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Editor in chief - Prof. **Kjiro Ivanovski**, PhD, e-mail: kiroivanovski@stomfak.ukim.edu.mk
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Одговорен уредник: Проф. д-р **Ќиро Ивановски**, e-mail: kiroivanovski@stomfak.ukim.edu.mk
Заменик одговорен уредник: Проф. д-р **Елизабета Ѓоргиевска**, e-маил: egjorgievska@stomfak.ukim.edu.mk
Секретар на списанието: д-р **Влатко Коколански**, e-mail: vkokolanski@stomfak.ukim.edu.mk

Адреса - Македонски стоматолошки преглед, ул. Мајка Тереза бр. 43 Скопје, Република Северна Македонија
http://stomfak.ukim.edu.mk/msp/

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THE SIGNIFICANCE OF HEMATOLOGICAL AND INFLAMMATORY BIOMARKERS IN DETERMINING THE SEVERITY OF ODONTOGENIC INFECTIONS: A NARRATIVE REVIEW

УЛОГАТА НА ХЕМАТОЛОШКИТЕ И ИНФЛАМАТОРНИ БИОМАРКЕРИ ВО ДЕТЕРМИНИРАЊЕ НА ТЕЖИНАТА НА ОДОНТОГЕНИТЕ ИНФЕКЦИИ

Cena N.[1], Popovik Monevska D.[2], Bozovik Dvojakovska S.[2], Koneski F.[2]*

[1]Department of Maxillofacial Surgery, Faculty of Dental Medicine, Ss. Cyril and Methodius University in Skopje, School for Third Cycle, North Macedonia, [2]University Clinic for Maxillofacial Surgery in Skopje, Ss. Cyril and Methodius University in Skopje, North Macedonia, [1]*Correspondence Author

Abstract

Introduction: Odontogenic infections can lead to a variety of complications, with cellulitis being one of the most potentially serious infection. This condition involves a rapid and widespread inflammation of the subcutaneous tissues, characterized by an acute and diffuse nature. It occurs when the infection spreads through the spaces between cells, affecting surrounding tissues and the entire connective tissue layer due to dental issues. **Aim:** In our study, we critically analyzed the results of most recent papers, all of them focusing on biological and inflammatory biomarkers in odontogenic infection. In routine clinical practice for managing cervicofacial infections and phlegmons, which can be life-threatening, the use of blood biomarkers and indices is essential. These tools aid in identifying patients with severe infections who may benefit from more intensive conservative and surgical treatments. This targeted approach is crucial for preventing complications and avoiding the progression to sepsis. **Results:** Although many studies emphasize the advantages of dental care and antibiotic treatment, the life-threatening nature of cervicofacial infections and phlegmons calls for a more careful and strategic treatment approach. Effectively managing these complex conditions requires comprehensive assessments and customized management plans. **Conclusion:** Utilizing blood biomarkers and indices will aid in identifying patients with severe infections who may benefit from aggressive conservative and surgical interventions, ultimately helping prevent complications and sepsis. **Keywords:** CRP, NLR, WBC, Odontogenic infections, Biomarkers

Апстракт

Вовед: Одонтогените инфекции можат да предизвикаат сериозни компликации, целулитис на главата и вратот како најчеста компликација. Целулитисот се развива со прогресија на инфекцијата дифузно и фрудрујантно во длабоките простори на главата и вратот. **Литература:** Во рутинската клиничка пракса при третман на цервикофацијалните инфекции , кои можат да бидат животозагрозувачки, употребата на крвните биомаркери е од есенцијално значење. Со помош на овие биомаркери може да се идентификираат пациентите со тешки инфекции и лоша прогноза и истите да се третираат со поагресивен конзервативен и хируршки пристап. Брзата и таргетирана терапија може да ја спречи прогресијата на инфекцијата и евентуални компликации како сепса. **Заклучок:** Многу студии укажуваат дека и покрај сеопфатната дентална превенција и терапија сепак мал дел од одонтогените инфекции можат да предизвикаат животозагрозувачки состојби. Ефективно менаџирање на денталните инфекции предпоставува индивидуални планови за третман , затоа ни се потребни крвните биомаркери за навремено препознавање на тешките одонтогени инфекции и превземање на соодветни терапеутски протоколи. **Клучни зборови:** CRP, NLR, WBC, Одонтогени инфекции, Биомаркери.

Introduction

Odontogenic infections can lead to a variety of complications, with cellulitis being one of the most potentially serious infection. This condition involves a rapid and widespread inflammation of the subcutaneous tissues, characterized by an acute and diffuse nature. It occurs when the infection spreads through the spaces between the cells, affecting surrounding tissues and the entire connective tissue layer due to dental issues[1,2].

Understanding the similarities in anatomy, pathophysiology, and pharmacokinetics between pediatric and adult

patients is essential. In children, odontogenic cellulitis in the head and neck is often associated with various microbes, predominantly aerobic bacteria. In contrast, adults are more commonly affected by infections caused by non-resident bacteria, such as staphylococci and streptococci.

These infections typically occur due to the bacteria that are usually found in the oral cavity.

Clinical signs such as dysphagia, dyspnea, restricted tongue movement, and oropharyngeal edema serve as crucial indicators of infection severity, prompting attention from deontologists and oral and maxillofacial surgeons.

The growing prevalence of underlying conditions such as alcoholism, immunodeficiency, and chronic diabetes may contribute to the trend of increasingly severe infections, compounded by rising antibiotic resistance.

Delays in diagnosis, frequently managed with various antibiotics or anti-inflammatory medications, may not effectively resolve the underlying illness and often serve only as a symptom relief.

Odontogenic infections are the most frequent source of bacterial infections in the maxillofacial region, but they rarely advance to sepsis. Nonetheless, the risk of progression to sepsis cannot be ruled out in cases of moderate or severe infections that involve the fascial spaces[6-10].

Diagnostic laboratory tests are important adjuncts for evaluating the severity of a patient's inflammatory and infectious conditions. Commonly used markers include white blood cell count (WBC), C-reactive protein (CRP), and procalcitonin (PCT). Additionally, presepsin (PSEP) is gaining recognition as a valuable indicator in this context[6,11,12].

Other examples of inflammatory bi omarkers in odontogenic infections are PLT, LYMPH and NEU. Among the various acute phase proteins, C-reactive protein (CRP) is recognized as the most dynamic member of the pentraxin protein family. Its primary biological function lies in its ability to identify pathogens and damaged host cells, facilitating their elimination by activating the complement system and recruiting phagocytic cells. The WBC count assesses the total number of white blood cells in the blood and is a non-specific measure. A count above 10,000 leukocytes/mm^3 may indicate leukocytosis, which can be caused by various health issues like inflammation, bacterial infections, tissue injury, or cancer. Furthermore, WBC levels can naturally increase after exercise or meals. Neutrophil counts rise with the severity of inflammatory conditions, while lymphocyte counts, which indicate immune function, generally decline as inflammation worsens. Therefore, the neutrophil-to-lymphocyte ratio (NLR) is regarded as a more accurate indicator of inflammation than the overall leukocyte count. Evaluating these parameters can be beneficial for diagnosing odontogenic cellulitis and guiding treatment decisions[1].

Inflammatory markers obtained from blood tests are often used to predict the severity of odontogenic infections. Key markers measured in clinical practice include C-reactive protein (CRP), white blood cell count (WBC), and its components (neutrophils, lymphocytes, monocytes). However, relying solely on these values has limitations in accurately determining infection severity, highlighting the need for alternative assessments. Recently, a new inflammatory prognostic score known as the Systemic Immune-Inflammation Index (SII) has been developed to enhance the evaluation of patients' biomarkers[3,5].

To address this issue, the Symptom Severity score (SS) was created to help physicians accurately assess the risk of infection and identify potential complications during patient admission[3,4].

Some studies suggested that PCT and PSEP levels were significant predictors of sepsis, with higher values indicating an increased likelihood of the condition. Despite progress in diagnosis and treatment, mortality and morbidity remain significant concerns. One particularly rare and fatal complication is necrotizing soft tissue infection (NSTI). It is vital to stay alert, as NSTIs can be difficult to differentiate from cellulitis in their early stages, making the use of specific parameters crucial for prompt detection. Inflammatory markers from blood tests are often used as objective evaluation parameters, with C-reactive protein (CRP), white blood cell count (WBC), and its components (neutrophils, lymphocytes, monocytes) as common references. However, these values alone do not give a complete picture of disease severity. Leukocyte levels respond quickly to infections, whereas CRP levels rise more slowly, typically peaking around 48 hours after inflammation or infection begins.

Infections originating from teeth or jaw in the head and neck region can lead to serious, sometimes fatal complications, such as airway obstruction, large abscesses, necrotizing fasciitis, purulent meningitis, cerebral abscesses, mediastinal infections, sepsis, and septic shock. Anesthesia options included general anesthesia with endotracheal intubation or local anesthesia with premedication, depending on the severity of the case. However, managing respiratory difficulties and complications with intubation remains a significant challenge in cases of head and neck odontogenic infections. Factors like trismus (jaw muscle spasms) and anatomical variations complicate the procedure even further. Some authors reported a case series where all patients were treated with incision and drainage under local anesthesia and analgosedation, with no need for advanced respiratory management. In contrast, other authors suggest that most patients required only a short hospital stay, with the majority being discharged within 5 days. This shorter hospitalization may reflect the advantages of early diagnosis and prompt intervention, leading to faster recovery and reduced complications[13].

The primary treatment for odontogenic infections consists of incision and drainage of the abscess, along with removal of the infection source in the oral cavity, when necessary. However, the optimal sequence of these surgical procedures is still a subject of debate[13,19].

Prompt identification and effective management are crucial for ensuring a swift recovery, shortening hospital stays, and minimizing the risk of serious systemic complications. Regular monitoring of vital signs, such as body temperature and blood pressure, along with inflammatory markers like leukocytosis, C-reactive protein (CRP) levels, and possibly procalcitonin levels, is essential. Systemic treatment typically includes empirical antibiotic therapy guided by the antibiogram. During abscess drainage, samples are collected for microbiological analysis in order to identify the microbial species, to assess their sensitivity to various antibiotics, and to determine the minimum inhibitory concentration (MIC). Understanding the MIC is vital for planning an effective drug dosage[13,20,21, 22,23].

Researchers are examining the effectiveness of inflammatory biomarkers from routine blood tests to assess infection severity, prognosis, and potential complications, much like they do with other treatment methods.

This review seeks to provide a comprehensive analysis of the scientific evidence regarding the effectiveness of hematological and inflammatory biomarkers in assessing the severity of odontogenic infections. We searched key data bases (PubMed, Google Scholar, Research Gate, MDPI, and Science Direct). Search terms concerning odontogenic infections, hematological biomarkers, and inflammatory biomarkers were combined. The reference lists of identified articles, available in English, were then utilized to locate additional relevant references.

Aim

The purpose of our study was to analyze 10 scientific papers from 2018-2024 year, all of them focusing on biological and inflammatory biomarkers in odontogenic infection.

In our study, we critically analyzed the results of these most recent papers and pointed out the important findings. (Table 1)

Results

Role of hematological and inflammatory biomarkers in odontogenic infections.

Severe odontogenic infections can be unpredictable in their progression, necessitating thorough clinical assessment along with specific laboratory tests to achieve an accurate conclusive diagnosis.

Inflammatory biomarkers are substances in the body that indicate inflammation, which can occur due to various conditions such as infections, autoimmune diseases, or chronic diseases. In routine clinical practice, the use of blood biomarkers and indices is essentialfor managing cervicofacial infections and phlegmons, which can be life-threatening. These tools aid in identifying patients with severe infections who may benefit from more intensive conservative and surgical treatments. This targeted approach is crucial for preventing complications and avoiding progression to sepsis.

Marius et al. performed regression analysis of the relationship between the Severity Score (SS) of odontogenic infections and the SII index values and they found a strong correlation (r=0.6314) with a p-value that is less than 0.05. This indicates a statistically significant association between the Symptom Severity score of odontogenic infections and the SII index values. The overall mean SII index for the entire cohort was 1303, while the mean values for severity groups were 696.3 in Group A and 2312.4 in Group B (p-value<0.001). Similarly, SS scores also showed a significant difference, with a mean of 6.1 in Group A and 13.6 in Group B (p-value < 0.001)[3].

In a recent study by Eun-Sung Kang and Ja-Hoon Lee, WBC, CRP, and PCT levels have been used to assess the severity of infection and sepsis in patients with odontogenic infections. However, the findings of this study suggest that PSEP may also be significant in evaluating the severity of these infections and sepsis. When used alongside current testing methods, PSEP is anticipated to enhance the assessment of patient prognosis. Specifically, the odds ratios for PCT and PSEP were 14.75 and 31.17, respectively. This implies that for every 1-unit rise in PCT, the chance of sepsis increased by a factor of 14.75, while a 1-unit increase in PSEP boosted the sepsis risk by a factor of 31.17. These findings were statistically validated. On the other hand, no diagnostic test values showed a significant link to prolonged hospitalization (P<0.05). The correlation between CRP, PCT, PSEP levels, and hospital stay duration was moderate, with coefficients of 0.44, 0.55, and 0.50, respectively, all significant at P<0.05. PCT levels begin to rise around 4 hours post-infection, continuing to increase between 8 to 24 hours before peaking at 24 hours. In comparison, PSEP levels increase more rapidly, detectable within 2 hours and reaching their peak at 3 hours. The quick result turnaround time of PSEP, approximately 20 minutes, makes it a useful tool for early sepsis detection in emergency departments. While PCT demonstrated a strong area under the curve (AUC), higher average PSEP levels were particularly associated with patients who died from sepsis within 60 days of hospitalization[6].

In a study by Junya et Kusumoto et alfound out that hematologic and inflammatory parameters derived from

routine blood tests can be useful as supplementary diagnostic tools for the early identification of potentially fatal odontogenic infections. SII of ≥282, or SII of <282 when accompanied by CRP + NLR of ≥25, can help determine the need for contrast-enhanced computed tomography imaging. The study demonstrated that nearly all hematologic and inflammatory markers escalated as the severity of odontogenic infections increased. Both CRP combined with NLR (using a threshold of 27) and the LRINEC score (with a threshold of 6) proved to be reliable supplementary diagnostic tools for identifying NSTI. This suggests that blood tests can provide a near-complete assessment of the severity of odontogenic infections. Moreover, CRP + NLR and SII were found to be valuable adjuncts for guiding decisions on CECT imaging. To our knowledge, this is the first study to utilize hematologic and inflammatory markers-particularly SII and CRP - NLR-as indicators for evaluating the severity of bacterial infections in head and neck, including NSTI. This study suggests that SII and CRP + NLR could be valuable tools in the decision-making process for whether to perform CECT. High values of SII or CRP + NLR were observed in Groups I and II, which were linked to sepsis, large but superficial abscesses, and inflammation extending into deeper anatomical spaces. As a result, the combined use of CRP + NLR and SII was found to closely mirror the severity of the infection and the extent of the inflammation[24].

A review about basic science studies highlighted that using hematological and biochemical inflammatory markers can be utilized to evaluate not only the therapeutic efficacy of different treatment regimens for infections but also to gauge the severity of the infection and the patient's prognosis.

While hematological and biochemical inflammatory biomarkers are essential for evaluating prognosis and infection severity, can they alone provide sufficient clinical insight to establish the appropriate length of a patient's hospitalization?

Related to hospitalization length, in her retrospective study, Adrianna Słotwińska -Pawlaczyk et al. found that, in addition to CRP, NLR can be regarded as a significant prognostic marker for both the progression of infection and hospitalization duration, as it shows a strong correlation between the length of stay and overall clinical symptoms[1].

In a retrospective study by Horatiu Ureches et al. they found that, alongside other inflammatory markers, WBC and CRP should be utilized as biological parameters for predicting the duration of hospitalization in adult patients with maxillofacial infections, with WBC identified as the most sensitive indicator in these situations[25].

Kaur et al. suggested that firstly, measuring serum markers quantitatively can help assess the effectiveness of different treatment approaches for infections, and secondly, it can guide decisions about how long antibiotics should be used. In this study, preoperative levels of WBC count, CRP, and ESR showed a strong connection with the severity of infection, particularly regarding pain and the ability to open the mouth ($p<0.01$). Additionally, there was a highly significant correlation ($p<0.001$) between clinical factors reflecting infection severity—such as swelling, difficulty swallowing, trouble breathing, fever, hoarseness, and active pus discharge—and the three biochemical markers, both before surgery and on day 14 after surgery. The study also found that the average hospital stay was 2.16 days, with a significant association ($p<0.001$) between the length of stay and the levels of all three biochemical markers[26].

