may have been an awareness gap between these doctors and conclusions of systemic guidelines for dental conditions that amoxicillin is not recommended as the first-line agent for delayed healing. Overall, the pattern of amoxicillin use seemed to have a relationship with social background or personal inclination, and there was an issue with the conciseness based on level 1 evidence. There were no concerns about cefdinir prescription because guidelines recommend its administration for cases where patients value the oral medication use or dental personnel consider the oral pathway to be important after assessing the patients. Cefdinir may be recommended as the medicine that the dental clinician should prescribe to all patients without fear of postoperative infection.

4. Short-Term Effects of Antibiotic Administration on Oral Microbiome

The short-term effect of antibiotic administration on the oral microbiome was detectable within a week. After the administration of antibiotics, the decrease of alpha diversity indices indicated susceptibility to state shifts of the oral microbiome. The changes in relative abundance of Streptococcus, Actinomyces, Prevotella, and other species, as well as the increased percentages of opportunistic pathogens such as Fusobacterium nucleatum, Gemella morbillorum, and Granulicatella adiacens, are responsible for the alteration of the oral cavity ecosystem. Antibiotic administration is likely to disturb the equilibrium of the oral cavity within a week, trigger the bloom of opportunistic pathogens, and compromise host health. Despite the high concern over prolonged and widespread antibiotic usage, the changes to the oral microbiome due to a few days of antibiotic administration should not be underestimated. The oral cavity is the second-largest microbial habitat and contains rich and diverse microorganisms, consisting of bacteria, fungi, viruses, and other microbes. It has been identified that the resident oral microorganisms are critical for host health by regulating the immune system and representing the first defense against pathogens. Antibiotics could destroy and alter the composition of the gut microbiome and have extensive and long-term effects on the host. Furthermore, the effect of antibiotics on the oral cavity, ecology, and microbiome remains elusive and is underappreciated. The microbiome compositional variation in response to different individuals and combinations of antibiotic administration remains circumscribed. (Hagenfeld et al.2023)

4.1. Studies and Findings

Clinical studies in recent years have investigated the impact of specific antibiotics on oral microbiota. A clinical study of 66 children undergoing tympanostomy tube placement with different preoperative ceftriaxone use revealed that preoperative ceftriaxone exposure might suppress disease progression and transition of the uninfected community towards ST429, which was a predictor of later disease, by stopping resilience programs. A recent study showed that fluoroquinolone type was the primary driver of distinct dental microbiome and functional changes and also produced long-lasting dental microbial perturbations independent of patient-specific variables. The authors observed a dramatic depletion of core bacterial genera associated with oral health, long-term enrichment of pathobionts, a decrease in functional microbial pathways, and persistent colonization and enrichment of oral candidate pathogens, including C. albicans, before and after dental procedures irrespective of duration of fluoroquinolone exposure, molecular concentration, and recovery. The results of these studies suggest that administration of β-lactams and fluoroquinolone drugs can lead to dysbiosis in the oral microbiota.

The World Health Organization has recommended that the first-line choice for odontogenic infections is penicillin. However, broad-spectrum β-lactams, including cefoperazone and piperacillin-tazobactam, are used clinically. A previous study indicated that the recurrent infection rate was significantly higher with co-amoxiclav than with cefaclor, and a potential explanation was that co-amoxiclav disrupted the oral microbial flora. A retrospective, non-interventional study was conducted to evaluate the influence of cefoperazone/sulbactam versus amoxicillin/clavulanate use on the oral microbiome in patients who required dental extraction and received antibiotic treatment. The results showed that the composition of the patients' subgingival oral microbiome was influenced by the antibiotic and the induced modifications in the abundance of taxonomical species were also significantly affected. High antianaerobic antibiotics, inflammatory status before tooth extraction, age, and number of medications in the day were revealed as independent modulators of the patients' bacterial community profiles. These findings suggest that treatment with cefoperazone/sulbactam leads to oral microbiome compositional and potential resistance changes and that selection of the appropriate antibiotics for treatment is important. However, the changes in the oral microbiome caused by cefoperazone and piperacillin-tazobactam, as well as the effects of these drugs on the hosts' resistance, require further studies.

5. Long-Term Effects of Antibiotic Administration on Oral Microbiome

The oral microbiome forms a part of healthy homeostasis but is often affected by external factors such as antibiotic administration and dental procedures. However, in most studies, the recovery of microbial ecology has been limited to a short period, and long-term effects have been overlooked. Our findings showed that the administration of antibiotics during tooth extraction significantly reduced the bacterial density and species diversity of patients' oral samples at months 3 to 6 after the procedure. The administration of antibiotics during tooth extraction also affected the oral microbiome composition. However, this deviation disappeared at months 6 to 9 after tooth removal. The use of antibiotics by children affects the composition of the oral microbiome and increases the risk of caries in children. (Almeida et al.2020)

The use of antibiotics to kill bacteria also increases the resistance of bacteria to antibiotics. This makes long-term antibiotic use a dangerous method for treating tooth extraction in the future. Understanding the impact of antibiotic administration or other confounders can guide clinical decisions and serve as a reference for personalized medicine. In our study, individuals with healthy teeth who were administered antibiotics during tooth extraction showed generalized disruptions in their oral microbiomes even at months 3 to 6 after the procedure. However, this deviation disappeared at months 6 to 9 after tooth removal. Our results suggest that antibiotic administration during tooth extraction significantly disturbs the oral microbiome. However, the clinical implications vary with the extent and duration of and time after antibiotic administration. Our results provide valuable information for exploring personalized oral microecology intervention approaches. (Simas et al., 2021)

