e-ISSN: 2980-1389

JDSE

Journal of Dental Sciences and Education

Volume: 1

Issue: 4

Year: 2023

MEDIHEALTH ACADEMY

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Dear Colleagues,

It is with great pleasure that I welcome you to the fourth issue of our peer-reviewed academic journal named, Journal of Dental Sciences and Education (JDSE). In this fourth issue, reviews of new developments in the field of dentistry and original researchs are included. One of our most important goals is to mediate appropriately the sharing of knowledge and experience among dental professionals, researchers and academicians. In this issue, we share with you six articles covering various topics in dentistry.

Our first article of the journal *"Effect of different tea solutions on the color stability of composite resins"* is an original article and the authors aimed to compare the color stability of composit resins and evaluate them. The second article *"Can a new cooling method be used in dental implant drilling? An in vitro pilot study"* is an original article. The authors have evaluated the effectiveness of the CryoKB cooling method in increasing the heat-induced temperature during implant drilling in bovine femur bone and to determine its potential usefulness for future in vivo studies. The third article *"An overview to biocompatibility of resin based restorative materials"* is a review article. The authors argue that the basic concepts and methods related to biocompatibility, to present data from studies on the cytotoxicity of resin-based materials, and finally to make recommendations for clinical application. The fourth article *"The importance of treating dental caries in the prevention of medication related osteonecrosis of the jaw"* another an review article. The fifth article , *"Management of initial and surgical management of amlodipine-induced gingival enlargement with multifactorial etiology: a case report with 6 months follow-up"*. Finally, the sixth article *"Creating smile aesthetics by using crown lengthening and upper lip repositioning surgical operations together in a gingival smile case: a case report"* is a case report. The authors aimed to diagnose gingival smile and explain the treatment of excessive gingival appearance due to vertical maxillary excess and hypermobile upper lip with crown lengthening and upper lip repositioning surgeries.

I would like to thank the authors, reviewers, editorial team and publisher for their hard work and dedication in bringing this fourth issue to fruition. We look forward to providing you with the latest insights and developments in dentistry, and we welcome your feedback and suggestions

Sincerely,

Assoc. Prof. Elif Pınar BAKIR, PhD
Editor-in-Chief

Journal of
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Journal of Dental Sciences and Education

Original Article

DOI: 10.51271/JDSE-0018

Effect of different tea solutions on the color stability of composite resins

Sema Yazıcı Akbıyık[1], Şeyhmus Bakır[2], Elif Pınar Bakır[2], Gamze Polat[3]

[1]Department of Restorative Dentistry, Faculty of Dentistry, Lokman Hekim University, Ankara, Turkey
[2] Department of Restorative Dentistry, Faculty of Dentistry, Dicle University, Diyarbakır, Turkey
[3]Department of Restorative Dentistry, Van Oral and Dental Health Center, Van, Turkey

Cite this article: Yazıcı Akbıyık S, Bakır Ş, Bakır EP, Polat G. Effect of different tea solutions on the color stability of composite resins. *J Dent Sci Educ.* 2023;1(4):101-104.

Corresponding Author: Sema Yazıcı Akbıyık, semadis86@gmail.com

Received: 20/11/2023 ◆ **Accepted**: 25/12/2023 ◆ **Published**: 31/12/2023

ABSTRACT

Aims: The aim of this study is to evaluate the discoloration of supra-nanophile (Estelite Σ Quick) and nano-hybrid (Clearfil Majesty Esthetic) composites kept in three different brands of black tea (İstikan, Yellow Label and Çaykur) for three different periods (24 hours, 7 days and 28 days).

Methods: Specially produced Teflon molds with an inner diameter of 10 mm, an outer diameter of 12 mm, and a thickness of 2 mm were used. 28 pieces of Tokuyama Estelite Sigma Quick composite material and 28 pieces of Kuraray Clearfil Majesty Esthetic composite material were placed in the molds and polimerized. All samples were polished and initial color measurements were taken. The samples were divided into three experimental groups (Istikan, Lipton yellow label, Çaykur tiryaki) and a control group (distilled water) (n=7). The samples were kept in this solution for 1 day, 7 days and 28 days, and at the end of the period, color measurements were measured with a spectrophotometer. Data were recorded according to the CIE Lab system. One-way analysis of variance (ANOVA) and Tukey test were applied to determine the data, and the Kruskal Wallis H test was used to make comparisons based on variables with more than two categories in the data.

Results: In this research, it was detected that there was a statistically significant difference between the 24-hour and 7th-day coloration results of Tokuyama brand according to the beverages ($p<0.05$). According to the beverages, it was found that there was a statistically significant difference between the 28-day coloration results of Tokuyama and Kuraray brands.

Conclusion: In the supra-nanofilled and nanohybrid filler composite resins we used in our study; it was observed that the coloration increased as the residence time in the solution increased.

Keywords: Composite resins, tea, discoloration, spectrophotometer

INTRODUCTION

In recent years, the use of dental composite resins as restorative materials in both anterior and posterior group teeth has become quite widespread due to their ability to restore tooth function, preserve the natural tooth appearance, bond to the tooth through adhesion, and are also conservative.[1] Today, with nanotechnology, the aesthetic and physical properties of dental composite resins continue to be improved in order to increase their clinical performance. It is desired that composite resins can maintain these improved properties as long as they remain in the oral environment.[2,3]

One of the biggest challenges in clinical practice is ensuring the aesthetics of restorative materials, particularly in the anterior region. One of the most important factors that may cause the restoration to be replaced and lead to extra time and financial loss is the inability of aesthetically restorative materials to maintain color stability.[4] Various factors such as temperature changes in the oral environment, individuals' drinking habits and oral hygiene influence the coloration of dental composite resins in the oral cavity.[5] In studies, it has been reported that composite resins are frequently affected by beverages containing coloring pigments such as tea, coffee, cola, and fruit juices.[6,7] In addition, the concentration and size of the filler particles of the dental composite and the organic matrix formulation are among the factors affecting the coloration of restorative materials.[8]

The coloration of composite resins can be measured with various devices, such as a spectrophotometer and a colorimeter.[9] The spectrophotometer measures tooth color using the CIE Lab color system. The L* coordinate points brightness, the a* coordinate indicates the red or green component, and the b* coordinate represents yellowness or blueness. The intersection of these three coordinates gives the value of that color. Color change is expressed by a value called ΔE.[10]

It is seen that black tea consumption habits are higher in our country compared to other beverages. In addition to the consumption of black tea grown in Turkey, Ceylon tea consumption is also quite high.

The aim of the study is to evaluate the discoloration of supra-nanophile (Estelite Σ Quick) and nano-hybrid (Clearfil Majesty Esthetic) composites kept in three different brands of black tea (İstikan, Yellow Label and Çaykur) for three different periods (24 hours, 7 days and 28 days).

METHODS

Ethics committee approval is not required because of designed of the study. All procedures were carried out in accordance with the ethical rules and principles. Tokuyama Estelite Sigma Quick (A2) and Kuraray Clearfil Majesty Esthetic (A2) were used to check the color change in our study. Black Ceylon tea (Istikan), black tea (Lipton yellow label tea bag), and black tea (Çaykur tiryaki tea bag) were used as three different coloring solutions, and distilled water was used as the control group.