In the study by Povan et al., patients were divided into two categories based on the complexity of their cases: Group 1, consisting of more complex cases with longer hospital stays, and Group 2, consisting of simpler cases with shorter stays various factors, such as patient demographics, pre-existing conditions, symptoms, vital signs, and lab results, were assessed across both groups. The findings showed a statistically significant inverse relationship between hospital stay duration and several important clinical factors, such as heart rate ($p = 0.028$), leukocytosis ($p=0.045$), neutrophilia ($p=0.033$), neutrophil-to-lymphocyte ratio ($p=0.041$), and CRP levels ($p = 0.003$)[27].

Ciprian et al. reported in their studies that patients were admitted and evaluated for hospitalization in accordance with the standards set by the Maxillofacial Department. Blood samples were collected from the ante cubital vein on Day 1 (admission) and again on the day prior to discharge. A routine blood test was performed immediately after blood collection to measure various biomarkers. The Systemic Inflammation Index (SII) was calculated using the following reference ranges for biomarkers: neutrophil counts (2.04–7.60 × 10^3/μL), platelet counts (150–410×10^3/μL), and lymphocyte counts (1.0–3.0×10^3/μL). The formula for calculating SII was:
SII=(neutrophil count×platelet count)/lymphocyte count
with results expressed as × 10^3/μL.For the Neutrophil-to-Lymphocyte Ratio (NLR), the following reference ranges were used: neutrophil counts (2.04–7.60 × 10^3/μL) and lymphocyte counts (1.0–3.0 × 10^3/μL). NLR was calculated by dividing the neutrophil count by the lymphocyte count. Normal NLR is between 1 and 2, while values greater than 3.0 or less than 0.7 in adults are considered abnormal. Additional blood parameters assessed upon admission included C-reactive protein (CRP) levels (0–9 mg/L), white blood cell (WBC) count (4.0–10.0 × 10^3/μL), and neutrophil, lymphocyte, and platelet counts (150.0–410.0 × 10^3/μL).All patients underwent identical

Table 1. Biochemical inflammatory and hematological parameters in odontogenic infections: are view of the most recentstudies

Authors	Study	Patients	Gender %	Results
Adrianna Słotwi ´ nska-Pawlaczyk 1 et al (2023)	Analysis of Clinical Symptoms and Biochemical Parameters in Odontogenic Cellulitis in Head and Neck Region in Children	85	40% Male 60% Female	Differences in biochemical test results in SS and CS were statistically significant ($p<0.05$). in the SS group, the mean values of biochemical parameters exceeded the clinical norm. A statistically significant positive relationship was found between CRP and extra oral swelling. The NLR correlates significantly with extra oral swelling and the length of hospitalization.
Horatiu Urechescu 1, et al. (2023)	Inflammatory Markers as Predictors for Prolonged Duration of Hospitalization in Maxillofacial Infections	108	61.11% Male 38.9 % Female	This study confirmed a positive linear correlation ($p<0.001$) between the predictors and the outcome variable.
Marius Pricop 1 et al. (2022)	The Predictive Value of Systemic Immune-Inflammation Index and Symptom Severity Score for Sepsis and Systemic Inflammatory Response Syndrome in Odontogenic Infections	108	61.1% Male 38.9% Female	The correlation between OI's SS and SII index values was positive and statistically significant ($r = 0.6314$). The total SII index mean was 1303, whereas the mean values by severity were 696.3 in Group A and 2312.4 in Group B. Group A's mean SS score was 6.1, while Group Bs was 13.6.
Eun-Sung Kang and Jae-Hoon Lee (2022)	Diagnostic value of presepsin in odontogenic infections	43	21 Female 22 Male	The results of this study showed a moderately positive correlation between CRP and PCT, CRP and PSEP, and CT and PSEP levels.
Ewa Zawislak et al. (2021)	Odontogenic Head and Neck Region Infections Requiring Hospitalization	85	31.8% Female 68.2% Male	The inflammatory markers varied with the location of the infection. The highest mean lymphocyte counts were observed in patients with infections in the PM (20.3×109/L) and M spaces (20.3×109/L). The highest mean CRP levels were found in infections of the neck phlegmon (245.8mg/dL). Patients with infections of the CF exhibited the lowest leukocyte (8.0×109/L) and CRP levels (36.9mg/dL).

Authors	Study	**Patients**	Gender %	Results
Junya Kusumoto 1,2 et al. (2022)	Hematologic and inflammatory parameters for determining severity of odontogenic infections at admission	271	50.9% Male 49.1% Female	The decision tree analysis showed that the systemic immune-inflammation Index (SII) of ≥ 282 or < 282, but with a CRP + NLR of ≥ 25 suggests Group III + IV and the classification accuracy was 89.3%.
Amreen Kaur1 et al. (2018)	Correlation Between Clinical Course and Biochemical Analysis in Odontogenic Space Infections	50	40% Female 60% Male	There was a significant correlation between all the clinical parameters and biochemical markers preoperatively as well as on various postoperative days.
Ciprian Ioan Roi 1,2 et al (2023)	Impact of Treatment on Systemic Immune-Inflammatory Index and Other Inflammatory Markers in Odontogenic Cervicofacial Phlegmon Cases: A Retrospective Study	39	17 females (43.6%) 22 males (56.4%).	After the analysis of the clinical and preclinical aspects, in the case of all the patients included in the study, the causative odontogenic agent was the lower molars. The average calculated hospitalization period related to the included cases was 16.6 days (SD = 11.8). swelling and the length of hospitalization
Eduardo P. Pavan1, et al. (2020)	Changes in Vital Signs and Laboratory Tests in Patients with Odontogenic Infections Requiring Hospitalization	84	//////////////////	There was a positive and statistically significant correlation between the length of hospital stay and the variables of heart rate (p=0.028), leukocytosis (p=0.045), neutrophil (p=0.033), N/L ratio (p=0.041) and CRP level (p=0.003) .
Ovidiu Rosca 1 et al. (2023)	The Role of C-Reactive Protein and Neutrophil to Lymphocyte Ratio in Predicting the Severity of Odontogenic Infections in Adult Patients	108	Men 30 (55.6%) 36 (66.7%) Women 24 (44.4%) 18 (33.3%)	However, there was no significant difference in mortality rates. The SS and systemic immune inflammation index (SII) scores of Group B patients were substantially higher than Group A patients (13.6 vs. 6.1 for the SS score, p-value < 0.001), respectively, 2312.4 vs. 696.3 for the SII score (p-value < 0.001).

surgical procedures and were administered the same antibiotic treatments[28].

Rosca et al. concluded that the logistic regression analysis was to assess how biological markers predicted the severity of odontogenic infections (OI), as measured by the SS scale. The analysis revealed that patients with lower white blood cell (WBC) counts were 5.54 times more likely to have mild OI. Similarly, lower neutrophil counts (odds ratio [OR]=7.10), lymphocyte counts (OR=8.62), and Neutrophil-to-Lymphocyte Ratio (NLR) (OR=4.46, $p<0.001$) were all strongly associated with a reduced likelihood of severe infection. Low CRP levels were also linked to a 6.65 higher likelihood of having a mild OI, and the CRP-NLR combination was found to decrease the risk of severe infection by 7.28 times (95% CI=4.83–10.16). Receiver Operating Characteristic (ROC) analysis of CRP-NLR showed an Area under the Curve (AUC) of 0.889 ($p<0.001$), with high sensitivity (79.6%) and specificity (85.1%) for predicting mild OI at hospital admission. Additionally, NLR could be an effective predictor for non-surgical treatment in submandibular abscesses and as an indicator of less severe recovery in odontogenic infections. Multiple studies have suggested that NLR is inversely related to factors such as pus formation, hospital stay duration, and the need for antibiotics. Furthermore, NLR is unaffected by physiological and environmental factors, such as dehydration, physical activity, or blood sample processing, which could otherwise skew test results[29].

In their research, Junya Kusumoto et al. found that most blood and inflammatory markers decreased as the severity of odontogenic infections improved; neither CRP+NLR (cut-off of 27) nor LRINEC score (cut-off of 6) serves as a reliable additional diagnostic tool for NSTI[25].

The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score is recommended as an additional diagnostic tool for identifying necrotizing soft tissue infections (NSTIs). At the same time, a new predictive marker, the systemic immune-inflammation index (SII), has been recently introduced, although its application in infectious diseases is still not fully clarified.

Discussion

Despite good access to dental services, effective antibiotic treatments, and positive socioeconomic factors, infections originating from dental issues are still the most common reason for admissions in maxillofacial surgery units. Analyzing different research studies suggests that regular blood tests assessing inflammatory markers are crucial for quick diagnosis of severe bacterial infections in the head and neck area.

Based on recent studies, we can conclude that inflammatory markers narrate numerous advantages for their usage.

According to them, quantitative determination of serum markers can be used for determining therapeutic efficacy of different treatment regimens of infections and the duration of antibiotic usage. In addition, the length of hospitalization plays a vital role in the prognostic assessment of odontogenic infections. Although some authors reach different conclusions in prior studies regarding hospitalization length, they all agree that NLR, CRP, and WBC are the most dependable indicators for evaluating this duration[1,6,26,27,28].

When the infection spreads to the cellular-adipose tissue of the head and neck, it becomes odontogenic cellulitis. Most of the cases are acute localized forms without signs of severity, and are rapidly resolved through appropriate medical and surgical treatment. However, the infection can disseminate deeply along the fascial planes, becoming life-threatening and causing extensive morbidity. In the maxilla, it is common to observe extension into the canine, buccal, and masticator spaces. Although maxillary odontogenic infections rarely pose a threat to the airway, they do have the potential to cause serious but exceptional complications, such as orbital abscess, cavernous sinus thrombosis, and cerebral abscess. In the mandible, the thin lingual cortex in the posterior molar region allows for the rapid spread of the infection in the fascial planes and can lead to airway obstruction and, ultimately, to mediastinitis. Even today, mortality and morbidity are not negligible, despite the progress made in diagnosis and treatment of the disease[13,31,33,34].

While many previous studies have indicated that markers such as CRP, white blood cell count (WBC), and its components (neutrophils, lymphocytes, monocytes) are commonly used to assess inflammation and are believed to be effective in identifying maxillofacial infections. Several authors are focused on the Systemic Immune-Inflammation Index (SII) as a potential predictor of the severity of odontogenic infections (OI). The SII, a relatively novel inflammatory marker, is calculated using the absolute counts of neutrophils, platelets, and lymphocytes in the bloodstream[3,13,24,29].

Conclusions

In conclusion, the use of CRP, ESR, and WBC count together offers a dependable method for assessing the progression of odontogenic infections. By quantitatively measuring these serum markers, clinicians can better determine the effectiveness of various treatment approaches and more accurately decide on the duration of antibiotic therapy.

Among these three biomarkers, CRP showed the earliest increase at the time of initial presentation, followed by a swift decline in its levels after surgery.

Based on literature review and the authors' analysis, minor dental problems are increasingly viewed as less significant. Enhanced access to dental care and antibiotic treatments has shifted the focus away from odontogenic infections in the head and neck region in many studies.

However, hematologic and inflammatory markers from routine blood tests remain important as additional diagnostic tools for early identification of potentially life-threatening odontogenic infections. Although many studies emphasize the advantages of dental care and antibiotic treatment, the life-threatening nature of cervicofacial infections and phlegmons calls for a more careful and strategic treatment approach.

Effectively managing these complex conditions requires comprehensive assessments and customized management plans. Utilizing blood biomarkers and indices will aid in identifying the patients with severe infections who may benefit from aggressive conservative and surgical interventions, ultimately helping to prevent-complications and sepsis.

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DENTOALVEOLAR MANAGEMENT OF PERIOPERATIVE BLEEDING IN PATIENTS WITH PLATELET HYPOAGGREGABILITY

ДЕНТОАЛВЕОЛАРНО МЕНАЏИРАЊЕ НА ПЕРИОПЕРАТИВНОТО КРВАВЕЊЕ КАЈ ПАЦИЕНТИ СО ХИПОАГРЕГАБИЛНОСТ НА ТРОМБОЦИТИТЕ

Gashi S.[1]*, Dvojakovska S.[2], Pepic S.[2]

[1]Istog Dubrava -The health station, correction institute, [2]JZU U Clinic for maxillofacial surgery - Skopje,

[1]*Correspondence Author

Abstract

Introduction: Platelet hypo aggregability, consequence of the reduction of the levels of ADP, collagen and ristocetin, is a life threatening condition, and present prolonged post extraction bleeding (PEB). Usage of Tranexamic acid (TXA) prevents excessive bleeding, accompanied by carefully performed surgical technique and local suturing, leads to a safe postoperative success. **The aim** of this study was to establish the protocol for perioperative management of hypoagreggability patients and to correlate PEB with levels of ADP, collagen and ristocetin and extensiveness of treatment. **Materials and Methods:** We analyzed 64 patients with hypoaggregability, treated at the University Clinic for Maxillofacial Surgery in Skopje, between 2019- 2024. Laboratory tests for ADP, collagen and ristocetin; clinical data of location and extensiveness of dentoalveolar treatment were correlated with bleeding tendency. TXA was applied perioperatively. Surgery was performed with minimal traumatic technique, and local hemostatic methods were evaluated. **Results:** Mean BT before diagnosis was (Me=4 IQR (2.5-9.5) versus PEB (Me=4 IQR (1-7)) (p =.000000). The difference is significant between dentoalveolar versus maxilla and dentoalveolar versus mandible for p=.0453). The difference between bleeding time (BT) and localization of the extraction is significantly longer in dentoalveolar surgery vs. maxilla and mandible (p =.0032). Tranexamic acid demonstrated a significantly lower risk of developing PEB. **Conclusion:** Bleeding control performing dentoalveolar procedures under the proper evaluation of hemostasis usingbenefits of perioperative TXA and local hemostasis is necessary for reducing PEB in thrombocytopathia. **Keywords:** platelet hypo aggregability, Dentoalveolar surgery, post extraction bleeding, Tranexamic acid.

Апстракт

Вовед: Хипоагрегабилноста на тромбоцитите, последица на смалени нивоа на АДП, колаген и ристоцетин, понекогаш може да биде животозагрозувачка, поради опасноста од абудантни постекстракциони крвавења (PEB). Употребата на Транексамична киселина (ТХА) спречува прекумерно крвавење, а придружено со внимателно изведена хируршкиметоди на хемостазаводи до безбеден постоперативен успех. **Целта** на оваа студија е да се воспостави протокол за периоперативно менаџирање на пациентите со хипоагрегабилност на тромбоцитите и да се корелираат нивоата на АДП, колаген и ристоцетин, со времетраењето и инвазивноста на PEB. **Материјал и методи:** Анализиравме 64 пациенти со хипоагрегабилност, третирани на Универзитетската клиника за максилофацијална хирургија во Скопје, во периодот 2019–2024 година. Лабораториски тестови за АДП, колаген и ристоцетин; клиничките податоци за локацијата и обемот на дентоалвеоларниот третман беа корелирани со тенденцијата за крвавење. Покрај интравенски предоперативна доза на ТХА, по потреба, доколку има крвавење, после 8ч. беше аплицирана уште една доза. Операцијата беше изведена со минимална трауматска техника, а беа евалуирании локалните хемостатски методи. **Резултати:** Просечното време на крвавење (ВТ) пред дијагнозата беше (Me=4 IQR (2,5–9,5) наспроти PEB (Me=4 IQR (1–7), (p=,000000). Разликата помеѓу (ВТ) и локализацијата на екстракцијата е значително подолга кај дентоалвеоларната хирургија во споредба со обична екстракција во максила и мандибула за p=.0453) и (p=,0032), соодветно. Транексамична киселина покажа значително помал ризик за развој на PEB (p=0,00). **Заклучок:** Контролата на крвавење при изведување дентоалвеоларни процедури со правилна евалуација на хемостазата, користејќи ги придобивките од периоперативната ТХА и локални техемостатски методи, е неопходна за намалување на PEB кај пациентите со хипоагрегабилност. **Клучни зборови:** хипоагрегабилност на тромбоцити, дентоалвеоларна хирургија, крвавење после екстракција, Транексамична киселина.

Introduction

Decreases of platelet aggregation deserve special attention due toserious postextractionbleeding (PEB) tendency. This condition includes deficiencies of receptors for adenosine diphosphate- ADP, collagen, and ristocetin, with episodes of spontaneous or induced mucocutaneous bleeding, epistaxis[1], hematomas, menorrhagia, and severe bleeding episodes after surgery, sometimes requiring-bloodtransfusion[2,3]. When the bleeding history is suspicious, it is a common practice to proceed to a staged series of investigations to confirm an abnormality of primary hemostasis or coagulation and to determine a precise diagnosis, in order toreduce the need of blood transfusion requirements and reoperations caused by bleedings[4].