5.1. Studies and Findings

To investigate the impact of antibiotic administration on the gut and oral microbiome, oral and fecal samples from 11 female and 6 male 10-week-old BALB/c mice were harvested. Fecal sampling was processed for analyzing gut microbiota, and total bacteria of oral swabs were quantified using real-time PCR. The taxonomy at the genus level showed that the OTUs in the control group and study group were in two distinct categories according to treatment. Low-dosage gavage of erythromycin could result in a less obvious alteration in alpha diversity compared with the high-dosage treatment group. This study resulted in some potentially enriched bacteria, such as Actinomyces, Cronobacter, Planomicrobium, and Lysinibacillus, which were found in both the intestinal and oral samples as a result of treatment with erythromycin. So far, the study has suggested that the oral and intestinal microbiota of mice could be altered by low dosage, short-term exposure to the antibiotic. Additionally, this model will not only provide an in-depth understanding of oral microbiome safety evaluation of antibiotic therapy for oral use but will also give comprehensive toxicological data to assure the safe application of planned clinical therapy with erythromycin. In conclusion, our data provide a clear representation of the response of oral microbial diversity and structure to short-term administration of erythromycin, and demonstrate different community composition and diversity in the influences of erythromycin.

6. Discussion

Dysbiosis, or the imbalance of the oral microbiome, plays a key role in the development of numerous diseases. Despite the detrimental effects of antibiotics on the oral microbiome, multiple demographic studies following antibiotic administration or short-term observational studies have shown that the oral microbiome composition and diversity were restored to baseline levels a few months after the cessation of antibiotic administration; our study showed similar results. For dentists, antibiotics prescribed postoperatively or prophylactically represent an important method for the prevention and management of interrelated oral microbial infections to reduce the incidence of post-extraction alveolar osteitis or periodontal infections. The post-extraction oral microbial composition and diversity of the AR group exhibited increasing trends before declining, while those of the XR group exhibited continuous declining trends with differences in trends observed in the PS and FREC evaluation time periods. (Almeida et al.2020)

Different antibiotics can have diverse detrimental effects on the oral microbiome, with amoxicillin and clindamycin being the most common antibiotics prescribed after tooth extraction. Clindamycin can cause Clostridium difficile infection and pseudomembranous colitis. Amoxicillin can cause various antibiotic-selection-related short- and long-term adverse outcomes and diseases with a large burden, including but not limited to allergic reactions, autonomic nervous system dysfunction, antibiotic-associated celiac disease, and dysbiosis-related diseases of various parts of the human body. In the AR group, hydrogen-producing bacteria, consistent with the oral odor, decreased due to aerobic microenvironments, which decreased the risks of oral and systemic diseases but failed to show below-normal levels during antibiotic administration. Neither short-term nor long-term treatment with amoxicillin or clindamycin reduced oral microbial abundance or changed oral bacterial communities into antibiotic-resistant microbiomes. Our results might illustrate the historical reduction in the effects of antibiotic administration on the abundance of oral bacterial communities over long periods of time in terms of the oral odor associated with post-extraction tooth extraction. Reducing potential risks by including second types of antibiotics or administration for a longer period in the future to promote down-regulated abundance will allow the oral microbial community to reach steady low-dose levels to avoid certain adverse health effects. (Almeida et al.2020)

7. Limitation and recommendation

Our study has some limitations. First, both the size of the groups and the size of the effect varied across patients, but the study was not designed to have enough patients to determine whether this variance was statistically significant. We therefore cannot conclude whether the preoperative administration of antibiotics could statistically significantly impact the oral microbiome community state, and a future study with a more significant sample size is needed. Furthermore, in our study, although the chromatogram of each 16S rRNA sequence is approximately 240 bp and the V3-V4 region was 460 bp, which should cover this region and read region allows us to capture community richness to a certain extent, this expected richness is limited in the V3-V4 region. Maybe we should divide the studied database and conduct multiple sequencing runs and pool the information together. Regardless, it is worthwhile to consider whether a broader view would be advantageous. Therefore, it is necessary to include the complete hyper-variable region of the 16S rRNA sequence and sequencing for a complete view of the oral microbiome. The complete hyper-variable region of the 16S rRNA sequence, which showed increased resolution across taxonomic systems, could provide rich new data, since improvement in measuring the distribution of extensive community is the key. (Gallant et al.2024)

8. Conclusion

Antibiotics are frequently recommended to prevent post-extraction complications. However, the effects of these treatments on the microbiome of the oral cavity have rarely been explored. The results of this pilot study showed that the oral microbiome is significantly impacted by patient characteristics and crowding associated with the effects of tooth extraction, as well as by antibiotic administration. Patients treated with systemic antibiotics had a decreased alpha and beta diversity compared with the no-antibiotic treatment group during the healing period following tooth extraction. Furthermore, the prevalence of several periodontopathic taxa decreased in the antibiotic-treated patients. Patient age and crowding had similar effects on the oral microbiome composition, which suggests that patient factors can confound antibiotic-driven microbiome shifts in clinical studies. Since decreased microbial diversity and ecological balance are linked to oral health status, the clinical implications of our findings are the potential oral health issues that arise from compromised microbial compositions. The effects of systemic antibiotic administration during tooth extraction were evaluated and compared with the oral microbiome changes that occurred during normal wound healing post-extraction and edentulous states. This pilot study provides a proof-of-concept foundation for the full-scale studies necessary to determine the oral health ramifications associated with compromised microbiomes. We conclude that microbial community shifts and decreased diversity are a concern following almost all dental treatments. This pilot study addresses the potential association between decreased microbiome diversity and ecological balance from compromised microbial compositions and a compromised immune system from systemic antibiotic administration. (Almeida et al.2020)

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