Sample Preparation

In our study; specially produced Teflon molds with an inner diameter of 10 mm, an outer diameter of 12 mm and a thickness of 2 mm were used to prepare the samples. 28 pieces of Tokuyama Estelite Sigma Quick composite material and 28 pieces of Kuraray Clearfil Majesty Esthetic composite material were placed in the molds, smoothed with the help of a mouth spatula, and overflow of excess material was ensured by first applying transparent tape and then glass coverslip. The overflowing material was removed from the molds. Each sample was then polymerized from both surfaces with an LED-B light device (Woodpecker Led-G / China) according to the manufacturer's instructions. To ensure surface standardization, Sof-Lex (3M ESPE, St. Paul, MN, USA) polishing discs were applied to all specimens by a single operator at 20,000 rpm.

Since there were four different experimental solutions, including three different brands of tea solutions and one distilled water, the samples from each composite group were divided into 4 groups, and a total of 8 groups were obtained, with 7 samples in each group.

Solution Preparation

For the preparation of tea solutions, 200 ml of 100°C boiling water was used for each tea bag. All solutions were prepared according to the manufacturer's instructions. During the preparation of the tea solution, the tea bags were gently shaken at 0, 2, and 5 minutes and removed from the water at 5 minutes.

Color Measurement

Samples prepared for color measurement were kept in an incubator at 37°C for 24 hours. The specimens were washed with distilled water before each measurement and then dried completely with blotting paper. The first color measurements were then performed with a Vita Easyshade spectrophotometer (VITA Easyshade V, Vita Zahnfabrik, Bad Sackingen, Germany). Each color measurement was performed under standard conditions in a dark room under fluorescent daylight lamp (Master TL-D 90 Graphica 18W965SLV/10, Philips, The Netherlands) illumination and on a gray background. For each sample, measurements were repeated three times, and L, a, and b values were recorded. The spectrophotometer was calibrated before each measurement. After the first measurements, all samples were divided into groups, 8 in each group, and placed in experimental solutions. The solutions were divided into 5 ml per group to cover each sample completely. All samples in the solutions were kept in an incubator at 37°C between measurements. The solutions were changed regularly, once a week. On days 1, 7, and 28, color measurements were repeated.

Statistical Analysis

The data obtained in the study were analyzed using the SPSS (Statistical Package for Social Sciences) for Windows 25.0 program. Descriptive statistical methods (mean, standard deviation) were used when evaluating the data. Compliance with the normal distribution was checked with normality tests and kurtosis and skewness values. The normal distribution of the data used depends on the skewness and kurtosis values being between ±3.[11]

In normally distributed data, independent sample t-test was applied for comparisons based on variables with two categories, one-way analysis of variance (ANOVA) was applied for comparisons based on variables with more than two categories, and Tukey test was applied to evaluate which groups caused the difference. In data that did not show normal distribution, the Kruskal Wallis H test was applied for comparisons based on variables with more than two categories. The significance level was accepted as 95%.

RESULTS

When 24-hour coloration results were examined, it was observed that there was no statistically significant difference between the results of distilled water, Lipton, and Çaykur according to the brand (p>0.05).

It was found that there was a statistically significant difference between the 24-hour Ceylon tea coloration results according to the brand (p<0.05). In Ceylon tea results, it is seen that Tokuyama brand 24-hour coloration values are higher than Kuraray brand values.

It was detected that there was no statistically significant difference between Kuraray brand 24-hour coloration results according to beverages (p>0.05).

It was observed that there was a statistically significant difference between Tokuyama brand 24-hour coloration results according to beverages (p<0.05). It is seen that Ceylon tea coloration values are higher than distilled water and Çaykur coloration values; Lipton coloration values are higher than distilled water and Çaykur coloration values. **(Table 1)**

Table 1. 24 hours

	24 hours				
	Distilled Water	**Ceylon Tea**	**Lipton**	**Çaykur**	**p**
Kuraray	1.77±0.79	1.74±0.59	3.55±2.25	2.94±1.24	0.059
Tokuyama	1.83±1.28	3.44±1.64	3.46±1.44	1. 88±0.99	**0.041***
p	0.923	**0.034***	0.932	0.104	

When 7-day coloration results were researched, it was observed that there was no statistically significant difference between the results of distilled water, Ceylon tea, Lipton, and Çaykur according to the brand (p>0.05).

It was observed that there was no statistically significant difference between Kuraray brand 7-day coloration results according to beverages (p>0.05).

It was seen that there was a statistically significant difference between Tokuyama brand 7-day coloration results according to beverages (p<0.05). Lipton coloration values were higher than distilled water coloration values. **(Table 2)**

Table 2. 7 days

	7 days				
	Distilled Water	Ceylon Tea	Lipton	Çaykur	p
Kuraray	2.76±0.87	5.12±1.59	4.86±2.12	4.77±2.14	0.069
Tokuyama	2.48±1.75	4.90±2.38	5.42±1.59	3.25±1.15	**0.016***
p	0.713	0.843	0.587	0.125	

When 28-day coloration results were researched, it was determined that there was no statistically significant difference between the results of distilled water, Ceylon tea, Lipton, and Çaykur according to the brand (p>0.05).

It was found that there was a statistically significant difference between Kuraray brand 28-day coloration results according to beverages (p<0.05). It is seen that Ceylon tea coloration values are higher than distilled water, Lipton, and Çaykur coloration values; Lipton coloration values are higher than distilled water and Çaykur tea coloration values.

It was seen that there was a statistically significant difference between Tokuyama brand 28-day coloration results according to beverages (p<0.05). It is seen that Ceylon tea and Lipton coloration values are higher than distilled water coloration values. **(Table 3)**

Table 3. 28 days

	28 days				
	Distilled Water	Ceylon Tea	Lipton	Çaykur	p
Kuraray	2.99±0.86	8.99±2.22	6.12±1.51	5.36±2.02	**0.000***
Tokuyama	3.29±1.78	7.04±2.80	6.64±1.76	4.61±1.16	**0.005***
p	0.690	0.174	0.560	0.415	

DISCUSSION

Color plays an important role in achieving optimum aesthetics. One of the biggest disadvantages of resin composites is the discoloration of the restoration.[12] Color change of composite resins may be the result of various internal or external factors. The degree of discoloration can vary depending on various intrinsic factors such as resin material composition (filler particles, organic matrix, activators and photoinitiators), hydrophilic-hydrophobic structure of monomers, water absorption and degree of polymerization.[13,14] For this reason, two restorative materials with different monomer structures and filler particle sizes were used in our study. In addition, external factors that contribute to discoloration include eating habits, smoking and inadequate oral hygiene.[15]

In restoration finishing processes, it has been stated that the coloration properties of dental composite resins are influenced by the application of different finishing and polishing methods.[16] In many studies, aluminum oxide discs have been reported to be effective materials for creating smooth surfaces.[17,18] In our study, Sof-Lex (3M ESPE, St. Paul, MN, USA) polishing discs were applied to all specimens by a single researcher at 20,000 rpm in the polishing procedure following the finishing process applied with diamond finishing burs to ensure standardization.

Composite resins are constantly exposed to saliva, food, and beverages in the mouth. A wide variety of test solutions or beverages, such as tea, coffee, red wine, cola, acidic drinks and artificial saliva, have been used in the literature to evaluate the discolorations of dental restorative materials.[19-21] Since black tea consumption habits are higher in Turkey compared to other beverages, two different brands of black tea grown in Turkey and Ceylon black tea were used as coloring solutions.