Understanding the appropriate diagnostic and therapeutic approaches can only enhance thepatients' safety: (1) adiagnostic approach to the management of a patient's hypoaggregability is in close collaboration with transfusionspecialist. There is a consensusfor carrying out a few tests: platelet counts, prothrombin time (PT), and activated partial thromboplastin time (aPTT). To exclude congenital or acquired defects of plasmatic coagulation factors that influence primary hemostasis, in the first instance, the von Willebrand factor vWF and the aggregation levels of ADP, collagen, and ristocetin[5]; (2) protocol for perioperative management of patients with prophylactic usage of Tranexamic acid. The majority of guidelines recommend using intravenous/i.v. application of a Tranexamic acid as a gold standard for preventing excessive bleeding in platelet hypoaggregability, which works by slowing the breakdown of blood clots and helps to prevent prolonged bleeding[3,6].Tranexamic acid was the only agent that demonstrated a significantly lower risk of developing postoperative bleeding events (OR 0.27, P= 0.007)7; and (3) proposing an updated clinical practice guideline for local and systemic hemostatic methods. Although tooth extraction has been shown to be safe in patients with higher bleeding risk, PEB events have still been reported[8].

Therefore, finding the best supplementary measures for achieving more effective hemostasis has become vital[9,10]. In literature, correctmanagement and perioperative treatment with aadequate hemostasis consist of systemic intravenous tranexamic acid-an antifibrinolytic agent and local hemostatic measurements is crucial for the success of invasive dental treatment in platelet hypo aggregability patients[11]. Many authors found that this success rate decreased from 88.9%-98%, depending on the comorbidities of patient, when TXA and appropriate local methods were usedinpatients undergoing minor dental procedures. Some of them applied at least 2 repeated doses of TXA every 2–6 hours[12].

Acknowledgement for these circumstances, we evaluated the difference between PEB incidences beforeachieving diagnosis (not treatedand correlate them with PEB in prepared patients). Guidelines for hypoaggregability in patients requiring dental extraction was also investigated due to the risk factors for the incidence of postextraction bleeding[13].

Local hemostatic agents and techniques, such as pressure, surgical packs, sutures of the edges of the postextraction wound may be used individually or in combination in the local hemostatic agents, such as topical socket with solution of TXA[14]. Topical TXA is an effective agent used in conjunction with other hemostatic measures when applied directly on the bleeding wound as it converts fibrinogen to fibrin and allows rapid hemostasis in a wound. There is a wide array of techniques suggested for the treatment of PEB, which include interventions aimed at both local and systemic hemostatic methods.

Aim

We aimed to identify the significant predictors of PEB and to assess the efficacy of TXA for preventing bleeding complications in patients with hypoaggregabilityundergoing minor oral surgery or dental extractions. We will determine and incidence of PEB in correlation with extensiveness of treatment in order to assess guideline for managing PEB in these patients.

Material and method

Retrospective study was conducted on 64 patients diagnosed with platelethypoaggregability, treated at the University Clinic for Maxillofacial Surgery in Skopje (2019- 2024 year).

Preoperative diagnostic management:1) clinical symptoms and screening hemostasis and coagulation-laboratory tests: complete blood count (CBC); partial thromboplastin time (pTT); activated PTT (aPTT); prothrombin time (pT); optical aggregometry tests for levels of ADP, collagen and ristocetin were made to determine significant predictors for diagnosing platelet hypoaggregability (completed, within one week before the surgery), were evaluate in collaboration with the Institute for Transfusion Medicine; 2) Rtg orthopantomogram or CBCT were performed in order to confirm the indication for extraction (location and extensiveness of treatment: single tooth extraction or minor dentoalveolar surgery, all dates were noted and analyzed).

Operative procedures: 1) the usage of preoperative TXA for one-day elective surgery procedures is substantial (singleprophylactic dose of i.v. TXA (1-1,5 gr.) was administrated 45 min. before surgery; 2) single tooth

extraction or dentoalveolar surgery (cystectomy or impacted toothextraction with osteotomy and raising a mucoperiosteal flap) were conducted under a local anesthesia. Minimally invasive extraction techniques were used by experienced maxillofacial surgeons. 3) Local hemostatic methods such as washing the socket with topic tranexamic acid, gauze pressure for 30 min.and suturing the wound, were used to control bleeding. Extra measures were applied provided the socket was still bleeding (moderate or heavy);for ensuring successful hemostasis: repeating the dose of i.v. TXA, every 8 hours, revision of wound or electro cauterization were applied. Postoperative cautions were given to all patients, especially to avoid NSAID drugs.

Postoperative evaluation and follow-up of bleeding events were monitored and recorded for the next 7 days. PEB, which cannot be controlled with basic hemostatic procedures (bleeding that cannot be stopped by gauze packing and requires medical treatment between 30 minutes and 7 days), is considered clinically significant bleeding time (BT). According toAmeer's model, depending on the intensity and types of PEB, we defined bleeding event as: oozing/ light, moderate and heavy bleeding. Referent ranges for bleeding timeis 9-20 minutes.

The variables and the examined parameters of all 64 patients were analyzing and correlated: clinical data; levels of ADP, ristocetin and collagen (as significantpredictors for hypoaggregability), localization and extensiveness of treatment were correlated with PEB before achieving the diagnosis and after prophylactic use of TXA and local hemostatic methods. Statistical analyses were performed using IBM SPSS Statistics 20.0 (IBM, Somers, NY) and Statistic 10, using the following statistical methods: coefficients on relationships and proportions, chi-square test was performed to compare bleeding events, and T-test for dependent samples was applied to compare the relative volume of bleeding. Correlative relationships between variables are determined by the Pearson coefficient of correlation (r). For univariate analyses, a chi-square test was performed, and the significance of the difference was tested with the non-parametric Kruskal-Wallis ANOVA test, and the individual difference with Multiple Comparisons p-values. Shapiro-Wilk`s test examined the normal distribution of the variables and for CI (confidence interval $^{238}_{93}$ 95% CI) statistical significances were considered significant for $p< 0.05$.

Results

In 64 patients, diagnosed with platelet hypoaggregability,according to the demographic characteristics, 68.75% of the patients are female and 31.25% are male, the registered difference is significant for p<.05 (p=.0000) between female and male. The average age is 42.9±18.4 years (females 42.89±18.4, ranging 12-82; males (42.95±18.9, ranging 10-82), no difference in terms of age is registered.

Analyzesscreening laboratory diagnostic tests and risk factors for PEB, showed that: CBC, BT, pTT, (aPTT) and PT demonstrate a normal, reference ranges and insignificant correlation with bleeding time (r=0978, p=.446). In all patients, the values of ADP (69-88), Ristocetin (87-102), Collagen (70-94) and PT (9.8-14.2) are below the reference values. Analyzingthe average value of ADP in our patients is 36.6±13.3, ranging from 7.0 to 60.0. In 50.0% of patients, the value is under 39.5 (Me=39.5 IQR (24.5-47), for Ristocetin is 61.4±14.0, ranging from 23 to 86.0 and in 50.0% the value is under 65.0 (Me=65.0 IQR (51-71). The average value of collagen in patients is 49.1±15.5, ranging from 19.0 to 90.0. In 50.0% of patients, the value is under 50.0 (Me=50.0 IQR (39-58). (Table 1)

The average value of ADP in moderate intensity of bleeding is 43.8±10.4, range from 7 to 60. The average value of ADP in severe intensity of bleeding is lower and is 27.9 ±10.5, in range from 7 to 49. The value of ADP in light bleeding intensity is 58.0 (one patient). The average value of Ristocetin in moderate intensity of bleeding is 66.2±9.3, ranging from 47 to 83. The average value of Ristocetin in severe intensity of bleeding is lower and is 55.6 ±16.6, in range from 23 to 86. The value of Ristocetin in light bleeding intensity is 68.0 (one patient). The average value of

Table 1. Average value of ADP, Ristocetin, Collagen and PT in patient with platelet hypoaggregability

	No.	average	Me	Min.	Max.	/IQR	IQR	Stand. Dev.
ADP	64	36.9	39.5	7.0	60.0	24.5	47.0	13.27471
Ristocetin	64	61.4	65.0	23.0	86.0	51.0	71.0	14.03044
Collagen	64	49.1	50.0	19.0	90.0	39.0	58.0	15.49615
PT	63	11.5	11.0	9.7	26.0	10.0	12.0	2.39639

Table 2. Presentation of the mean value of ADP, Ristocetin, Collagen in correlation with bleeding intensity before achieving diagnosis

Bleeding intensity/ ADP	%	No	St.dev.	Min.	Min.
Light	58.0	1	0.00000	58.0	58.0
Moderate	43.8	34	10.41890	7.0	60.0
Heavy	27.9	29	10.51846	7.0	49.0
Ristocetin					
Light	68.0	1	0.00000	68.0	68.0
Moderate	66.2	34	9.34127	47.0	83.0
Heavy	55.6	29	16.60984	23.0	86.0
Collagen					
Light	59.0	1	0.00000	59.0	59.0
Moderate	52.4	34	11.34050	27.0	86.0
Heavy	44.9	29	18.81855	19.0	90.0

Table 3. Presentation of the average value of ADP, Ristocetin, Collagen in relation to the intensity of post-extraction bleeding in treated patient with TXA

Bleeding intensity/ ADP	average	No.	St.dev.	Min.	Min.
oozing	43.5	8	3.46410	38.0	49.0
light	35.6	54	14.01563	7.0	60.0
moderate	45.0	2	5.65685	41.0	49.0
Ristocetin					
oozing	69.4	8	9.10161	58.0	83.0
light	60.2	54	14.55164	23.0	86.0
moderate	63.0	2	2.82843	61.0	65.0
Collagen					
oozing	59.0	8	12.08305	49.0	86.0
light	47.6	54	15.63670	19.0	90.0
moderate	50.0	2	15.55635	39.0	61.0

Collagen in moderate intensity of bleeding is 52.4 ± 11.3, in range from 27 to 86, of Collagen in severe intensity of bleeding is lower 44.9 ± 18.8, in range from 19 to 90. And for Collagen in light bleeding intensity, the average value is 59.0 (Table 2.).

Local hemostatic procedures are performed in 98.4% of the patients (topic TXA applied locally with gauze and suturing the edges of the wound) data is missing for one patient.After i.v. application of TXA, performing dentoalveolar surgery and implementation of local hemostasis measurement: Heavy bleedings were not registered postextraction compared to preoperatively (before diagnosis), were registered in almost half (45.3%) of the patients and the absence of bleeding after extraction was registered in 8

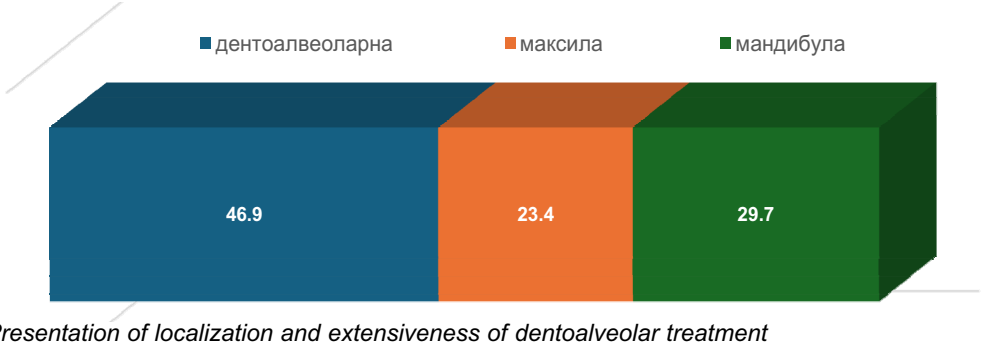
Table 4. Presentation of average bleeding time before diagnosis/days after TXA application and local hemostasis methods/ hours

	No.	average	Med	Min.	Max.	Std.Dev.	IQR/ rank	IQR rank
(BT) before diagnosis/days	64	5.9	4.0	1.0	14.0	3.995502	2.5	9.5
(BT) after TXA application/ hours	62	5.1	4.0	0	30.0	5.741133	1.0	7.0

*(BT) Bleeding time

Table 5. Analyzing the effectiveness of i.v. application of TXA and local hemostasis methods following tooth extraction correlation with bleeding time. Presentation of T-test for Dependent Samples between preoperative versus post-extraction bleeding time

Bleeding time	Mean	Std.Dv.	N	Diff	Std.Dv. - Diff.	t	df	p	Confiden. - 95.000%	Confiden. +95.000%
Before diagnosis	138.97	94.52677								
After i.vapplication of TXA	5.1	5.74113	62	133.8871	93.00293	11.33543	61	0.000000	110.2688	157.5054



Graph 1. *Presentation of localization and extensiveness of dentoalveolar treatment*

(12.5%) patients; Light intensity was registered in 54 (84.4%) versus (1.6%) only in one patient before achieving diagnosis (p<.05; Diff. test, p = ,0000); Moderate bleeding intensity was registered in two (3.1%) patients vs. pre-diagnosis in 34 (53.1%) patients (p<.05; Diff. test, p=.0000) (Table 3.).

The average bleeding time before dentoalveolar procedure in patients is 6 ± 4 days, ranging from one to 14 days. In 50% of patients, the bleeding is over 4 days (Me=4 IQR (2.5-9.5) (Table13.). The average post-extraction bleeding time in patients after establishing the diagnosiswas 5.1±5.7 hours, ranging from 0 to 30 hours, but only light bleeding. A high standard deviation is registered, which indirectly speaks of large variations of the statistical units around the average value. In 50% of patients, the bleeding is under 4 hours (Me=4 IQR (1-7) (Table 4.).

The difference between prediagnostic bleeding (expressed in hours) versus postextraction bleeding is statistically significant for p<.05 (p=.000000) (Table 5.).

Out of a total of 64 patients who underwent surgery, in 30 (46.9%) dentoalveolar surgery (cystectomies, impacted tooth extraction) was performed; and maxillary single tooth extractions in 15 (23.4%) and in mandibulae, 19 (29.7%).

The difference between dentoalveolar surgery versus maxilla and dentoalveolar versus mandible is significant for p<.05 (Difference test, p=.0054, p=.0453), the other differences are not significant (Graph 1.).

A significant association was registered between the registration of postextraction bleeding time and the localization and extensiveness of the treatment before proper diagnostic protocol (Chi Square, =9.39950, df=2, p=.009098) (Table 6.)

Post-extraction bleeding in the dentoalveolar procedure, after performing complete protocol (systemic and local hemostatic methods), lasts 5.0±5.9 hours, in the maxilla 6.7±2.7 and in the mandible 3.9±7.1, withoozing and light intensity.The difference in the duration of bleeding in relation to the localization of the extraction and extensiveness

Table 6. Contingency table for bleeding event in relation with localization and extensiveness of treatment

BT	Dentoalveolar procedures	maxillae	Mandibulae	total
No bleeding	2	0	6	8
Prolongated bleeding	28	15	13	56
total	30	15	19	64

Table 7. Presentation of bleeding time in relation to localization of extraction and extensiveness of treatment, after performing complete protocol (systemic and local hemostasis methods)

Dentoalveolar procedures	average	No	St.dev	Min.	Max.
Dentoalveolar surgery	5.0	29	5.916080	0	30.0
maxilla	6.7	15	2.716791	2.0	12.0
mandibula	3.9	18	7.128145	0	30.0

of treatment: significantly longer in the maxilla in relation to the mandible and dentoalveolar (Kruskal-Wallis test: H (2, N= 62) =11.48415 p =.0032) (Table 7.).

According to the dynamics index, a 530% increase in oozing and light intensity PEB,was registered compared to the PEB before achieving diagnosis.

According to the dynamism index, the rate of decrease in the light intensity of PEB is registered by 94.1% in relation to the pre-diagnosing moment.Tranexamic acid demonstrated a significantly lower risk of developing postoperative bleeding events (OR 0.27, P=0.007). Based on the comparative statistical analysis of the diseases of the most frequently used dose of TXA (1-1,5gr)/one dose before intervention in 92% of the patients, the need for second dose was registered only in 2 patient (3%) and it was due to comorbidities (1 patient with cirrhosis and the second one with diabetes mellitus).

Discussion

In daily practice, dental practitioners frequently meet patients with platelet hypoaggregability, suffering from excessive bleedings after dentoalveolar procedures. Currently, guidelines regarding the diagnosis or treatment of patientsare a great challenge in order to achieve a systemic and local hemostatic measures[15]. We performed a review of all relevant literature from 2013-2023 for managing platelet hypoaggregability and comparingto our results[16].Alamelu J. et al.[16], reported that most often, 88.8% of the cases were diagnosed due to gingival bleeding and his high percentage is due to dentoalveolar surgery. Further in the study, she confirmed that 80 - 90% of the patients have a normal number of platelets, but have reduced values of ADP, collagen and ristocetin, as a high-risk factor of bleeding. In agreement with all other authors, we confirm that reduced levels of ADP, Collagen and Ristocetin as a significant predictors for diagnosis in all patients: ADP/36.6±13.3, range: (7.0-60.0); <39.5 (Me=39.5 IQR(24.5-47), Ristocetin / 61.4±14.0, range: (23- 86.0); <65.0 (Me=65.0 IQR(51-71) and Collagen/ 49.1±15.5, range: (19.0 - 90.0); <50.0 (Me=50.0 IQR(39-58), as a risk factors for diagnosing hypoaggregability and prolongated bleeding.

In addition, our results are consistent with the findings of allother authors, meaning that the decrease in levels of ADP, Collagen and ristocetin is directly proportional to prolonged and excessive bleeding (Table 2.). Moenen F. et al.[17], confirmed that in 86% of patients the difference was significantly lower in those with excessive bleeding than in controls for ADP (118±27 s vs 94±13 s, p=0.007); for ristocetin (mean±1 SD (range): 81±31 U dL−1 (36–163) vs. 92±32 (26–199) p=0.039 and for collagen, 97 (162; 51–191) p<0.001[18]. OnlyFrontroth JP et al[19], describe the results of the study, prove that the mean values for platelet aggregation responses to collagen, ADP, ristocetin within much

smaller reductions: (p=0,5; p=0,51 and p=0,6, respectively.

Evaluating the available literature for the usage of TXA as a hemostatic agent, and based on our experience for minimizing bleeding risk of periprocedural dentoalveolar surgeries, we confirmed 530% increase in the light intensity bleeding after TXA application compared to the pre-diagnosing extractions, and decrease in the moderate intensity of postextraction bleeding in 94.1% versus pre-diagnosing extractions bleeding, according to the dynamics index. After i.v. application of TXA, performing dentoalveolar surgery and implementation of local hemostasis measurement, heavy bleedings were not registered postextraction compared to bleeding time and intensity before diagnosis. Oozing bleeding was significantly dominant in 84.4%versus 1.6% before achieving the diagnosis (p<.05; Diff. test, p=.0000); moderate intensity ofbleeding was registered in 3.1% patients vs. pre-diagnosis in 53.1% (p<.05; Diff. test, p=.0000)[20]. Several randomized studies in many different fields of surgery have confirmed its efficiency innoteworthy reduction in post-operative bleeding following dental extraction when TXA was used, in addition to topic TXA and suturing the postextraction wound. Patients receiving TXA showed a decrease in postoperative bleeding (SMD= -0.26, 95% CI -0.51 to -0.01, p=0.04) and following the grade rating system, the quality of evidence of bleeding wasobserved as oozing and low, respectively[21]. Contrary to our findings only Lam et al.[7], following the grade of quality of evidence of bleeding, she observed thatthe intensity is moderate 13% and low in 78%, respectively,contrary toour results, oozing in 84.4% and moderate in 3.1% patients, perhaps this is due to the inconsistency of the group of patients.

The average bleeding time before establishing the diagnosis in our study was 6 ± 4 days, (Me=4 IQR (2.5-9.5) and after usage of TXA is 5.1±5.7 hours, range: 0 - 30 hours (Me=4 IQR (1-7) (Table 3.). The percentage difference is significant between heavy bleeding vs. light and moderate vs. light bleeding for p<.05 (Difference test, p=.0000). (Table 1.). These findings are in accordance with previously reported figures, which proved significant difference (p<0.001- 0,003) and established the usage of TXA as a most important in achieving postextraction hemostasis in thrombocyte patients with hypoaggregability[22].

Exploring the extensiveness and type of the surgery (single-tooth extraction or extraction of impacted tooth, and cystectomies) and prevalence of post-operative bleeding event, in our study: out of total of 64 patients/30 (46.9%) underwent dentoalveolar surgery (cystectomies, impacted tooth extraction); maxillarysimple tooth extractions 15 (23.4%) and mandibular single tooth extraction, 19(29.7%). Our results confirm significant difference in incidenceof PEB in dentoalveolar surgery versus maxilla and mandible p<.05 (Dif. test, p=.0054, p=.0453), duration of BT after dentoalveolar surgeries was two times more than single tooth extractions. In our study, we confirm the significant association between PEB and the localization and extensiveness of the treatment after proper diagnostic protocol (systemic and local hemostatic methods), TXA (Chi Square, = 9.39950, df=2, p=.009098).PEB in dentoalveolar procedure lasts 5.0±5.9 hours, in the maxilla 6.7±2.7 and in the mandible 3.9±7.1, with oozing and light intensity and doesn't require additional hemostatic measures[23,24]. The difference in BT, in relation to the localization of the extraction and extensiveness of the treatment was significantly longer in the maxilla,related to the mandible (Kruskal-Walli's test: H (2, N= 62) =11.48415 p=.0032). Our finding is result of not consistent group of dental extraction like in other studies where the prevalence of bleeding is much more frequent in the mandibula than in the maxilla 62-83% vs 38-17%, respectively. Ockerman A. et al.[25], confirmed the reduction in delayed bleeding after multiple extractions (rate ratio, 0.40; 95% CI, 0.20 to 0.78) to be lower in the TXA group[26]. The analysis of all processed dates present in study data shows that in total of 64 dentoalveolar procedures, theprimary bleeding was stopped. There was no difference related to the location or extensiveness (whether it is a single-tooth extraction or dentoalveolar surgery), implementation ofthe correct diagnosis, preoperative preparation with TXA and the use of local hemostatic methods, lead to reliable, safe and secure dealing with PEB[27].

Conclusions

Determination of reduced levels of ADP, ristocetin and collagen as a significant predictor for bleeding, and systemic and local usage of TXA is effective and safe in minimizing the risk of bleeding event after performing dentoalveolar surgery. The close collaboration with the Transfusion Medicine Institute is the only successful pathway for managing patients with thrombocyte hypo aggregability. Management of perioperative bleeding is complex and involves multiple assessment tools and strategies to ensure optimal patient care with the goal of reducing morbidity and mortality. Future studies should focus on genetical investigation to assess the precise diagnosis forthe condition platelethypoaggregability and targeted therapy to impair the long-term impact on reducing the PEB complications.

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IMPACT OF ANTIOXIDANTS ON COMPLETE BLOOD COUNT PARAMETERS AND THEIR ASSOCIATION WITH THE SEVERITY OF CHEMOTHERAPY-INDUCED ORAL MUCOSITIS – ANIMAL STUDY

ВЛИЈАНИЕТО НА АНТИОКСИДАНТИТЕ ВРЗ ПАРАМЕТРИТЕ ОД ДИФЕРЕНЦИЈАЛНАТА КРВНА СЛИКА И НИВНАТА ПОВРЗАНОСТ СО СТЕПЕНОТ НА ОРАЛЕН МУКОЗИТИС ИНДУЦИРАН ОД ХЕМОТЕРАПИЈА – АНИМАЛНА СТУДИЈА

Ivanovski K[1], Kokolanski V[1], Mitik K[1], Stefanovska E[1], Ristoska S[1], Risteska N[1], Shopkovski K[1], Poposki B.[1]*

[1]Faculty of Dentistry – Skopje, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia,
[1]*Correspondence Author

Abstract

Aim of the study: To evaluate the impact of antioxidants on complete blood count parameters and to investigate their relationship with the intensity of chemotherapy-induced oral mucositis on an animal model. **Material and methods:** An animal rat model for oral mucositis induced by cancer chemotherapy was used in the study. The study involved 40 healthy male adult 9 weeks-old Wistar rats, divided into 5 groups: negative control group; positive control group (5-FU + acetic acid); treatment group 1: 5-FU + acetic acid + vitamin C in alkaline water + glutathione; treatment group 2: 5-FU + acetic acid + zinc sulfate; treatment group 3: 5-FU + acetic acid + vitamin C in alkaline water + glutathione + zinc sulfate. For each treatment group, prior to 5-FU administration, solutions of antioxidants (individually or combined) were prepared and given each day for 14 days to assess their protective effects. The cytostatic agent 5-fluorouracil (5-FU) was administered intraperitoneally at a dose of 40 mg/kg on days 15, 17, and 19 to induce immunosuppression. On day 20, oral ulcers were induced using 25 μL of a 30% acetic acid solution applied to the left buccal mucosa under ether anesthesia. The complete blood count (CBC) was also done on day 20. The initial size of the lesion was measured on day 21. **Results:** Significant differences between the groups were identified for the following parameters based on the Kruskal-Wallis test: WBC (p=0.020), RBC (p=0.006), HGB (p=0.003), HCT (p=0.005), MCH (p=0.002) and PLT (p=0.004). There was no statistically significant difference in the initial lesion size between the four groups treated with 5-FU [Kruskal-Wallis H (χ^2=1.574; p=0.665)]. No statistically significant association was registered between the blood parameters and the initial lesion size in the four groups treated with 5-FU and acetic acid. **Conclusion:** The modulatory effects of antioxidants may influence oxidative stress and, consequently, impact the hematological profile. While significant differences in WBC, RBC, HGB, HCT, MCH and PLT were observed among the groups treated with antioxidants and the negative control group, no significant differences in lesion size or associations between complete blood count parameters and lesion size were detected. The findings underscore the influence of chemotherapy and antioxidants on hematological parameters, paving the way for further investigations into the interactions between antioxidants, complete blood count parameters and oral mucositis severity. **Key words:** oral mucositis, chemotherapy, antioxidants, oxidative stress.

Апстракт

Цел на трудот: Да се утврди влијанието на антиоксидансите врз параметрите на диференцијалната крвна слика и да се истражи нивната поврзаност со степенот на оралниот мукозитис индуциран од хемотерапија на анимален модел. **Материјал и методи:** Беше употребен анимален модел на стаорци за орален мукозитис индуциран од хемотерапија. Во студијата беа вклучени 40 машки стаорци од сојот Wistar, стари 9 недели, поделени во 5 групи: негативна контролна група, позитивна контролна група (5-FU + оцетна киселина), испитувана група 1: 5-FU + оцетна киселина + витамин Ц во алкална вода + глутатион ; испитувана група 2: 5-FU + оцетна киселина + цинк сулфат; испитувана група 3: 5-FU + оцетна киселина + витамин Ц во алкална вода + глутатион + цинк сулфат. Во секоја третирана група, секојдневно, во времетраење од 14 дена пред администрирањето на 5-FU, беа подготвени и администрирани раствори на антиоксиданти (поединечно и во комбинација), со цел евалуација на нивниот протективен ефект. Цитостатикот 5-флуороурацил (5-FU) беше администриран

интраперитонеално во доза од 40 mg/kgна 15-от, 17-от и 19-от ден, за да се предизвика имуносупресија. На 20-от ден беше индуцирана орална улцерација со помош на 25 μLна 30% раствор на оцетна киселина во левата букална лигавица под анестезија со етер. Диференцијалната крвна слика исто така беше направена на 20-от ден. Големината на иницијалната лезија беше измерена на 21-от ден. **Резултати:** Статистички значајна разлика помеѓу групите беше определена со помош на тестот Kruskal-Wallis за следните параметри: WBC (p=0.020), RBC (p=0.006), HGB (p=0.003), HCT (p=0.005), MCH (p=0.002) иPLT (p=0.004). Не беше регистрирана статистички значајна разлика во големината на иницијалната лезија помеѓу четирите групи третирани со 5-FU [Kruskal-WallisH (χ^2=1.574; p=0.665)]. Не беше регистрирана статистички значајна поврзаност помеѓу хематолошките параметри и големината на иницијалната лезија во четирите групи третирани со 5-FU и оцетна киселина. **Заклучок:** Модулаторниот ефект на антиоксидантите може да влијае на оксидативниот стрес, а последователно и на хематолошкиот профил. Иако беа регистрирани значајни разлики во WBC, RBC, HGB, HCT, MCH и PLT помеѓу групите третирани со антиоксиданти и негативната контролна група, не беше регистрирана значајна разлика во големината на иницијалната лезија помеѓу групите, ниту пак поврзаност на параметрите од диференцијалната крвна слика и големината на лезијата. Овие резултати го нагласуваат влијанието на хемотерапијата и антиоксидантите врз хематолошките параметри, отворајќи го патот за понатамошни истражувања за интеракциите помеѓу антиоксидантите, диференцијалната крвна слика и степенот на оралниот мукозитис. **Клучни зборови:** орален мукозитис, хемотерапија, антиоксиданти, оксидативен стрес.

Introduction

Oral mucositis (OM) is one of the most prevalent and painful side effects experienced by cancer patients undergoing radiotherapy and/or chemotherapy, affecting 20–40% of patients receiving conventional chemotherapy, approximately 80% of those with hematological malignancies undergoing myeloablative conditioning prior to stem cell transplantation, and nearly all patients with head and neck cancer receiving radiotherapy[1].

This complication not only reduces the quality of life for affected patients but also poses significant challenges to the integrity and efficacy of the cancer therapy program, having a profound and adverse impact on the patients' clinical outcomes and overall survival prognosis[2]. Depending on the intensity, OM is clinically characterized by erythema, ulcers, pain and eating difficulties, consequently leading to weight loss[3]. OM patients are often readmitted to the hospital and their hospital stay is prolonged which increases the economic and social costs[3].

Chemo-/radiotherapy-induced reactive oxygen species (ROS) are associated with OM, thus making the oxidative stress pathway a target for potential therapeutic effect and prophylaxis (4). Chemotherapy and oxidative stress can affect the functions of blood cells, leading to anemia, neutropenia and thrombocytopenia[5,6].

Studies[3,7-12] report that certain biochemical parameters, like complete blood count (CBC) parameters, before starting chemoradiotherapy were highly associated with the development of severe OM. Identifying the risk factors for oral mucositis could lead to more accurate clinical evaluation and treatment. However, even though many factors have been associated with OM[13-17], literature still requires additional research to provide a clearer understanding of this topic.

The aim of this study was to evaluate the impact of antioxidants on complete blood count parameters and investigate their relationship with the intensity of chemotherapy-induced oral mucositis on an animal model.

Material and methods

To realize the set goal, we used the animal rat model for oral mucositis induced by cancer chemotherapy by Takeuchi et al[18].

The study was conducted at the Institute of Biology (Faculty of Natural Sciences and Mathematics – Skopje) (Faculty of Veterinary Medicine – Skopje), Ss. Cyril and Methodius University in Skopje, after approval by the Ethical Committee for Medical-Dental Research of the Ss. Cyril and Methodius University in Skopje, Faculty of Dentistry – Skopje (02-284/2), as well as after receiving the approval for conducting an animal study by the Food and Veterinary Agency of the Republic of North Macedonia (10-3338/8). All procedures were conducted in compliance with ethical standards approved by the Animal Ethics Committee of the Ss. Cyril and Methodius University in Skopje, North Macedonia (03-2525/1), adhering to the International Guiding Principles for Biomedical Research Involving Animals as outlined by the Council for International Organizations of Medical Sciences (EEC Directive of 1986; 86/609/EEC).

Animals

In this study, 40 healthy male adult Wistar rats, weighing between 250 and 400g (300.4±38.6g) and 9-weeks-old, were obtained from the Vivarium at the Faculty of Natural Sciences and Mathematics in Skopje, Macedonia. The rats were housed under controlled environmental conditions, including a temperature of 25 ± 2°C, relative humidity of 55 ± 10%, and a 12-hour light/dark cycle. They were provided with a standard pellet diet consisting of 20% protein, 30% carbohydrates, 9% fat, 2.5% cellulose, and 10% water, delivering an energy value of 310 kcal, along with free access to water.

Materials

As a chemotherapeutic agent we used ≥99% (HPLC) 5-fluorouracil (5-FU) (Sigma-Aldrich, Saint Louis, MO

63103, USA). To induce the oral lesion, we used an aqueous solution of glacial acetic acid (Alkaloid AD Skopje, Skopje, Republic of North Macedonia). As non-enzymatic antioxidants we used Vitamin C (Galenika a.d., Belgrade, Serbia) dissolved in alkaline water (Faculty of Natural Sciences and Mathematics – Skopje, Ss. Cyril and Methodius University in Skopje), glutathione (NOW Sports – Nutrition and Wellness, Bloomingdale, Illinois 60108, USA) and zinc sulfate heptahydrate (Sigma-Aldrich, Saint Louis, MO 63103, USA). To measure the oral lesions, the animals were narcotized with ether (Alkaloid AD Skopje, Skopje, Republic of North Macedonia).