Visual or color measurement devices can be used to evaluate color stability.[22] Anusavice et al.[23] stated that instrumental colorimetric measurements can eliminate subjective errors. For this reason, colorimetry and spectrophotometry techniques have been used dependable in various dental studies.[1] In our study, a spectrophotometer device (Vita Easyshade) that allows quantitative color assessment and the CIE L*a*b* system was used to measure color change to avoid error due to subjective evaluation.

Some researchers have pointed out that the retention time of restorative materials in beverages may affect the level of coloration.[13,24] Based on the study of Ertaş et al.[25], who mentioned that 24 hours of soaking time in beverages corresponds to one month in vivo, 24 hours, 7 days, and 28 days of soaking time were preferred in this study.

In our study, when the 24-hour coloration results were researched, it was found that there was no statistically significant difference between the results of distilled water, Lipton yellow label black tea, and Çaykur black tea according to the beverage brand (p>0.05), but when the beverages were compared among themselves, it was seen that there was a statistically significant difference between Ceylon black tea and other brands of teas and distilled water (p<0.05). We think that the statistically significant difference may be due to the color pigment in the structure of Ceylon tea.

When compared by beverage, there was a statistically significant difference (p<0.05) in Estelite Σ Quick (Tokuyama Dental Co., Tokyo, Japan) compared to Clearfil Majesty Esthetic (Kuraray Medical Co., Tokyo, Japan) at 24 hours and 7 days. Clearfil Majesty Esthetic is a nano-hybrid composite resin whose organic matrix consists of Bis-GMA, hydrophilic aliphatic dimethacrylate. Estelite Σ Quick is a supra-nanofilled composite resin with an organic matrix consisting of Bis-GMA and TEGDMA. Studies have shown that while water absorption is 0-1% in Bis-GMA-based resins, this rate can increase up to 3-6% depending on the rate of TEGDMA added.[26] In a study, it was reported that TEGDMA was the monomer structure that caused more water absorption than Bis-GMA, Bis-EMA, and UDMA.[27] In our study, similar to this study, Estelite Σ Quick, whose organic matrix consists of Bis-GMA and TEGDMA, showed statistically more coloration in tea solutions at 24 hours and 7 days compared to Clearfil Majesty Esthetic. However, there was a statistically significant difference between the 28th-day coloration results of both composite resins according to the solutions (p<0.05). It was observed that coloration increased in both materials as the exposure time to the solution increased.

According to the 28th day coloration result, it is seen that the coloration values of Ceylon black tea and Lipton yellow label in Estelite Σ Quick are higher than distilled water coloration values. In Clearfil Majesty Esthetic, Ceylon black tea coloration values were higher than distilled water, Lipton yellow label and Çaykur black tea coloration values; Lipton yellow label coloration values were higher than distilled water and Çaykur black tea coloration values.

Filler properties also have important effects on the coloration of composite materials. Inorganic fillers on the surface can break away from the structure of the resin matrix during the clinical life of the material and cause a cavity to form in that area. Since the filler particle sizes of nano-filler composite resins are very small, it is thought that they show

a lower degree of surface discoloration than other materials when they are detached from the surface. In some studies, it has been reported that increasing the filler ratio in this type of composite material causes less coloration due to the decrease in the organic matrix ratio.[28-31] One of the composite materials used in our study was supra- nanofilled (Estelite Σ Quick), and the other was nano-hybrid (Clearfil Majesty Esthetic), and their filler ratios were close to each other by weight. Although Estelite Σ Quick had a smaller filler particle size and a higher filler ratio, the tea solutions showed statistically more coloration than Clearfil Majesty Esthetic at 24 hours and 7 days. We think that not only the filler ratio and particle size but also the organic matrix of the material may have an effect on the degree of coloration.

Limitations of This In Vitro Study

In the oral cavity, teeth are not exposed to a drink for 24 hours, and saliva has a washing effect, but in our study, the specimens were exposed to solutions during the study period. Additionally, factors such as wear or thermal changes were not simulated in our study.

CONCLUSION

In the supra-nanofilled and nanohybrid filler composite resins we used in our study; it was observed that the coloration increased as the residence time in the solution increased. We suggest that these composite materials, which have been developed in recent years with the aim of making aesthetic restorations, should be investigated with composite resins containing different organic matrix and inorganic fillers and different solutions by simulating the oral environment.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval is not required as the study. All procedures were carried out in accordance with the ethical rules and the principles.

Informed Consent: Because of designed of the study, informed consent is not required.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declared that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of Dental Sciences and Education

Original Article

DOI: 10.51271/JDSE-0019

Can a new cooling method be used in dental implant drilling? An in vitro pilot study

Kubilay Barış, Meltem Karşıyaka Hendek, Ebru Olgun

Department of Periodontology, Faculty of Dentistry, Kırıkkale University, Kırıkkale, Turkey

Cite this article: Barış K, Karşıyaka Hendek M, Olgun E. Can a new cooling method be used in dental implant drilling? An in vitro pilot study. *J Dent Sci Educ*. 2023;1(4):105-108.

Corresponding Author: Kubilay Barış, kubilaybaris60@hotmail.com

Received: 16/10/2023 ◆ **Accepted**: 28/12/2023 ◆ **Published**: 31/12/2023

Abstract

Aims: The aim of this in vitro pilot study was to evaluate the effectiveness of the CryoKB cooling method in increasing the heat-induced temperature during implant drilling in bovine femur bone and to determine its potential usefulness for future in vivo studies.

Methods: The study included four groups defined as follows: the G1 group, in which stainless steel materials were cooled using the CryoKB method (n=13); the G2 group, in which bone was cooled using the CryoKB method (n=13); the K1 group, in which stainless steel materials were cooled using an external irrigation solution (n=13); and the K2 group, in which bone was cooled using an external irrigation solution (n=13). The temperature was measured by creating a 5-mm-deep socket in the bone. The measurements were made every 5 minutes from 0 minutes to 1 hour, using a thermometer device with a type K probe.

Results: The temperature changes in 52 samples were evaluated. Statistically significant differences in temperature change were found between the G1 and G2 groups. Statistically significant differences in temperature were found between the G2 and K1 groups and between the G2 and K2 groups.

Conclusion: The newly developed cooling method provided more effective and long-lasting cooling than the traditional irrigation method.

Keywords: Bovine femur bone, external irrigation method, implant drill, traditional irrigation method

INTRODUCTION

Dental implants offer excellent treatment options to reduce the limitations of normal dentures, bridges, and missing teeth. However, for an implant to be placed in the jawbone, the implant socket must be prepared in the area with a sufficient amount of bone. The physiological state of establishing direct contact between the immobile implant placed in the implant socket and the bone has been defined as osseointegration.[1]

Many parameters must be considered for proper osseointegration to occur. If these parameters are not met, early implant failure can occur.[2] The causes of early implant failure are the development of postoperative infection, too high or too low torque, trauma that may cause implant mobility, improper early loading protocol, and heat-induced thermal necrosis during the preparation of the implant socket.[3,4]

Thermal necrosis is generally described as an undesirable condition characterized by the frictional heat generated during implant drilling, causing cellular destruction, matrix degeneration and enzymatic degradation.[5] As the spongiosis bone has richer cellular and vascular resources, it allows for better distribution of the heat generated by friction and has a higher regeneration capacity. In the cortical bone, the heat generated by friction inhibits regeneration.[6] In the literature, the recognized threshold temperature for regeneration is 44-47°C for 1 minute.[7]

Various techniques for temperature control during implant drilling have been described. External and internal cooling methods are used separately or in combination.[8] Laser thermometers, thermography and thermocouple can be used for temperature measurements.[9]

The CryoKB method involves the process of cooling the material in a freezer (at a temperature of –18 - –20°C controlled from the outside by a thermometer) without the use of any irrigation solution (Oztiryakiler Metalware Industry and Trade Joint Stock Company, Istanbul, Turkey).