Experimental design

The animals were divided into five groups to evaluate the effects of antioxidants on chemotherapy-induced oral mucositis, as follows:

1) Negative control group: received 1 mL of physiological saline intraperitoneally.
2) Positive control group: 5-FU + acetic acid, without antioxidant treatment.
3) Treatment group 1: 5-FU + acetic acid + vitamin C in alkaline water + glutathione
4) Treatment group 2: 5-FU + acetic acid + zinc sulfate
5) Treatment group 3: 5-FU + acetic acid + vitamin C in alkaline water + glutathione + zinc sulfate

For each treatment group, prior to 5-FU administration, solutions of antioxidants (individually or combined) were prepared and given each day for 14 days to assess their protective effects, including:

- vitamin C in alkaline water (8 mg/kg body weight; given intragastrically),
- glutathione (4 mg/kg body weight; given intragastrically) and
- zinc sulfate (40mg/kg body weight; given intragastrically).

The cytostatic agent 5-fluorouracil (5-FU) was administered intraperitoneally at a dose of 40 mg/kg on days 15, 17, and 19 to induce immunosuppression. On day 20, oral ulcers were induced using 25 µL 30% acetic acid solution applied to the left buccal mucosa under ether anesthesia. The complete blood count (CBC) was also done on day 20. The initial size of the lesion was measured on day 21.

The data was processed using IBM SPSS Statistics v24 for Windows.

Results

The complete blood count parameters are presented in Table 1 as Mean±SD. The Kruskal-Wallis H test was conducted to assess the difference in the complete blood count parameters between the 5 groups. Significant differences were identified for the following parameters based on the Kruskal-Wallis test: WBC ($p=0.020$), RBC ($p=0.006$), HGB ($p=0.003$), HCT ($p=0.005$), MCH ($p=0.002$) and PLT ($p=0.004$). Post hoc pairwise comparisons were conducted using the Bonferroni-adjusted Mann-Whitney U test to control for Type I error. Significant differences between groups were marked with

Table 1. Complete blood count parameters (Mean±SD)

	WBC ($x10^3/\mu L$)	RBC ($x10^6/\mu L$)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT ($x10^3/\mu L$)
G1	9.1±1.6[a]	6.6±0.2[a,b]	13.4±0.4[a,b]	38.9±4.5[a,b]	53.2±15.8	27.2±2.9[a,b]	36±11	859±70[a]
G2	11±7	9.3±2.3	18±3.2	53.1±12.9	57.3±1.1	19.8±2.4	34.6±3.8	450±348
G3	5±2.4[a]	10.7±1.4[a]	20±2.3[a]	62.1±7.7[a]	57.9±0.9	18.7±0.4[a]	32.3±0.4	324±155[a]
G4	5.9±1.3	10.5±0.3[b]	19.9±0.8[b]	60.7±2.4[b]	58±1.3	19±0.5	32.7±0.5	391±100
G5	7.2±2.3	10.3±0.4	19.4±1.1	59.9±3.3	58±2.2	18.8±1[b]	32.4±0.8	484±118

Table 2. Initial lesion size

Group	N	Size (mm) / Mean±SD	Minimum	Maximum
G2	8	4.5±2.7	1	9
G3	8	3.6±3	0	8
G4	8	4.4±1.9	1	7
G5	8	3.1±3	0	7

Table 3. Correlations between the blood parameters and lesion size

	WBC	RBC	HGB	HCT	MCV	MCH	MCHC	PLT
Lesion size	r=-0.202 p=0.421	r=-0.011 p=0.965	r=0.065 p=0.797	r=-0.085 p=0.738	r=0.133 p=0.600	r=0.140 p=0.579	r=-0.289 p=0.245	r=0.035 p=0.891

superscript letters in Table 1, where groups sharing a letter are significantly different.

Table 2 presents the initial size of the lesion in the groups treated with 5-FU and acetic acid, presented as Mean±SD, minimum and maximum values. There was no statistically significant difference in the initial lesion size between the four groups [Kruskal-Wallis H ($\chi2$=1.574; p=0.665)].

Spearman's rank correlation coefficient was conducted to determine the association between the blood parameters and the initial size of the lesion. No statistically significant association was registered between the blood parameters and the initial lesion size in the four groups treated with 5-FU and acetic acid (Table 3).

Discussion

Oral mucositis is an adverse effect of chemotherapy and/or radiotherapy (head and neck), and in aspect of chemotherapy, its pathogenesis occurs both by direct tissue damage of the chemotherapeutic agent and by formation of reactive oxygen species as a result of direct tissue damage[19]. Different risk factors for oral mucositis are mentioned in the literature, such as: advanced age[20,21], lack of appetite[20], duration of chemotherapy[20], type of chemotherapy[21], disease stage[21], salivary composition[22] and biochemical parameters[3,7-9, 11,23]. According to the literature[7,8,10,11,12,24], hemoglobin, platelets and white blood cells are the most mentioned complete blood count parameters associated with oral mucositis, making them the primary focus of this study.

***Hemoglobin**:* Soutome et al.[11] conducted a retrospective study of 181 patients to examine the risk factor for developing severe oral mucositis in patients with oral cancer undergoing radiotherapy. Their analysis revealed that lower hemoglobin levels receiving concurrent cisplatin or cetuximab and not receiving pilocarpine (low unstimulated salivary flow) correlated with a significantly higher incidence of severe oral mucositis. A similar study by Nishii et al.[7] evaluated 326 patients, who underwent radiotherapy for oral and oropharyngeal cancer, to investigate the factors associated with severe oral mucositis, concluding that low hemoglobin levels, low leukocytes/lymphocytes, concurrent cisplatin or cetuximab treatment, and oral feeding were found to be significantly associated with a higher incidence of severe oral mucositis. Mendonça et al.[24] found no association between oral mucositis severity and hemoglobin levels, while Curra et al.[12] reported lower levels of hemoglobin in patients with severe oral mucositis. In our study, hemoglobin levels increased in the groups treated with 5-FU, withstatistically higher hemoglobin levels being detected in Groups 3 and 4, compared to Group 1 (control group) (Table 1). Finkelstein et al.[25] reported an association between higher plasma vitamin C levels and higher hemoglobin levels. Vitamin C serves a key role in the kinetics of iron metabolism and the utilization of iron for erythropoiesis[25]. Hanson et al.[26] reported a significant improvement in hemoglobin levels in patients with zinc supplementation, which might be due to the importance of zinc as a catalyst, structural element and regulatory ion in the metabolic processes of erythropoiesis. Groups 3 and 4 exhibited smaller initial lesion size compared to the other groups, but the difference was not statistically significant [Kruskal-Wallis H ($\chi2$=1.574; p=0.665)] (Table 2). No statistically significant association was observed between the initial lesion size and hemoglobin (r=0.065; p=0.797) (Table 3). While it is expected for chemotherapy to cause myelosuppression, anemia and lower hemoglobin levels, in our study, the hemoglobin levels increased in the treatment groups, which can be explained by the increase of hemoglobin levels in the plasma, caused by the ROS damage toerythrocytes. Plasma hemoglobin levels can beconsidered a very good indicator of the oxidative damage of the erythrocyte membrane[27]. While it is logical for low hemoglobin levels to be negatively associated with the severity of oral mucositis, the findings in literature are inconsistent.

Platelets: Platelets are a key factor in the injury repair of ulcers and studies have demonstrated a variety of cytokines released by the platelets which are important for wound healing[8,28-32]. Given that the platelet-derived growth factor (PDGF) attracts mesenchymal cells which play a vital role in cell division regulation and growth, angiogenesis, stimulation of neutrophils and macrophages chemotaxis, as well as fibroblast proliferation, indicates that platelet count may be an important sign for wound healing capability[33]. Studies[8,10,12,24] report

that there is an increased risk of occurrence and inverse association between platelet count and mucositis grade, i.e. higher pretreatment platelet count resulted in milder oral mucosal reactions. Contrarily, Damascena et al.[34] reported that an increased platelet count was identified as a risk factor for severe oral mucositis. They elaborate that these findings might be due to platelet concentrate transfusions done during the myelosuppression which can lead to the occurrence of side effects, such as severe oral mucositis. The platelets in our study decreased in all groups treated with 5-FU, compared to the control group (Table 1), with significantly lower platelet levels being registered in Group 3 compared to Group 1 (control group). It is already recognized and reported that 5-FU injections can lead to significant platelet decrease[35]. Lesion size was not statistically significantly different between the treated groups [Kruskal-Wallis H ($\chi 2$=1.574; p=0.665)] (Table 2) and no statistically significant association was registered between platelet count and initial lesion size (r=0.035; p=0.891) (Table 3).

White blood cells: Patients with leukopenia have an impaired immune system and are at higher risk of bacterial colonization of the damaged epithelium, which can lead to an increase of pro-inflammatory cytokines in the oral mucosa, thus aggravating oral mucositis[34,36,37]. Studies demonstrate that patients with lower leukocyte count had severe oral mucositis[12], and that low neutrophil count might be a predictor[38] and risk factor[39] of chemotherapy-induced oral mucositis. In our study, the white blood cells exhibited an increase in Group 2, as well as a decrease in Groups 3-5, compared to the control group (Table 1). The decrease in white blood cells was expected due to the effect of 5-FU to reduce the circulating leukocytes. A statistically significant difference was registered in the white blood cells count between Groups 1 and 3. Controversially, the white blood cells count was highest in Group 2 (Table 1), where the initial size was also largest, but not statistically different than the other treated groups [Kruskal-Wallis H ($\chi 2$=1.574; p=0.665)] (Table 2). No statistically significant association was registered between white blood cells count and initial lesion size (r=-0.202; p=0.421) (Table 3). The adequate inflammatory response to the chemotherapy cytotoxic effects on the oral mucosa might be a result of a decrease in neutrophils[24], which was not the case in Group 2 of our study. Additionally, even minor mucosal toxicity may progress to evident ulceration provided the neutrophil counts are low[40].

The lack of a statistically significant association between the complete blood count parameters and oral mucositis severity may be attributed to the limitations of the animal model, which induces lesions irrespective of the biochemical parameters within the body, due to the injection of acetic acid. However, these results could provide valuable insights into how chemotherapy and treatments influence complete blood count parameters, contributing to a better understanding of the physiological changes induced by these interventions.

The findings reported in this study are only a small fraction of a more extensive research project, which may clarify certain methodological peculiarities in the study

Conclusions

The modulatory effects of antioxidants may influence oxidative stress, and, consequently, may have an impact on the hematological profile. While significant differences in WBC, RBC, HGB, HCT, MCH and PLT were observed among the groups treated with antioxidants and the negative control group, no significant differences in lesion size or associations between complete blood count parameters and lesion size were detected. This lack of correlation might reflect limitations of the experimental model, where lesion induction occurs independently of systemic biochemical factors due to acetic acid injection. Nonetheless, the findings underscore the influence of chemotherapy and antioxidants on hematological parameters, paving the way for further investigations into the interactions between antioxidants, complete blood count parameters and oral mucositis severity.

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INTERDISCIPLINARY TREATMENT OF IMPACTED MAXILLARY INCISORS – CASE REPORT

ИНТЕРДИСЦИПЛИНАРЕН ТРЕТМАН НА ИМПАКТИРАНИ МАКСИЛАРНИ ИНЦИЗИВИ - ПРИКАЗ НА СЛУЧАЈ

Maneva Ristovska M.[1], Simjanovska Lj.[2], Bajraktarova - Mishevska C.[1], Troni R.[1]

[1]Department of Orthodontics, Faculty of Dentistry- Skopje, " Ss. Cyril and Methodius " University in Skopje, Republic of North Macedonia,
[2]Department of Oral Surgery, Faculty of Dentistry- Skopje, "Ss. Cyril and Methodius "University in Skopje, Republic of North Macedonia

Abstract

Although the frequency of impacted frontal teeth is relatively lower than the impactions of other teeth in dental arch, their localization in the most noticeable part of the face represents a great problem for the patient and a major challenge for the doctor as well. The absence of these frontal teeth plays great role in dental and facial aesthetics, also decreasing self-confidence and self-perception in young patients. The reasons for their occurrence are diverse - from hereditary origin to altered position of the tooth buds, loss of space in the dental arch, or the existence of an obstacle in the eruption path. A crucial part of their treatment is early diagnosis which can ensure the possibility for planning appropriate interventions. Usually, dental history of frontal teeth trauma, clinical and radiographic examination are the main indicators for impactions or delayed eruption of frontal teeth. In this study, we want to present a case of impacted maxillary central incisors as a result of presence of supernumerary teeth in their path of eruptionin an 8-year-old boy. The treatment was preformed with combination of mobile and fixed appliances after surgical procedure and removal of supernumerary teeth. With traction and alignment of the incisors in their place in the dental arch, not only functional and aesthetic results were obtained, but also an increase in the self-confidence and social interaction of the patient. Orthodontic-surgical treatment is the optimal therapeutic approach in the treatment of impactions, in general, and therefore, also of the impactions of the maxillary central incisors. **Key words:** impacted teeth, impaction of maxillary incisors, treatment of impactedanterior teeth

Апстракт

И покрај тоа што зачестеноста на импактирани фронтални заби е релативно помалку застапена од импакциите на другите заби во денталниот лак, нивната локализација во најзабележителниот дел од лицето, претставува голем проблем за пациентот и голем предизвик за терапевтот. Отсуството на овие фронтални заби игра голема улога во денталната и фацијалната естетика, но има ивлијание на самодовербата и самоперцепцијата кај младите пациенти. Причините за нивното појавување се разновидни - од наследен карактер, недоволно простор во денталниот лак; до променета положба на забните зачетоци или постоење на пречка на нивниот пат на ерупција. Клучен дел од нивниот третман е раната дијагноза која дава можност и услови за планирање соодветни интервенции. Вообичаено, историјата на траума на фронталните заби, клиничкиот и радиографскиот преглед се главни показатели за импакциите или одложената ерупција на фронталните заби. Овде сакаме да прикажеме еден случај на импактирани максиларни централни инцизиви, како резултат на присуството на прекубројни заби на нивната патека на ерупција, кај момче на возраст од 8 години. Третманот беше спроведен со примена на комбинација на мобилен и фиксен ортодонтски апарат, по отстранувањето на прекубројните заби од страна на орален хирург. Со извлекувањето и поставувањето на инзицивите на нивното место во забниот лак се добија не само функционални и естетски резултати, туку и зголемување на самодовербата и социјалната интеракција на пациентот. Ортодонтско-хируршкиот третман е оптималниот терапевтски пристап во третманот на импакциите воопшто, а со тоа и на импакцијата на максиларните централни инцизиви. **Клучни зборови:** импактирани заби, импактирани максиларни инцизиви, третман на импактирани антериорни заби.

Introduction

The term "impaction of teeth" is associated with disturbances in eruption at expected timeframe of normal development[1]. Among impacted teeth, the maxillary canine is the most commonly impacted tooth following third molars. Impaction of maxillary central incisor is rare, accounting for around 0.2%–1 % of all cases, and it is usually a result of range of causative factors, including abnormal tooth dilaceration, fusion of tooth roots, disturbances in the normal eruption mechanisms, the presence of tumors, cysts and underlaying systemic conditions such as vitamin deficiencies, hormonal imbalances, or genetic predisposition[2] and in many cases there is a positive family history. But, in

almost 56%- 60% of the cases of impaction of maxillary incisors, the reason for this eruption disturbance is theexistence of a physical barrierin the form of presence of supernumerary teeth[3,4]. There is a diversity among racial and ethics group[5,6], therefore, in the Caucasian population, the prevalence is between 1%-3%; in Asians, is higher than 3%; Hispanics dominate with frequency of 5,6%, whereas Afro-Americans have the smallest prevalence of this condition - only 0,42%. As an obstacle for eruption, supernumerary teeth are most frequent in the male population. Some syndromes also have supernumeraries and some of them are localized in the maxillary incisor region, like cleidocranial dysplasia[6].

The shape of supernumerary tooth varies. The form of supernumeraries that is usually accompanied with more severe impaction, and the disturbed eruption is tuberculate or has an invaginated form[7,8,9]. Tay[10] found that vertically oriented supernumerary teeth are the reason for delayed eruption of permanent maxillary incisors.

Maxillary incisors are the most prominent teeth in an individual's smile, they are also the teeth that are on maximum displayin most individuals during speaking and the normal eruption, position and morphology of these teeth are crucial to facial aesthetics and phonetics[11]. The absence of a central incisor not only affects one's appearance but it also has a negative impact on self-esteem, functionality, and social interactions. Therefore, it is very important to diagnose and address this issue at an early stage[11].

Usually, patients visita dentist's office after 8 or 9 years of age, which depends on the eruption pattern of the permanent teeth. Absence of one or, sometimes, two teeth in the midline region is alarming and in many cases, it may result in migration of adjacent teeth, space loss and midline deviation[11,12]. Primary causes of central incisor impaction have been attributed to two causes: trauma to the primary teeth and mechanical obstruction[12]. Trauma to the primary teeth is a common type of traumatic injury in the maxillofacial region, especially in children with protrusion of the maxillary deciduous incisors and prognathism of the maxilla. Usually, about one-third of children have had some injury to their primary dentition[13,14]. Since primary teeth are in close proximity to the tooth buds of the succeeding permanent teeth, any traumatic incident has the potential to negatively affect the eruption of the permanent teeth and be the reason for malformation or dilaceration of the permanent tooth. The degree of that damage depends on the stage of development of the tooth germ, and the type and direction of the trauma[15,16].

Diagnosis and estimation of treatment plan is essentialfor treating impacted teeth Diagnostic procedures, except for anamnestic findings, intraoral examinations, include use of panoramic X-ray which is first and most valuable diagnostic tool. In manycases, there is a necessity for additional intraoral periapical radiograph, cone beam and CBCT evaluation[17]. These methods allow us to estimate the reason for delayed eruption of the frontal teeth and to choose the most appropriate method for placement of impacted teeth in the dental arch.

In addition to radiographic examinations, an intra oral evaluation is also necessary to identify retained deciduous teeth: presence or absence of buccal-palatal swelling and appropriate place for the incisors[18]. The adjacent teeth can be rotated or inclined; elevation of the soft tissue of the palatal or labial mucosa depending on the tooth location; absence of a protuberance in the buccal sulcus at 1–1.5 years before the expected time of tooth eruption[18].

The pathognomic sign which indicates that an impaction of a central incisor is the presence of the both lateral incisors in the dental arch[19]. Namely, by inspection and palpation of the affected area, the presence or absence of lump is determined. The position of the neighboring teeth can also help in locating the impacted tooth; if an impacted tooth is high in the maxillary ridge it will lead to displacement of the neighboring teeth and closure of the space for its placement in the dental arch.

Radiographic assessment includes X-ray, retrolaveolar radiograph, cephalogram, cone beam and CBCT diagnostics.

In order to estimate the best treatment plan, the following information should be obtained: the exact positions of the crown and root apex of the impacted tooth and the 3-dimensional orientation of its long axis; the proximity of the impacted tooth to the roots of the adjacent teeth; the presence of pathology such as supernumerary teeth, odontomes, apical granulomas or cysts, and their spatial relationship with the impacted tooth; root resorption of the neighboring teeth; 3D anatomy of the crown and root of the impacted tooth.

The interceptive treatment consists of surgical removal of supernumerary teeth followed by two phase orthodontic treatment with removable appliance at the beginning of the treatment in order to create space and to position the impacted incisors in the dental arch, and the second one –with fixed appliances, for definitive and proper alignment of all teeth and correction of sagittal malocclusion as well.

Case Report

Patient B.I.8 years of age, visited our clinic for orthodontic treatment in order to find a solution for non-erupted maxillary frontal teeth. He had convex profile, deep bite, (Figure 1, 2) skeletal Class II division 2 and, according to the X-ray findings, had supernumerary teeth on both sides along the midline, and retained right and left deciduous central incisors (Figure 3).

Figure 1. *Extraoral photograps at the start of the treatment*

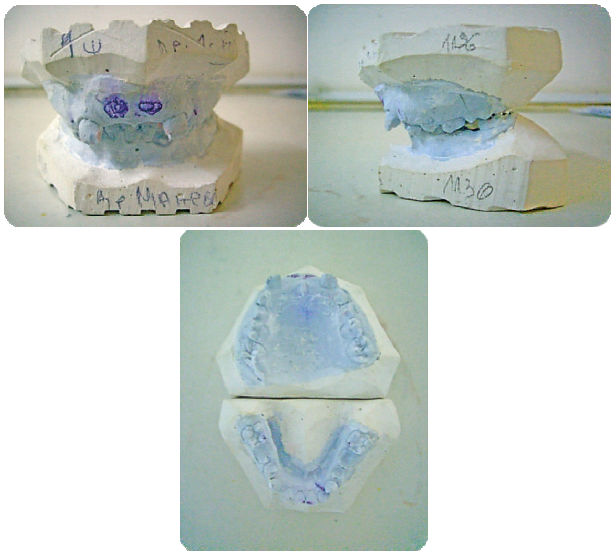


Figure 2. *Dental casts at the start of the treatment*

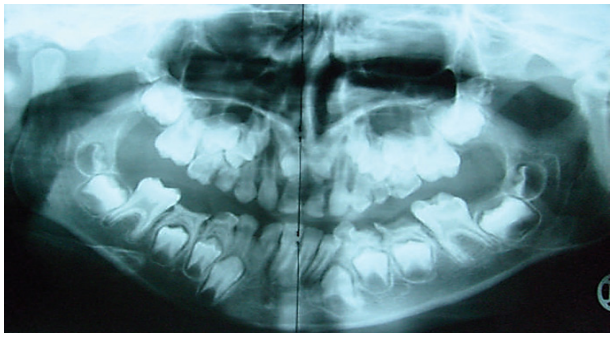
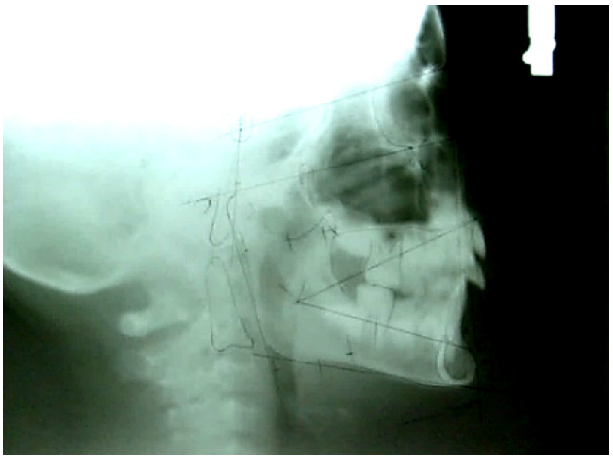


Figure 3. *Orthopantomography at the start of the treatment*

Cephalometric tracings revealed skeletal Class 2 division 2 with normognathism of maxilla and retrognathism of mandibula, retroclined incisors in both jaws, skeletal deep bite and horizontal type of growth.



SNA	81˚(82 ˚)
SNB	75˚ (80 ˚)
ANB	6˚ (2 ˚ -4 ˚)
A – NPg	5 mm (2mm)
1/SN	101˚ (104 ˚)
1/NA	21˚(25 ˚)
1-NA	2 mm (5mm)
1/NB	20˚(22 ˚)
1-NB	3 mm (5mm)
1/1	142 ˚(130 ˚)
N-Gn	120 mm (112mm)
N-Sna	59mm(51mm)
Sna-Gn	61mm (61 mm)
Sna-Xi-Pm	43˚ {47 ˚)
NPg/MPl	65 ˚ (67 ˚)
Bjork : NSAr	119 ˚ (123 ˚)
	SArGo 140 ˚(143 ˚)
ArGoM	121˚(130 ˚)
380˚	(396 ˚)
S-Go/N-Me	80/120
66,5 %	(62%-65%

Figure 4. *Cephalometric findings*

With the collaboration of oral surgeon, an extraction of deciduous central incisors was preformed and we started the treatment in order to create space, to correct deep bite and made settings for traction of both impacted maxillary central incisors. After removing the deciduous teeth, we managed to place the right maxillary central incisor in the dental arch (Figure 4) with elastic traction placed on the button of the tooth to the hook on the appliance. Since the retention on deciduous teeth was not satisfactory, we had to use active functional appliance by Haupl-Andresen. In order to create more space, and due to complexity of the planned surgery, the removal of supernumerary teeth was postponed forseveral months.

Figure 4. *Right maxillary incisor in the dental arch*

The progress of our treatment is revealed in Figure 5a and 5b.

Figure 5a. *OPG after the traction of 11 teeth, and 21 still high in maxilla*

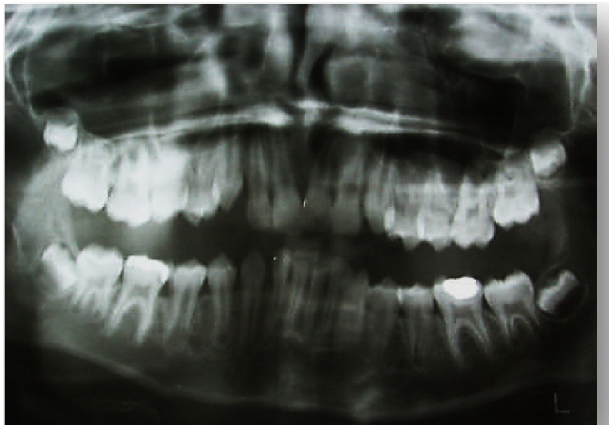


Figure 5b. *X-ray – both maxillary central incisors placed in the dental arch*

The treatment continued with mobile appliance, and after the completion of permanent dentition, fixed appliance was bonded in both jaws (Figure 6).

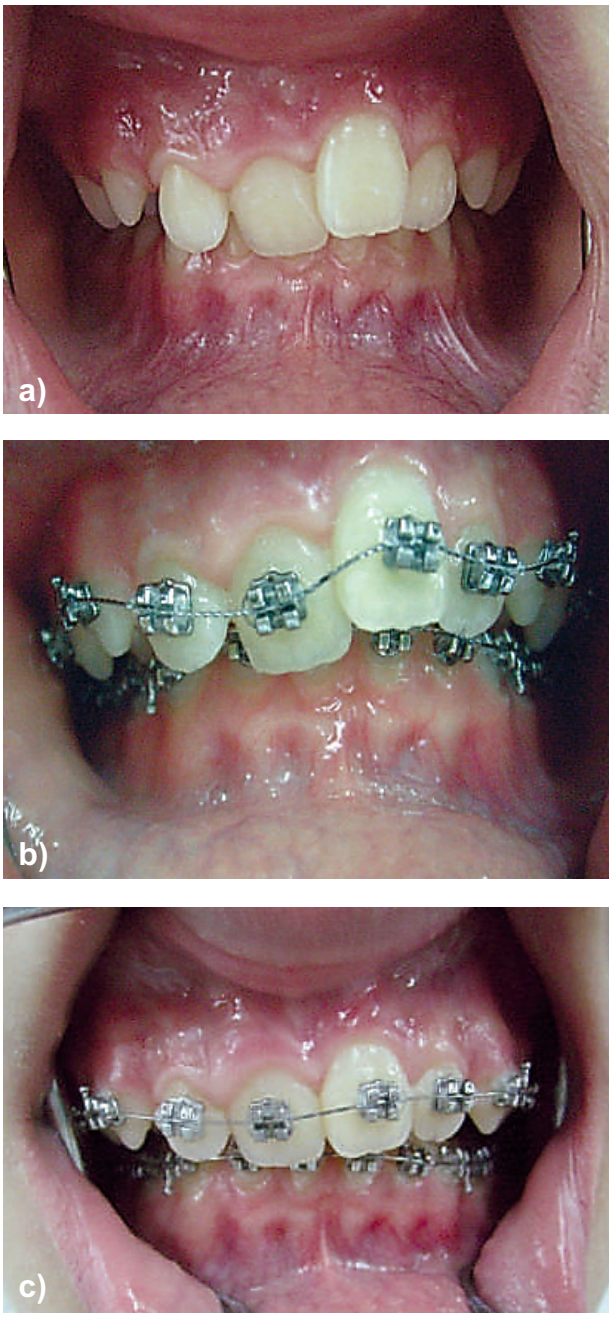


Figure 6. *a) before and b) after the bondingof the fixed appliance; c) phase of the treatment*

During the treatment with fixed appliances, we used intermaxillary traction Class II which allowed us to correct the anteroposterior relation of the jaw bases. Following the debonding of the appliance, a retention phase followed and we gained stabile occlusal relations, good function and good aesthetics (Figure 7).

Figure 6. *Intraoral photos one year after debonding of the fixed appliances*

Discussion

Impaction of maxillary incisors, although rare, always presents a big challenge for everyone involved - parents, patients, orthodontist, oral surgeons. The negative effect is even more pronounced because the absence of the frontal teeth has a great influence on facial aesthetics and it plays a big role in the social interaction of the affected individuals.

Several factors could cause the failure of the eruption of the impacted incisors, such as their excessive proximity to the adjacent teeth in the dental arch, the overlap of the crown on their roots, big distance from the occlusal plane, ankilosis, and abnormal morphology of the crown. Their repositioning in the dental arch may be accompanied with risk of necrosis, root resorption, alveolar bone loss, injury to adjacent teeth, gingival recession and increase in clinical crown length, aesthetic problems and tooth loss.

After the diagnostic procedures, a treatment plan is estimated and it usually involves oral surgeon too, because in most cases there is an obstacle in the eruption path of permanent incisors: cyst, odontoma or supernumerary tooth. Surgical exposure of impacted teeth can be done with open or closed method. The findings by Becker[20] suggest that closed method is a better approach because it doesn't interfere with the periodontal status of the tooth, the width of the attached gingiva and the crown length. In our case, the closed method was favored since the maxillary central incisors were very high in the alveolar bone, near the nasal spine[21].

In order to apply the orthodontic traction, the anchorage must be reinforced with a heavy rectangular arch wire on the fixed orthodontic appliance or a removable appliance. Factors such as dental age, compliance, and oral hygiene may influence the selection of the treatment.

In our case, traction of impacted teeth was performed with modified mobile appliance in the first phase of the treatment. The majority of patients with incisor impaction are usually in mixed dentition with only the first molars, and incisors present which are available for bonding, so the force that is produced with fixed appliances may impact the anchored teeth and may lead to root resorption. Application of a removable appliance allows forthe reaction force to be anchored by posterior teeth and palatal area, so there is no side effect to the adjacent teeth. Another issue with applying fixed appliance is the oral hygiene, which ischallenging in mixed-dentition patients, because there is a greater potential for decalcification and gingival inflammation if the oral hygiene is not proper. On the other hand, orthodontic traction with removable appliance shortens the length of further fixed orthodontics treatment and decreases the risk ofcomplications. Cooperation of the patient is the most important part, andmost of them are highly motivated to fill the gap in the frontal region and are satisfied when they see the results of their effort. Nonetheless, since all the movements cannot be done with the removable appliance, the additional alignment- the second phase of the treatment, has to be carried out with fixed orthodontic appliance.

Conclusions

Impacted maxillary central incisors represent relatively infrequent finding in everyday practice, but their characteristics and localization make them very important because they interfere with many functions like mastication, swallowing, speech and they affect the aesthetic appearance as well, causing low self-esteem and low confidence in the affected children.

Surgical orthodontic interventions can play a crucial role in guiding impacted teeth into their right position within a normal occlusion. At the end of the treatment, satisfactory functional and aesthetic results were obtained, gingival attachment was maintained and the integrity of the dental arch was restored.

As a conclusion, it is crucial that each case is treated independently in order to formulate the proper treatment plan and to achieve the best possible outcome with the collaboration of a team of specialists.

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CASE REPORT ON THE USE OF RIVA STAR AQUA AND RIVA SELF CURE GLASS IONOMER CEMENT RESTORATION IN PRIMARY TEETH

ПРИКАЗ НА СЛУЧАЈ ЗА УПОТРЕБА НА RIVA STAR AQUA И RIVA SELF CURE ГЛАС ЈОНОМЕРНА РЕСТАВРАЦИЈА КАЈ МЛЕЧНИ ЗАБИ

Mitrova O.[1], Sotirovska Ivkovska A.[2], Kocovski D.[3]

[1]*PHI General Hospital Gevgelija, [2]Department of Pediatric and Preventive Dentistry, Faculty of Dentistry – Skopje, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia, [3]PHI Medical Center, Demir Hisar

Abstract

Dental caries remains a severe oral health problem in children, and its impact in terms of pain, function impairment, and oral health-related quality of life of the population is high. In pediatric and operative dentistry, caries treatment benefits from a therapeutic option based on the use of silver fluoride (AgF) associated with potassium iodide (KI) to avoid dark colorations on dental tissues. The objective of this study was to evaluate the use of Riva Star Aqua and Riva Self Cure glass ionomer cement for restoration in deciduous teeth. Nowadays, Minimal and noninvasive approaches for management of dental caries are preferred, in lieu of conventional approaches. Silver diamine fluoride allows a more conservative tooth preparation, it is applied directly to carious lesions to arrest remaining decay, remineralize, and harden leathery dentin. Since management of dental caries with Riva Star Aqua is noninvasive and much comfortably performed, it can be a favorable means to treat dental caries in children. The present study is an insight into the use of Riva Star Aqua and Riva Self Cure glass ionomer cement for restoration in primary teeth and its clinical significance. **Keywords:** pediatric dentistry; silver fluoride; glass ionomer cement; tooth restoration; dental caries.