In this pilot study, we aimed to compare cooling using an irrigation solution with cooling using the CryoKB method. We hypothesized that the CryoKB cooling method provides better and long-term cooling than the irrigation method.

METHODS

This study has been evaluated by the Animal Experiments Local Ethics Committee Presidency of Kırıkkale University Rectorate within the scope of diagnostic and therapeutic clinical applications, and it has been concluded that there is no need for an Ethics Committee decision. (Date: 08.06.2022, Decision No: E-100143). All procedures were carried out in accordance with the ethical rules and principles.

In the pilot study planned in vitro, four groups were formed as follows: the G1 group, in which stainless steel materials (Nucleoss, Sanlilar Medical Devices Medical Chemistry Industry Trade Limited Company, Izmir, Turkey) were cooled using the CryoKB method (n=13) and stored in the freezer at –18 - –20°C to cool the material; the G2 group, in which the bone was cooled using the CryoKB method (n=13) and stored in the freezer at –18 - –20°C to cool the material; the K1 group, in which the stainless steel materials were cooled using an external irrigation solution (Biofleks, OSEL Pharmaceutical Industry and Trade Joint Stock Company, Istanbul, Turkey; n=13), with continuous irrigation using saline at 28-31°C; and the K2 group, in which the bone was cooled using an external irrigation solution (n=13), with continuous irrigation using saline at 28 - 31°C.

Bovine femoral bone was used in the study. Care was taken to ensure that all bones were of type 1 density, defined as Hounsfield units greater than 1250 on cone-beam computed tomography. Non-vital bovine bone was divided into bone segments (approximately 2.5 g in weight and 28×7×10 mm in size). The stainless steel materials were 25×5×4 mm in size and approximately 2.5 g in weight. One side of the block was cylindrical, while the other side was spherical. As non-vital bovine bone was used in the study, the ethics committee for animal experiments was consulted. The opinion expressed was that no ethics committee decision was required.

The study was conducted in a laboratory environment with a constant temperature of 28-31°C. The bone segments were stored in a refrigerator at a temperature of 5°C until the study was conducted. The bone segments and stainless steel materials were kept in a saline solution at 28-31°C for 24 hours before the start of the study. In the CryoKB method, 10, 5, 1, and 0.5 minute of cooling were applied.

The temperature changes were recorded using a CEM DT 8869H dual laser infrared (IR) and K-type thermometer (**Figure 1a**) and program called IR Thermometers (**Figure 1b**) version 2.3.1 (Shenzhen Everbest Machinery Industry Co Ltd, Shenzhen, China). The measurement sensitivity of the thermometer was ±0.1% of reading. The temperature measurement was measured with a type K probe by creating a 5-mm-deep and 1.5-mm-wide slot in the bone. In the stainless steel materials, the temperature measurements were recorded from a depth of 5 mm with a K-type probe. Temperature changes were measured every 5 minutes from the baseline (0 minute) to 1 hour.

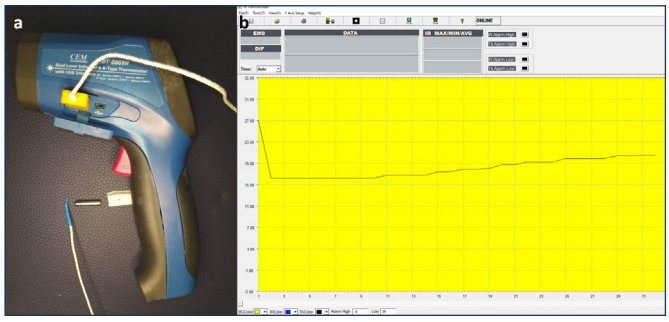

Figure 1a-1b. Temperature changes

The GraphPad Prism version 8 program was used to evaluate the data (GraphPad Software Inc., San Diego, CA). Normality was assessed using the D'Agostina and Pearson omnibus tests. Differences between the groups were assessed using the Kruskal-Wallis test and one-way analysis of variance. When the results were significant, Dunn's multiple comparison test was used to identify which groups were significantly different.

RESULTS

The temperature changes in 52 samples were evaluated. Of these samples, 26 were bovine femur bones and 26 were stainless steel materials. The descriptive statistical information of the temperature changes in the groups is given in **Table 1**. The minimum, maximum, and median temperatures were respectively 2.8°C, 30.9°C, and 29.7°C in the G1 group and –3.4°C, 20.7°C, and 18.9°C in the G2 group.

Table 1. Descriptive statistical information of the temperature changes in the groups

Groups	temperature °C		
	Median	Min; Max	95% CI
G1	29.7	2.8;30.9	25.68 to 29.21
G2	18.9	-3.4;20.7	13.93 to 17.33
K1	30	29.1;30.9	29.86 to 30.16
K2	30	29;30.9	29.84;30.1

While statistically significant differences in temperature change were found between the G1 and G2 groups (X^2=142.9, p<0.0001), no such differences were found between the G1 and K1 groups (X^2=142.9, p=0.0502; **Figure 2**). A statistically significant difference in temperature was found between the G2 and K1 groups (X^2=142.9; p< 0.0001) and, similarly, between the G2 and K2 groups. (X^2=142.9; p< 0.0001; **Table 2**).

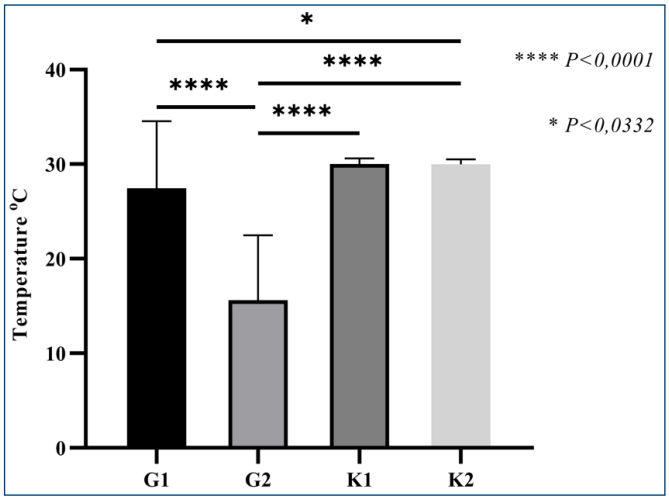

Figure 2. Comparison of temperature change between groups

Table 2. Multiple comparisons between groups

Dunn's multiple comparisons test	Mean rank diff	Mean rank	Kruskal-Wallis statistic	Adjusted P Value
G1 vs. G2	99.27	136.9 vs. 37.62	142.9	<0.0001
G1 vs. K2	-34.76	136.9 vs. 171.6		0.0187
G1 vs. K1	-38.97	136.9 vs. 175.9		0.0502
G2 vs. K2	-133.98	37.62 vs. 171.6		<0.0001
G2 vs. K1	-138.28	37.62 vs. 175.9		<0.0001
K1 vs. K2	-4.208	175.9 vs. 171.6		>0.9999

Diff: differences

From a temperature-time graph, we determined that the temperatures in the K1 and K2 groups were at the level of 29-31°C for a period of 60 minutes. In the G1 group, the temperature was maintained at its lowest level in the first 10 minutes but quickly returned to its initial level. In the G2 group, the temperature decreased to lower than 0°C. The rate of temperature increase was slower in the G2 group than in the G1 group. The temperature was lower than 21°C for the first 45 minutes (**Figure 3**).

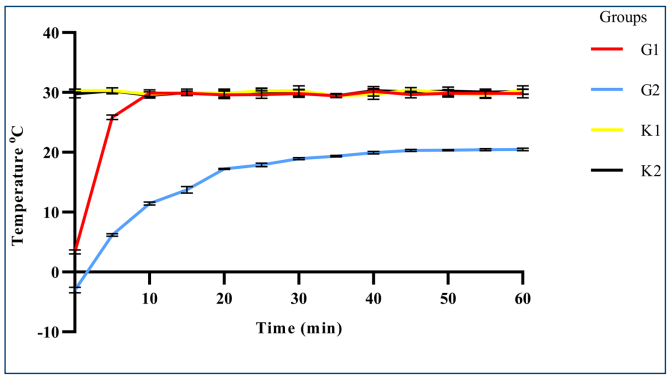

Figure 3. Apperance to temperature-time graph of groups

When the time factor of bone cooling was evaluated, the cooling effect from 10 minutes of cooling was statistically significantly different from that from 5.1 and 0.5 minutes of cooling. In addition, the cooling effect of 5 minutes of cooling was statistically significantly different from that of 1 and 0.5 minutes of cooling. No statistically significant difference in cooling effect was found between 1 and 0.5 minutes of cooling (**Table 3**, **Figure 4**).

Table 3. Evaluation of different cooling times in the cooling of bone.

Dunn's multiple comparisons test	Mean rank diff	Mean rank	Kruskal-Wallis statistic	Adjusted P Value
10 min vs. 5 min	-52.95	69.32 vs.122.3	72.38	0.0004
10 min vs. 1 min	-89.79	69.32 vs. 159.1		<0.0001
10 min vs. 0.5 min	-102.0	69.32 vs. 171.3		<0.0001
5 min vs. 1 min	-36.84	122.3 vs. 159.1		0.0313
5 min vs. 0.5 min	-49.04	122.3 vs. 171.3		0.0012
1 min vs. 0.5 min	-12.20	159.1 vs. 171.3		>0.9999

Diff: differences, min: minutes

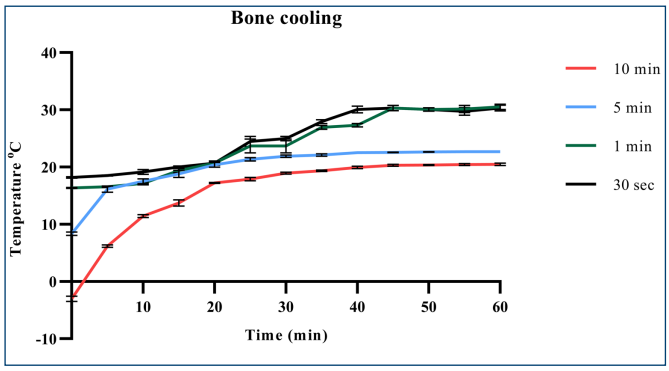

Figure 4. Evaluating time factor of bone cooling

DISCUSSION

Harmful effects may occur when creating the implant socket.[10] Among these harmful effects is thermal necrosis, which is thought to cause early implant loss. Today, irrigation solutions are often used to cool implant drills, but some clinicians do not use them because they impair the visibility of the surgical area.[11] In addition, the desire to use the bone particles that result from the drilling during the operation may also prevent the use of irrigation solutions. In our study, a cooling method without the use of an irrigation solution was designed to ensure both cooling and to overcome the disadvantages of using irrigation solutions. This is the first study to perform cooling using the principle of thermoelectric cooling.

Thermoelectric coolers balance an object's temperature without being affected by the surrounding temperature while lowering the object's temperature below the ambient temperature. Thermoelectric coolers, or Peltier coolers as they are commonly called, are semiconductors that work like a small heat pump.[12,13] They are usually manufactured in the form of semiconductor electrodes placed between two ceramic plates. Owing to the small voltage from a direct current source, heat moves from one end of the module to the other. Thus, while one side of the module heats up, the other begins to cool simultaneously. By adding a liquid tank to the cooling part (**Figure 5a**), cold transfer is ensured using the 4-×6-mm-diameter pipe of the cold and submersible pump (**Figure 5b**). As the thermoelectric cooler introduced herein is smaller than other cooling systems, it can be used in cooling the patient's mouth, except for in vitro studies. Although a deep freezer was used in this study, the intraoral cooling device we designed will be used in future studies.

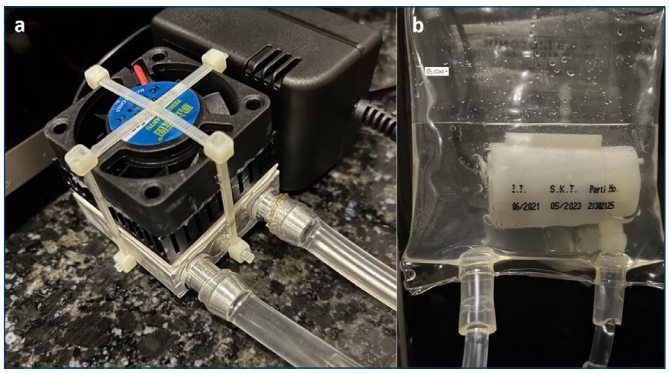

Figure 5a-5b. Cold transfer by adding a liquid tank

Cold therapy has been regularly used to provide analgesia in acute injuries. Its anti-inflammatory effects have also been reported.[14] Another study reported that cold treatment increased antioxidant concentrations. Cold has been shown to reduce inflammatory cytokine levels by increasing adrenaline and noradrenaline levels.[15] In our pilot in vitro study, we found that cooling using the CryoKB method was better than cooling using the traditional irrigation method described in the literature. In the traditional method, cooling the implant drills is preferred, but in our pilot study, cooling the bone provided more effective results than cooling stainless steel materials. This can be explained by the high thermal conductivity coefficient of stainless steel materials (16.2 W/mK) causing the quick transfer of low and high temperatures to the material or air that comes into contact with the blocks.[6,16] However, cortical bone cannot transmit high or low temperatures because of its low thermal conductivity coefficient (0.37-0.47 W/mK).[16]

The heat generated by the friction between the implant drill and the bone is transmitted to the bone in contact with the implant drill because of the high thermal conductivity of the drill. A temperature increase occurs in the bone in proportion to the amount of heat transmitted. Here, the formula used to calculate the temperature increase was – Q=m c ΔT, where Q is the amount of heat transferred and ΔT is the change from the initial temperature (Ti) to the final temperature (Tf). When the amount of heat transferred and the mass of matter are considered constant, the low Ti of the bone causes its Tf to be low.[17] The logic of the CryoKB method is to reduce the temperature of the bone before the operation and to ensure that the temperature increase as a result of the heat transfer is limited.