Апстракт

Денталниот кариес претставува сериозен проблем за оралното здравје кај децата и можност за предизвикување болка, пореметување на функцијата и квалитетот на животот на населението. Во детската и реставративна стоматологија, третманот на кариес има потреба од терапевтска постапка која вклучува употреба на сребрен флуорид (AgF) поврзан со калиум јодид (КИ) за да се избегнат темните пребојувања на забните ткива. Целта на оваа студија беше да се оцени употребата на Riva Star Aqua и Riva Self Cure глас јономер цемент за реставрација кај млечни заби. Во современата стоматологија се претпочитаат минимални и неинвазивни постапки за справување со денталниот кариес, наместо конвенционалните методи. Сребрениот диамин флуорид овозможува поконзервативен третман на забите, се нанесува директно на кариозните лезии за да се спречи понатамошно ширење на кариозната лезија, се овозможува реминерализација и зацврстување на деминерализираниот дентин. Бидејќи третманот на денталниот кариес со Riva Star Aqua е неинвазивен и многу лесен за изведување, може да биде средство кое е прифатливо за терапија на дентален кариес кај децата. Оваа студија дава увид за предностите кои ги има употребата на Riva Star Aqua и Riva Self Cure глас јономер цемент за реставрација на млечни заби и неговото клиничко значење. **Клучни зборови:** детска стоматологија; сребро флуорид; глас јономер цемент; реставрација на заби; дентален кариес.

Introduction

Dental caries is considered the most common disease in children. Factors that influence its occurrence are a diet rich in fermentable carbohydrates, the presence of bacteria in the biofilm, and oral hygiene habits. When left untreated, it can cause pain, dysfunction and can affect daily activities.

Local treatment with silver fluoride is important to stop carious lesions in primary teeth. The action of fluorine and silver can enhance the remineralization of the carious lesion, increase the resistance of hard dental tissues to further demineralization, cause the death of microorganisms and prevent adhesion and bacteria growth[1].

There are certain clinical conditions that present a challenge to pediatric dentists, even with the use of silver fluoride solutions, such as occlusal cavities. Due to the shape of the cavity, it is possible for some retentive parts,

that allow the growth and maturation of the biofilm, to remain, and therefore, even with the application of silver fluoride solution, these lesions can progress. This happens because during daily tooth brushing with a toothbrush and fluoride paste it is not possible to remove the biofilm in these retentive parts and the plaque becomes more and more cariogenic. In such cases, the efficacy of the treatment with silver fluoride alone decreases over time and the carious lesion is reactivated[2]. In such clinical conditions, the combination of a silver fluoride solution with a glass ionomer restoration is convenient, to ensure a faster remineralization of the carious dentin, together with an aesthetic restoration that closes the cavity and restores the shape of the teeth, eliminates the retentive parts and allows adequate biofilm control.

With the advance of science, Silver Fluoride (AgF) Riva Star Aqua product is available on the market, which is used as a dental caries control agent. It has proven to be effective, with its preventive and cariostatic properties, it is indicated for patients with a high risk of caries and has a simple procedure for application in dental practice[3].

The staining of the restoration's cavosuperficial margin becomes a problem when Silver Fluoride solutions are used alone. In order to overcome this deficiency, it is recommended to use Riva Star Aqua step 1 silver fluoride (AgF) and step 2 potassium iodide (KI), a combination that is available in Riva Star Aqua (SDI). Riva Star Aqua is a product that has a cariostatic effect, contains silver fluoride, and has similar performance to silver diamine fluoride products, without the disadvantages of ammonia-based solutions (odorless, unpleasant taste and soft tissue irritation). Riva Star Aqua (AgF) is an aqueous solution of silver fluoride without the presence of ammonia (with an improved formula unlike Riva Star), a non-invasive patented two-step system. The high concentration of silver fluoride ions inhibits cariogenic biofilm growth. 38% silver fluoride, used as the first step when using Riva Star Aqua, shows an effective inhibition of the biofilm, allowing immediate reduction of tooth hypersensitivity (by blocking the dentinal tubules). There is no risk of burns of the gingival tissue because it does not contain ammonia. Silver fluoride stimulates remineralization and provides an adequate ph value forforming minerals, protects collagen from degradation, and prevents growth and adhesion of bacteria[4]. Potassium iodide is used as a second step in the use of the agent by preventing teeth discoloration, and making it more aesthetically acceptable for patients[5,10]. The silver fluoride acts both in the inorganic portion of the dental structure and the organic portion; sodium fluoride being responsible for the mineral part, which is hydroxyapatite, and silver nitrate for the organic portion of proteins.

The reduction in the prevalence of cariogenic bacteria through cavity sealing and application of cariostatic agents is an important step that precedes the rehabilitating dental treatment. Therefore, the association between a cariostatic agent and an atraumatic restoring treatment is a therapeutic option of great value, especially in children with early childhood cavities.

The purpose of this paper was to show a clinical case of carious lesion treatment with Riva Star Aqua and Riva Self Cureglass ionomer restorative material.

Case Report

At the Clinic of Pediatric and Preventive Dentistry, at the "St. Panteleimon" University Dental Clinical Center in Skopje, a 6-year-old patient was admitted, who underwent a clinical examination and was diagnosed with occlusal carious lesions on the first and second lower right primary molars, classified according to ICDAS II as tooth 85 code 05 and tooth 84 code 04 (Picture 1). The clinical examination of the patient was performed in a dental office with visual inspection using a mirror and a probe for probing the carious lesions.

Picture 1. *Occlusal carious lesions on tooth 85 and 84*

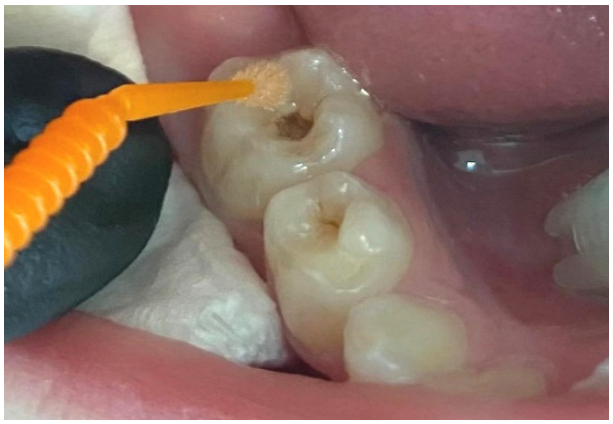
Picture 2. *Riva star aqua*

After discussing the possible treatment alternatives with the parents, the association of Riva StarAqua and glass ionomer cemen restoration was the procedure that was chosen to treat the carious lesions of the representative teeth (Picture 2).

According to the principles of Minimally Invasive Dentistry, selective caries removal was performed with manual instruments (dentin excavators); the cavo superficial margins of the cavity were kept free from carious tissue (Picture 2). It's important to point out that the restorative procedure was performed without local anesthesia, and with dental isolation with cotton rolls and an aspirator.

Application of Riva Star Aqua step 1 consisted of instilling one drop of silver fluoride on a non-absorbable pad and using a disposable brush applicator, teeth with carious lesions were treated with an active application of 60 seconds (Picture 3).

Next step was the use of Riva Star Aqua step 2, potassium iodide, by instilling two drops on a non-absorbable pad and, also with a disposable brush applicator, the carious lesions previously treated with silver fluoride were covered. The application of potassium iodide on silver fluoride, as a second step, contributed to the formation of a creamy white precipitate of silver fluoride which, after several applications of potassium iodide, neutralized and became clear (Picture 4). KI neutralizes the discoloration effect on teeth caused by silver ions.



Picture 3. *Application of AgF solution (Riva Star Aqua – step 1)*

Picture 4. *Use of Potassium Iodide (Riva Star Aqua - Step 2)*

After the application of Riva Star Aqua, restorations were placed on the treated teeth with glass ionomer cement (Picture 5) Riva Star Self Cure (SDI) to restore the shape and aesthetics of the tooth, and to enable easier control of the biofilm, (Picture 6).

Picture 5. *Clinical aspect of a placed glas ionomer restoration*

Picture 6. *Riva self-cure glass ionomer restoration cement*

Discussion

Although silver fluoride (AgF) applicationcan be considered a definitive treatment in posterior deciduous teeth, the desire for dental restorationis not unusual: par-

ents and patients want to recuperate teeth shape and aesthetics, while dentists aim to promote a better biofilm-control by cavity sealing.

Local treatment with Riva star aqua is important for preventing carious lesions in deciduous teeth. The principle of atraumatic work, the quick and easy application of the solution, without the need for local anesthesia is an easily acceptable method for children, especially for those who don't cooperate. Treatment of caries without the use of dental handpieces instruments minimizes the need for procedures that create aerosols, and by closing the cavity ensures the restoration of the shape and function of the tooth, and better control of the biofilm.

In dental caries treatment, especially in children who don't cooperate, children with disabilities who require sedation, it is a challenge to provide traditional restorative treatment. Many authors confirm that the use of Riva Star Aqua is a more effective, safer and more affordable option in the treatment of caries in children[8,11].

Compared to fluor protector (FP), the use of Riva star aqua and Riva star shows significantly higher antimicrobial activity. This is attributed to the ionic content of fluor and silver in AgF. These results confirm that both agents have antimicrobial activity against Streptococus mutans, and suggest that their higher potency is a more effective option for caries treatment[6]. Other authors, such as Hyunseok Lee, also confirm the great antimicrobial ability of AgF, compared to FP. AgF is comparable to ampicillin in its antibacterial effects against S. Mutans[7].

When treating occluso-proximal cavities, the shape of the lesion allows retention sites to remain, where there is growth and maturation of the biofilm, and despite the application of silver fluoride, carious lesions can progress, therefore it is necessary to close the cavity by placing a restorative material[8]. The use of these materials confirmed the efficacy of Riva star aqua and glass ionomer cement restorations in our patient as well. The principle of operation is considered acceptable by the patient, without fear and anxiety.

When AgF is mentioned, despite the aforementioned benefits, there are concerns about the possibility of restaining of teeth, restaining of the restoration margins, and possible non-acceptance by parents/children. This concern is unfounded, provided KI is used as a second step after the use of AgF (Riva star aqua), because tooth discoloration is reduced. It is an important advance that certainly widens the use of silver diamine fluoride, since the staining of teeth is greatly reduced. The possibility of purchasing both solutions together, inone single product, is an extra facility. This important data enables a wider use of Riva star aqua. According to Patel et al. the application of SDF, i.e. AgF, successfully stops dentine caries and it is 89% more effective than other agents for stopping the carious process, but the use of KI after SDF does not neutralize the repainting in its entirety[9]. However, according to Turton B et al. the use of KI resulted in a 6-times lower chance of developing black lesions on teeth compared to teeth treated with AgF or SDF alone[10].

In their study, Jiang et al. demonstrated that the physicochemical changes of dental tissue caused by pretreatment with AgFdid not affect the adhesive properties of glass ionomer cement restorations[2].

Minimally invasive preparation of the tooth, without the need for extensive removal of the carious lesion, using a cariostatic agent and atraumatic treatment with Riva Star Aqua and the possibility of quick and easy application is a therapeutic option of great value in many cases in dental practice[11].

Conclusions

The use of Riva star aqua and glas ionomer cement for restoration in primary molars has shown clinical success as a technique that allows prevention and prevents further progression of carious lesions, when used for treatment in children for restoring health and function of primary teeth.

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SPONTANEOUS REGENERATION OF BONE FOLLOWING MANDIBULAR RAMUS SURGERY FOR CYSTIC APPEARANCE LESIONS: A REPORT OF CASE SERIES

СПОНТАНА КОСКЕНА РЕГЕНЕРАЦИЈА КАЈ ЦИСТИЧНИ ЛЕЗИИ НА ВИЛИЧНА ГРАНКА-РАМУС НА ДОЛНА ВИЛИЦА: СЕРИЈА НА СЛУЧАИ

Stamatoski A.[1], Koneski F.[1], Trambulova J.[1], Popovik-Monevska D.[1], Kirkov A., Pancevski G.[1], Dvojakovska S.[1], Iliev A.[1]

[1]University Clinic for Maxillofacial Surgery Skopje, Faculty of Dental Medicine- Skopje, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia.

Abstract

Aim: Odontogenic cysts in mandibular ramus are pathological cavities with specific structure, containing epithelial rests and fibrous-connecting tissue that form a relationship with clinico-radiographic presentation, and it's difficult to differentiate them apart. The aim of this study was to illustrate and evaluate bone healing without the use of bone grafting materials. **Materials and methods:** This review of case series is based on the retrospective study of surgically treated patients during the past 12 months for 2022 year. All measurements with radiographic scans were made for the purpose of analysing bone cavities, where spontaneous bone healing of residual cavities occurred. **Results:** The imaging spectrum used in our study was made with CBCT scan producing 3D images as a problem-solving tool that have been used to help preoperative plan treatment, detecting the location of the lesions, assuming equal growth in all directions, identifying them by their shapes representing the extension to the ramus, swelling or bone defect of the lingual/buccal cortex. Jaw pain associated with swelling was the common presentation of clinical symptoms. All patients underwent surgical treatment and cystectomy of the mandible was performed. There was a difference in reduction rates by initial volume and no recurrence was observed during the study period. **Conclusion:** Voluminous jawbone cysts are often aggressive and CBCT scan is useful for evaluating morphological changes alongside the anatomical location of the lesions and bony margins which is crucial for differential diagnoses. Simplifying the surgical procedure for large mandibular ramus cysts without using graft materials is possible and can help reduce postoperative complications. **Key words:** mandibular cyst; cystectomy; Cone-beam computed tomography; surgery

Апстракт

Цел: Одонтогените цисти со локализација на мандибуларен рамус, претставуваат најчести патолошки промени со специфична структура, креирани со цистична празнина или лумен, епителни островца и фиброзно ткиво, чија клиничко-патолошка симптоматологија е предизвик за секој хирург. Целта на оваа студија е да ја евалуира коскената спонтана регенерација без аугментација со графт-материјали кај поголеми цистични лезии. **Материјал и метод:** За период од 12 месеци во тековната 2022 година, ретроспективно беа проследени сите хируршки третирани поголеми цисти на мандибуларен рамус чие радиолошко волуметриско испитување беше спроведено за потребните анализи на коскениот патолошки кавитет. **Резултати:** Предоперативни сликии идентификација на лигвален и букален кортекс во сите насоки со помош на апарат за тродимензионална визуелизација на структурата на цистичната празнина беше спроведена вклучително кај испитаници во студијата. Како доминантни симптоми се евидентирани болка и оток. Забележана е значајна разлика во волуметриските резултати на даденият примерок за цистични лезии. Хируршка интервенција беше изведена кај сите пациенти без притоа да се нотира рецидив во периодот на постоперативна рехабилитација. **Заклучок:** Локализацијата на цистичната промена, а особено на цисти со поголеми димензии со зафаќање на повеќе анатомски простори или се во колизија со нив, во тој случај, често пати, морфолошките отстапувања се евидентираат со помош на тродимензионална визуелизација и рендерирање, бидејќи одбележување на коскените маргини е од круцијално значење при планирање на дефинитивен третман. Изборот на тераписки пристап и соодветна оперативна техника за цисти на рамус на мандибула без користење на дополнителни материјали за коскена аугментација го минимизира времето за операција и превенција од појава на можни постоперативни инфекции. **Клучни зборови:** мандибуларни цисти; цистектомија; 3Д дигитална рентген дијагностика; хируршки третман.