While 47-55°C for 1 minute is known to be the threshold value of the thermal change in the bone before necrosis develops, a cold temperature of 3.5°C has histological effects.[18] In another study, the effects of hot and cold temperatures on bone were evaluated. Applying 51°C for 10 seconds and 5°C for 30 seconds created significant matrix degeneration. In osteocytes, deaths have been reported from 49°C up to 56°C. Osteocyte deaths at cold temperatures started at 5°C but showed a statistically significant difference in temperature of 1°C.[19]

The cooling time is important for applications in clinical studies. The longer the cooling time, the more and longer the cooling effect is expected to last.[20] In this study, long-term cooling lowered the bone temperature to less than 0°C. However, even after 0.5 minutes of cooling, the temperature remained lower than 20°C for the first 10 minutes. It is thought that 0.5 seconds of cooling will be sufficient for clinical studies.

CONCLUSION

Although our study was conducted at room temperature, the cooling of the bone and application of the CryoKB method did not increase the room temperature during the study period (60 minutes) and maintained the cold temperature. However, when irrigation methods and cooling techniques with stainless steel materials were used, the temperature of the material used returned to room temperature in less than 10 minutes. The advantage of the newly developed CryoKB method is that it is not affected by room temperature, unlike the traditional methods. The small number of samples and the in vitro design of the study can be considered as its limitations. The method of bone cooling without an irrigation solution caused more cooling of the bone than the traditional irrigation method. On the basis of the results of this study, temperature changes in the bone should be detected by applying in vitro drilling procedures.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study has been evaluated by the Animal Experiments Local Ethics Committee Presidency of Kırıkkale University Rectorate within the scope of diagnostic and therapeutic clinical applications, and it has been concluded that there is no need for an Ethics Committee decision (Date: 08.06.2022, Decision No: E-100143).

Informed Consent: Because of designed of the study, no written informed consent form was obtained.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: Kırıkkale University Scientific Research Projects Coordination Unit supported the study (Project No: 2022/068).

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of Dental Sciences and Education

Review

DOI:10.51271/JDSE-0020

An overview to biocompatibility of resin based restorative materials

İbrahim Halil Avcılar, Şeyhmus Bakır, Elif Pınar Bakır

Department of Restorative Dentistry, Faculty of Dentistry, Dicle University, Diyarbakır, Turkey

Cite this article: Avcılar İH, Bakır Ş, **Bakır EP.** An overview to biocompatibility of resin based restorative materials. *J Dent Sci Educ*. 2023;1(4):109-116.

Corresponding Author:İbrahim Halil Avcılar, dtibrahimavclr@gmail.com

Received:20/12/2023 ◆ **Accepted**:29/12/2023 ◆ **Published**:31/12/2023

ABSTRACT

Nowadays, resin based materials find a wide range of use in dentistry due to their aesthetic properties, mechanical durability and cost advantages. Dentistry materials;They can have an effect because they are in direct contact with various tissues such as gums, tongue, lips and cheeks, in addition to periodontium, pulp, dentin and enamel. It is important that resin materials produced with new technologies to be used in restorative dentistry not only have mechanical, physical, functional and aesthetic properties, but also be carefully evaluated in terms of biological compatibility. The purpose of this review is to review the basic concepts and methods related to biocompatibility, to present data from studies on the cytotoxicity of resin-based materials, and finally to make recommendations for clinical applications.

Keywords:Biocompatibility, cytotoxicity, resin based dental materials, residual monomer

1. INTRODUCTION

Today, resin-based materials are widely used in dentistry due to their aesthetic properties, mechanical durability, and cost advantages.[1] Light-curing resin-based restorative materials are becoming widespread by undergoing innovations in every field of dentistry. The materials in this group include resin-based composites, resin cements, resin-modified glass ionomer cements, compomers, ormocers, fissure sealants, and dentin bonding agents. The goal of dental treatment is to achieve effective, yet safe, and long-lasting results for the benefit of patients. In order to achieve the desired physical and biological properties of resin-based restorative materials, it is critical to ensure effective polymerization.[2]

Dental materials can produce effects because they are in direct contact with various tissues, such as the gingiva, tongue, lips, and cheeks, in addition to periodontium, pulp, dentin, and enamel. Such contact can lead to allergic, toxic, mutagenic, carcinogenic, or inflammatory reactions. It is important that resin materials produced with new technologies to be used in restorative dentistry not only have mechanical, physical, functional, and aesthetic properties but also be carefully evaluated in terms of biological compatibility.[3]

The biocompatibility criteria of materials used in dentistry are as follows:

- Should not be harmful to pulp and soft tissues.
- They should not contain toxic substances that cause a systemic response by being released into the circulatory system and absorbed by diffusion.
- It must not contain potentially allergenic agents that may cause an allergic response.
- It should not have carcinogenic potential.[4]

Therefore, it is necessary to evaluate the potential harmful effects of these materials on oral tissues before they enter widespread clinical use.[5] Assessing the biocompatibility of materials is a step to ensure the safety of patients and the healthcare team, and this process involves various biological and physical property tests and risk-benefit analysis. It is of great importance that the analyses clarify any interaction of components released from materials with living tissues.[6]

Biocompatibility is a dynamic process that can change depending on time and conditions. In parallel with the changes that occur in the body over time, such as disease or aging, corrosion, load, occlusion, fatigue, or nutritional changes can be observed in materials. Therefore, it should be kept in mind that the initial biological response may change over time.[7]

Tests to assess the biocompatibility of materials, which in the past were usually performed on humans, now require a new material to be evaluated through extensive testing prior to human use. To determine whether a new material is biologically acceptable, a variety of standardized test methods have been applied. The biological properties of materials are usually started to be examined with simple in vitro testing methods using cell cultures. Animal experiments that are more expensive and time-consuming can come after these investigations. Following the

successful results of these tests, more extensive studies, such as utilization tests, should be performed.[8]

2. BIOCOMPATIBILITY OF RESIN-CONTAINING RESTORATIVE MATERIALS

It has been reported that resin-based materials may cause allergic reactions, apoptotic reactions, local immunologic effects, systemic estrogenic and carcinogenic effects, postoperative sensitivity, and long-term pulpal inflammation.[9]

In light-polymerized composite resins, the polymerization rate varies between 40% and 70%, and approximately 10% of the monomers do not participate in double bond formation and are released from the restoration as residual monomers. To overcome the negative effects of residual resin monomers released from resin materials, a number of studies have been conducted focusing on the biocompatibility of these materials. In addition to these monomers, initiators and fillers also have an impact on the biocompatibility of resin materials. The degree of conversion after polymerization, the release of free monomers, and the degradation of the resin matrix causes various degrees of cytotoxicity.[10]

Most of the composite resins available on the market used in treatments are not antibacterial because they contain inert inorganic fillers and organic monomers. Studies have reported that residual monomers released from composite resins may promote the growth and proliferation of microorganisms with the potential to cause caries.[11]

Studies have reported that chemically and light-cured resin materials generally cause moderate cytotoxic reactions in vitro at 24-72 hours of contact, while cytotoxicity decreases significantly after 24-48 hours, especially in the presence of the dentin barrier. It is known that light-cured resins are less cytotoxic than chemically cured resins, but this effect is largely dependent on the light source used and the type of resin system. Three days after putting chemical or light-curing resin in cavities with 0.5 mm of dentin, usage tests show that there is low to moderate pulpal inflammation. On the other hand, there is almost no pulpal reaction when a sealer or bonding agent is used.[12]

During the polymerization process of resin-containing fissure sealants, residual monomers such as Bis-DMA and Bis-GMA may be released into saliva. Although a disadvantage due to the estrogenicity of BPA and DMA in fissure sealants has been mentioned, it has also been reported that this effect is negligible.[13]