Introduction

Jaw cysts in oral and maxillofacial pathology constitute the largest percentage of appearance in clinical practice, and they are classified into several groups. Among all cystic lesions, the 5th edition of World Health Organization (WHO) from 2022 for Head and neck lesions and the 4th edition (2017) is not different for the classification of odon-

togenic lesions[1-5]. In 2017, they reclassified the odontogenic keratocystic tumor into odontogenic keratocyst believed to emerge from the dental lamina. The diverse spectrum of clinical signs and symptoms can be a challenge for physicians, regarding imaging modalities used for evaluation of odontogenic cysts, because they can mimic more aggressive cyst-like lesions and tumors on x-ray. In recent years, several surgical methods using various grafts materials, which help preserve and repair the bone defects after removal of the cystic-appearing lesion in the jaw, have been described[6-10]. This paper demonstrates valuable information for clinicians about spontaneous bone regeneration after the removal of large jaw cysts, making their treatment more challenging.

Material and methods

The retrospective study subjects were patients who underwent CBCT scans before and after jaw surgery of the mandibular ramus for large cystic lesions, and whose complete medical records were kept at the University Clinic for Maxillofacial Surgery in Skopje for a period of one year. This study was conducted bycollecting data on age, gender, lesion location and size, and histopathological diagnosis from medical records. All images were obtained using a Planmeca Romexis (90 kV 9.0 mA 5.07 s / thickness 0.4 mm / 3D rendering) using the soft tissue window to allow clear delineation. Two clinicians performed the manual segmentations to obtain three-dimensional (3D) representation of pathological structures. The anatomical analysis of mandibular rami was labelled as point A in three different distances in lateral view: Ao (reference point), A- (1 cm proximal and below the mandibular canal), and A+ (1 cm distal and bellow the mandibular canal). The zero reference point Ao was identified using a curve, between the occlusal plane and the anterior border of the vertical mandibular rami. Coronal (maximal widthin bucco-lingual direction), axial (maximal length in anteroposterior) and saggital plane (maximal height in coronal-apical direction, or between alveolar crest and base of mandible) were measured and then manually checked on every single slice. The linear dimension (preoperatively) was calculated using this formula: Intraosseous defect (%) = cystic appearance lesion (sum measured in coronal-X, axial-Y, and saggital-Z plane) / sum distance from the outside cortical bone measured in three directions to the cyst wall x 100.

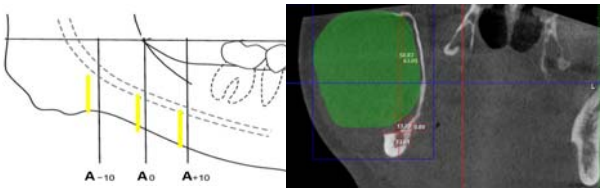

Figure 1. *Reference lines and measurement points in the mandible*

Results

Between January and December 2022, ten patients were diagnosed with large-size mandibular cysts. Two patients were excluded due to the lack of follow-up CBCT scan, and finally eight patients were included in this retrospective study, five male and four female patients, with mean age of 41.6 years (range 25–63). The male-to female ratio was an approximate 1.25:1. The majority of patients (56%) were between 20-39 years of age. In total, 3 of 8 patients were asymptomatic on presentation, discovered with routine orthopantomography. Five patients with these cystic lesions were initially seen with swelling or pain, and two of them with experience with trismus. The surgical approach involved enucleation of the entire cyst with any impacted teeth. Two patients reported paresthesia, but without significant implications. Their characteristics and digital data of pre-operative volumetric changes are summarized in Figure 1. The most common histological type of cysts was radicular (4), followed by dentigerous cyst (2), and odontogenic keratocyst (2). The measurements of cyst volumes in bone tissue indicated that the reference point Ao have shown significant dislocation of inferior alveolar nerve (IAN) trajectory caudally (Table 1). A preoperative manual segmentation results from CBCT scans illustrate the most significant volume-rendered image showing in Figure 1 and Figure 2. All patients had complete resolution and no sign of recurrence at the last follow-up visit.

Table 1. Distance (mm) between referencepoint (A) and the mandibular canal in lateral view between the occlusal plane and base of mandible

Odontogenic cysts (n)	A-	Ao	A+
radicular (3)	30.53	43.41	21.49
dentigerous (2)	43.16	35.71	42.67
keratocyst (2)	26.9	39.35	10.00
residual (1)	21.8	55.03	21.50
mean distance (mm)	32.36	42.29	25.90

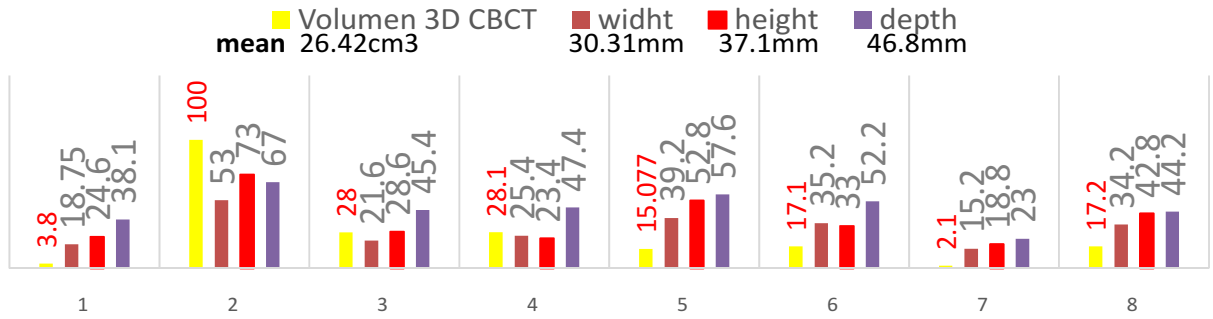

Figure 2. *Comparison between measurements of cyst volume pre-treatment size by equation with manual segmentation*

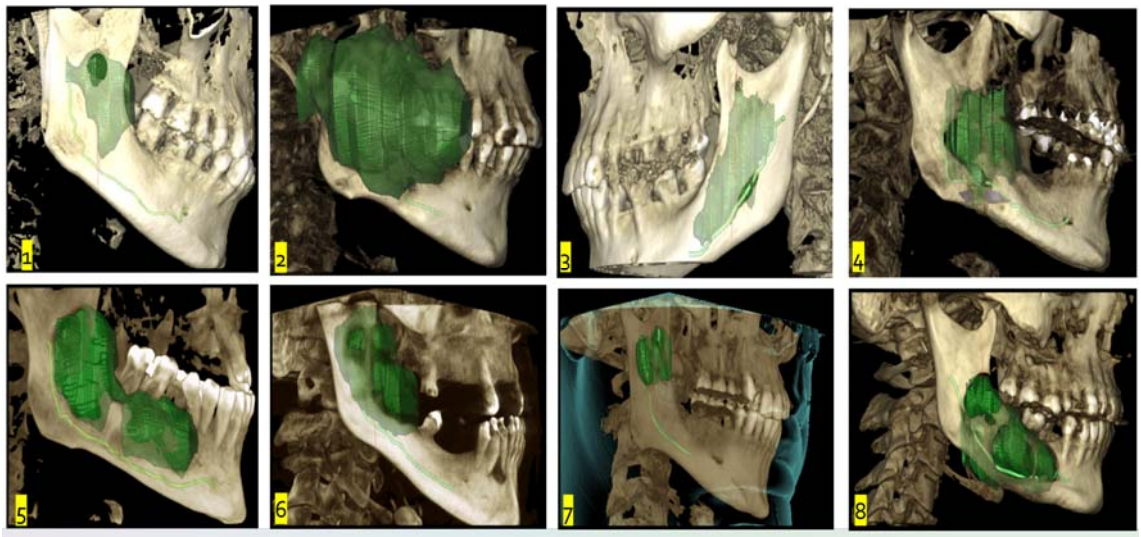

Figure 3. *Volumetric evaluation with final 3D volumetric rendering of all patients*

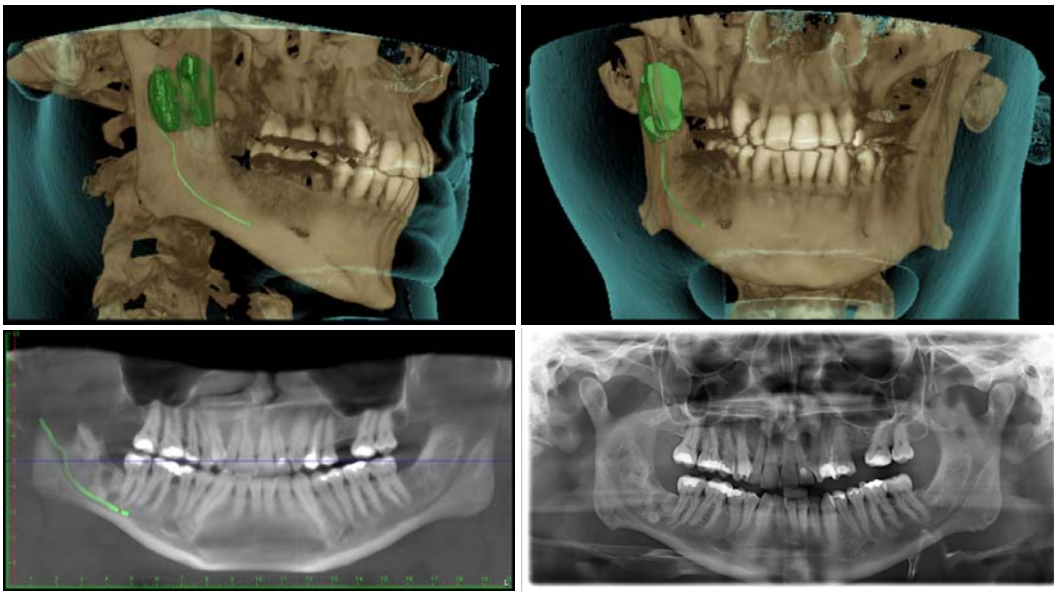

Figure 4. *Significant bone regeneration (with a ground glass appearance) and reconstitution of normal anatomic structures were observed in the patient with number 7 over a period of 5 months.*

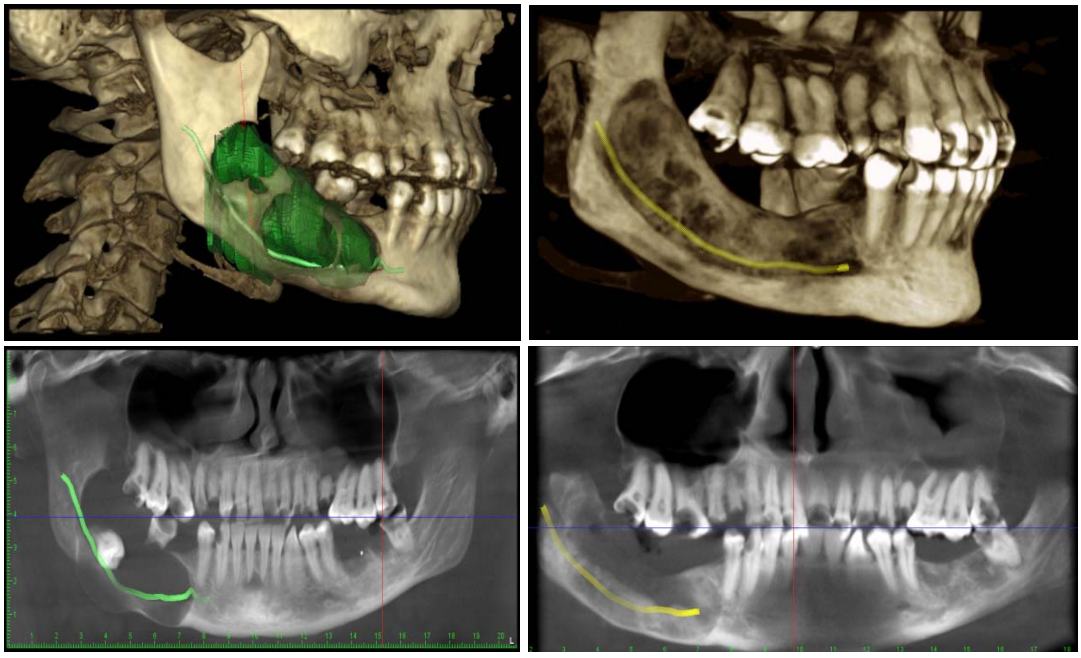

Figure 5. *Changes in bone density and cyst volume, along with marked inferior alveolar nerve (IAN) involvement, were observed before surgical treatment of a mandibular odontogenic keratocyst in the patient represented by case number 8. This assessment includes pre - and postoperative follow-up over a period of 3 months.*

Discussion

Cystic lesions are common pathologies in the maxillofacial region, often requiring invasive surgical treatment[11-15]. These lesions are typically diagnosed through routine.

Orthopantomographic images in primary dental care units, but the final diagnosis is confirmed by histopathological examination. The primary treatment goal is the surgical enucleation of the cystic lesion, which is usually the preferred approach and plays a crucial role in postoperative bone healing. When dealing with large intraosseous cysts, especially in the mandible and its ramus, surgeons must consider the specific anatomy of nearby structures and the size of the lesion. Cone beam computed tomography (CBCT) is valuable for preoperative analysis. Surgical protocols for treating cysts, particularly those of odontogenic origin, focus on regenerative strategies that involve graft materials to enhance patient outcomes and manage bone defects. However, the choice of graft material and its potential for bone contact, distance osteogenesis, and regeneration capacity remain areas of ongoing research. Remarkably, some published studies demonstrate spontaneous bone regeneration after surgical treatment of large cystic lesions in the jaws. While many trials explore factors related to graft materials and prognoses, other studies suggest that new bone formation without graft materials may yield similar results[3,4,16,17]. Our current manuscript evaluates spontaneous bone healing following enucleation of large mandibular cysts, minimizing morbidity risk. Radiographic controls reveal differences in bone density for representative clinical cases. Although the study is based on a limited number of patients, it aligns with other published papers that support the hypothesis of complete bone healing after cyst enucleation without graft materials[15-20]. Notably, this technique warrants further research, especially for cysts in the mandibular ramus region. Comparing changes in the cortices of the mandibular canal between the primarily affected skeleton and the normal contralateral side highlights visibility differences in CBCT and panoramic radiography. Overall, wound healing after cyst enucleation and tooth removal, including wisdom tooth extraction, appears to occur effectively even in larger defects without the use of bone grafting materials. Taking into account factors related to graft materials and certain prognoses that can reduce overall treatment time while improving the quality of bone regeneration, many studies continue to explore these aspects[3,7,8,11,12,15]. However, contrary to some findings, other studies have suggested that the quality of new bone formation without the use of graft materials may not significantly differ from the results reported above[15,17,19]. Additionally, our current manuscript evaluates spontaneous bone healing after enucleation of large mandibular cysts, minimizing the risk of morbidity. Radiographic controls reveal differences in bone density for represen-

tative clinical cases[16,17,20]. Interpreting bone regeneration and changes in bone density, which were completely or partially ossified, and comparing cystic areas provide insights into the course of bone healing in our patients. Although the analysis is based on a limited number of patients, it aligns with other published papers supporting the hypothesis that complete bone healing can be achieved after cyst enucleation without the need for graft materials. It is worth noting that this technique requires further research due to the significant dilemma it poses, especially for cysts in the mandibular ramus region. Characterizing and comparing changes in the cortices of the mandibular canal between the primarily affected skeleton and the normal contralateral side differences in visibility using CBCT and panoramic radiography. Additionally, wound healing after enucleation of cysts and tooth removal, including wisdom tooth extraction, appears to occur effectively even in larger defects without the use of bone grafting materials[15-20]. Race, with the most frequently reported factors in published studies and factors associated with minority and majority results, we should also focus on evaluating more critical data covered in meta-analysis associated with interventions who should be used going forward for spontaneous bone healing framework after odontogenic cysts remova[15-7,19,20]. However, this study has limitations as well as evaluating immunomodulatory mediators and assessing the quality of regenerated bone after surgery when periosteum is not lost or the majority of the contour of bone is not detracted, and interpreted themselves in micro-computed tomography data conducted by histomorphometric analysis.

Conclusions

We emphasize the importance of CBCT scans for cystic lesions and evaluating nearby anatomical structures. This approach minimized the risks of failure by directly informing preoperative surgical planning. Nevertheless, these cysts can cause significant local bone destruction. We also anticipate that pushing the boundaries of 3D CBCT reconstruction with artificial intelligence will play a significant role in delineating the boundaries of bone cavities in the future. Enucleation and primary closure without additional bone substitutes facilitate the physiological organization of the blood clot, simplifying the surgical procedure and spontaneous bone healing is possible after removal of large cysts inmandible ramus.

Conflict of interest

The authors declare no conflict of interest.

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