Many studies show that a significant number of organic compounds remain as unbound residual monomers in the polymerized material. Increasing the size and number of fillers in the material content also leads to a decrease in the amount of residual monomer released. It has also been reported that these monomers cause inflammation in the tissue and inhibit dentin mineralization when applied in direct contact with pulp tissue. Hydrophobic monomers (Bis-GMA, UDMA) in adhesive systems show more cytotoxic effects than hydrophilic monomers (HEMA, TEGDMA). Hydrophilic monomers can move in dentinal fluids and carry hydrophobic monomers in dentinal tubules, causing cytotoxic effects in the pulp. The toxic effect of hydrophilic and hydrophobic groups together is more than the toxic effect they produce alone.[14-16]

Composite resins exhibit cytotoxic properties before and immediately after polymerization. However, their cytotoxicity decreases significantly after polymerization. After curing, oxygen-inhibition areas on composite resin surfaces contain unpolymerized monomers. If this surface is not removed after polymerization, the composite may show higher cytotoxicity.[17]

It has been reported that especially unpolymerized monomers that separate from the resin material can affect the course of the pulpal reaction. Therefore, it is recommended to use total-etch adhesive systems in superficial cavities and self-etch adhesive systems in young, deep, and permeable cavities for a successful post-op restoration. Self-etch adhesives are better for biocompatibility because their acid content doesn't completely destroy the smear plugs that stop unpolymerized monomers from getting into the pulp. This means that they can be used more often. Results showing that resin-based materials cause systemic toxicity have not yet been obtained.[9]

The monomer-rich oxygen inhibition layer formed on the surface leads to decreased durability and long-term discoloration of the restoration surface. In order to prevent the formation of the oxygen inhibition layer, methods such as performing the polymerization in an argon-rich environment, isolating the restoration surface by applying glycerin, or preventing its contact with oxygen by applying transparent tape should be applied. The use of finishing and polishing agents is critical to removing residual monomers, preventing plaque accumulation, and extending the clinical life of the restoration.[18]

In the long term, monomers can be released into the oral environment as a result of the degradation of the material. The degradation of the polymer structure is caused by saliva components, chewing forces, temperature changes, and microorganisms.[19]

3. BIOCOMPATIBILITY EVALUATIONS

3.1. Biocompatibility and Cytotoxicity

Biocompatibility is defined as the ability of a material to trigger appropriate biological responses at the tissue level without causing systemic and local toxicity, allergic reactions, mutagenic effects, or carcinogenic effects. A material does not necessarily have to be completely inert to be considered biocompatible, but that corresponds to the definition of a tolerable biomaterial. Biocompatibility is more than a static concept;it is a continuous state. There is a constant state of interaction between the complex biological system and the material;both the material can affect the biological environment and the biological system can affect the material.

A material that is biocompatible at first may become incompatible with changes in environmental conditions over time.[20] This is because as the body changes due to factors such as disease or aging, the material may deteriorate due to corrosion or fatigue, or the force interactions on the material may change due to factors such as occlusion or nutritional changes.[21]

Apart from the term biocompatible, biomaterials used in dentistry can also be referred to as biotolerant, bioinert, and bioactive. Biotolerant materials represent materials that are separated from bone tissue by a layer of fibrous tissue;polymethyl methacrylate, stainless steel, and cobalt alloys are examples in this category. Bioinert materials are materials that have the ability to form chemical bonds with bone tissue;materials such as titanium, zirconium, aluminum

oxide (alumina), and carbon are examples of this class. Bioactive materials are materials that are in direct contact with bone and tissue without chemical reactions;examples of this group include calcium phosphate, hydroxyapatite, calcium carbonate, and glass ceramics.[22]

Biocompatibility refers to the safety of a material, while toxicity refers to the material's ability to cause potential damage to biological systems by chemical means. The term cytotoxicity describes cellular damage, while apoptosis refers to programmed cell death. If a material causes changes in the DNA structure, it is called genotoxic;if these changes are passed on to the next generation, the material is described as mutagenic. This can lead to permanent changes in the genetic material and potentially cause genetic disorders or diseases.[23]

Before every new dental material is introduced to the market, it should be investigated for biological risks, and its biocompatibility should be evaluated by various methods before clinical use. The main principle of biocompatibility testing is to determine in advance the type and number of potential reactions between a material and a biological system and the type and amount of structural and functional changes in the living organism. Testing programs include a hierarchical order in which various procedures are applied in a hierarchical sequence. Recently, a procedure has been adopted by a number of standardization bodies and certain international organizations that includes in vitro (primary) tests, animal experiments (secondary tests), and clinical studies in humans (use tests).[3]

3.2. In Vitro (Primary) Tests

Initial experimental tests were applied to determine the cytotoxic properties of materials. In in vitro tests, the biological reactions that occur as a result of contact with the tested materials placed on or in various cells or tissues outside the living organism are examined in the laboratory environment. In-vitro tests have many advantages over other tests;they are relatively less costly, simple to perform, experimentally manageable, reproducible, and standardized compared to other types of tests. In addition, they do not pose ethical and legal problems, such as the use of animals and humans for testing. One of the disadvantages is that they do not accurately reflect the in vivo situation. Materials that show success in these tests move to the next stage to be evaluated by animal experiments and clinical use test methods.[3,24]

In-vitro biocompatibility tests are performed in special test tubes outside a living organism using a wide range of cultures of cells and cell components. These biological systems consist of mammalian cells, cell organelles, tissues, bacteria, or specific enzymes. However, it is important to note that when materials are found to pose a risk in terms of biocompatibility under in vitro conditions, this does not necessarily mean that the same materials will show toxic effects under in vivo conditions.[25]

Cell culture tests, agar diffusion tests, filter diffusion tests, and dentin barrier tests are among the commonly used test methods for in vitro cytotoxicity evaluation of dental materials.

3.2.1. Cell culture test method: The working principle of this test method is based on the production and survival of tissue fragments mechanically separated from living tissues in appropriate nutrient solutions (animal embryonic extracts, serum and plasma amino acids and minerals, sugar salts, vitamins, and antibiotics) by providing in vitro conditions and the determination of potential cytotoxicity using a dose-response curve following the placement of the material into these cells.[26]

In cell culture studies, three different types of cell cultures are used:primary cell cultures, diploid cell cultures, and continuous cell cultures. Primary cell cultures are cultures that are taken from living tissues and cultured for more than 24 hours without in vitro cell proliferation. Pulp and gingival fibroblasts (GF) are a typical example of primary cell cultures. After the first passage of primary cell cultures, the transfer from one culture medium to another is called subculture. Diploid cell cultures are obtained from subculturing primary cultures. Compared to primary cell cultures, diploid cell cultures are more homogeneous, standardizable, and reproducible, and they have the advantage that they continue to reflect at least 75% of the karyotype of the tissue from which they are derived. Continuous cells (MDPC-23 mouse odontoblast cells, WI-38 human embryonic lung cells, L-929 mouse fibroblast cells, BALB/3T3 mouse embryo fibroblasts, HeLa human epithelial cells, ECV-304 human endothelial cells) are examples of transformed primary cells and have the ability to proliferate indefinitely. In the establishment of cell cultures, 95% humidity, 37 ˚C temperature and 5% CO2 are generally preferred and some antioxidative substances and antibiotics are added to the culture. Although the results obtained provide information about the potential cytotoxicity of the material, it is important that the available data should not be directly related to clinical conditions. Because immunologic and biologic reactions in the living organism may affect cytotoxicity.[3,8,27]

Direct contact testing is the application of materials or components directly onto cells in culture for short periods of time (> 24 hours). In a direct contact test, the material is in physical contact with the culture medium or cells. Since water-soluble materials will dissolve well in the culture medium, very good contact between the material and the cells is ensured. In the extract contact test method, after the material is kept in a liquid solvent, the soluble components of the material are brought into contact with the cells and their cytotoxicity is examined. This suspension of the components dissolved from the material with the liquid is called "extraction liquid". Serum-free medium, serum-containing medium, physiological salt solution or other suitable solvents can be used as solvent.[28]

Traditional cell culture studies are based on the establishment of monolayer, two-dimensional (2D) cultures by placing cells on various planar surfaces to provide mechanical support or suspending them in a thin layer of liquid media. 2D cell cultures are easily applicable for cell-based screening studies and have proven to be a convenient and effective tool for discovering drug candidate molecules. However, the 2D surface does not reflect the in vivo cell properties more accurately, as the cells do not lay flat and form a multilayered structure. With the creation of 3D in vitro cell-based systems with multilayered cell clusters, cell tests that are more like living tissues are giving more accurate results and can better mimic the specificity of in vivo tissues.[29]

3.2.2. Agar diffusion test method: This method, which is one of the common barrier tests used in cytotoxicity evaluations, is easy and inexpensive to apply. When assessing cellular activity, trypan blue, which can stain dead cells, or

neutral red dye, which accumulates in the lysosomal matrix of living cells and is released when the membrane is damaged, is used. The response of the material in the cell is examined by evaluating the decolorization and lysis of the cells. If the test material or its components cannot dissolve or diffuse in agar, these materials cannot be evaluated because they cannot show any effect on the cells.[30,31]

3.2.3. Filter diffusion test method: Since many materials frequently used for restorative treatment do not come into direct contact with the cells, it is thought that it would be more appropriate to add a filter between the material and the cell culture in order to obtain a more objective result. In the filter diffusion test, which is one of the indirect contact tests, cellulose acetate with a pore size of 0.45 µm is used as a barrier agent. In order to evaluate the cytotoxicity of the material, primary cells (fibroblasts and epithelial cells) are placed on one surface, and the material to be evaluated is placed on the other surface in the filter diffusion test. The components released from the test material must diffuse through the pores on the filter. Evaluation is performed by measuring the decolorized area formed in the cultured cells or by examining the dye intensity.[8,32]

3.2.4. Dentin barrier test method: Dentin barrier tests are a complementary method to cytotoxicity tests. Dentin tissue functions as a barrier to protect the pulp against dental materials applied to the tooth. In this method, which was developed to mimic this property of dentin structure, the diffusibility of the tested material is measured. In this test method, which mimics in vivo conditions more than other tests, human dentin tissue or dentin samples obtained from bovine teeth are used as a barrier between the components released from dental materials and the target cell. Although the use of human dentin seems to be more appropriate in terms of mimicking in vivo conditions, the use of bovine dentin is more advantageous because it differs less in permeability compared to human dentin and can be obtained in desired amounts.[3,25,33]

3.3. Cytotoxicity Assessment Methods

In order to evaluate the cytotoxic effect of dental materials or components released from the material, some biological markers such as cell viability and death, cell membrane permeability, cell organelles, protein, DNA, RNA synthesis, and cell division are examined.

MTT and neutral red are widely used to evaluate the cytotoxicity of materials. XTT, Acid Phosphatase, Resazurin, LDH, Kenacid Blue, and Sulforhodamine B are known as other cytotoxicity stains.

Four different test methods are used for the evaluation of cytotoxicity.

3.3.1. Tests to assess vitality: These tests allow colorimetric or fluorescent measurements and are used to determine the proportion of viable cells in culture. These methods are limited to measuring membrane permeability and cannot measure sublethal cell changes. Diacetyl fluorescent or neutral red dye taken into cells with intact membrane integrity or dyes such as trypan blue, erythrosine, or naphthalene black that enter the cell structure with disrupted membrane integrity are used and examined spectrophotometrically.[34]

3.3.2. Tests to assess life: These are very fast and easy-to-apply methods in which only dead cells are evaluated, which can be seen in the first few days or after the cells are exposed to toxic effects. However, the toxic effects to which cells are exposed may be reversible or may be seen in the long term. Therefore, long-term tests are more useful in determining the viability rate.[3]

3.3.3. Tests to assess cell proliferation: This method includes 3H-thymidine and bromodeoxyuridine immunohistochemical techniques, which are applied when there are few samples. To assess cell proliferation of material components, a growth curve obtained by counting cells in culture after a few days is used.[28]

3.3.4. Tests to assess cell metabolism: Some of the ways to check how metabolically active cells are the colorimetric MTT, XTT, LDH, MTS, WST-1, and alamar blue tests. These give quick results and are used to see what kind of long-term damage will be done.

The MTT test is the most widely used test method among biocompatibility evaluation methods because it can give fast and sensitive results, and even materials with very low toxicity can be evaluated. It makes it possible to examine the cytotoxicity of a large number of samples with fewer experimental steps. The colorimetric MTT test measures how active the dehydrogenase enzyme is by looking at how it changes yellow MTT into purple formazan crystals that can't be dissolved in water. A succinate dehydrogenase enzyme is found in the mitochondria of living cells in culture medium. It breaks down yellow tetrazolium salts into purple formazan crystals that can't be dissolved. If the dehydrogenase enzyme activity of the cell is affected due to the cytotoxic effect of the material, formazan crystals are not formed.[35]

3.4. Animal Experiments (Secondary)

The material to be tested is placed in some experimental animals (mice, rats, sheep, cats, dogs, and pigs) in order to examine the interactions that may occur between the material and the biological environment. In these experiments, it is important to control various variables such as the species, age, and sex of the animals, the way the animal is exposed to the material, the duration of contact, and the method by which the biological response will be evaluated. Some of the methods used in secondary tests are intraoral and intra-abdominal tests, inhalation tests, dominant lethal tests, irritation and sensitization tests, and intramuscular and intra-bone or subcutaneous implantation tests. Since a complex organism is used in this test method, the biological response of tissues is more meaningful than in vitro tests. However, the control of variables in in vivo testing is more difficult, and the complex ways in which the biological response occurs make it difficult to quantitatively evaluate the results obtained. Ethical debates and the growing importance of issues such as animal rights are gradually reducing the use of these tests. Another disadvantage of these tests is that they are time-consuming and expensive. There are also doubts about the similarity of the response in animals to the response in humans.[36,37]

3.5. Clinical Studies (Usage Tests)

Tests have the potential to reflect the clinical picture. This method, which is based on observing the response of a material that has been determined to be safe as a result of laboratory and animal experiments by using it on volunteer humans, provides more realistic results in terms of biocompatibility. This test method defines the situation that

may occur when the material is used in the clinic. Usage tests can be performed on animals or humans. When these tests are performed on humans, they are called "clinical trials." Tests of use can only be carried out after the material is ready for clinical use. The material can only be implanted in a human volunteer after all pre-clinical tests have been performed. These tests, which give very close information about the clinical use of the materials, have some disadvantages. These disadvantages include the complexity and expense of the tests, difficulties in controlling the experiment and evaluating the data obtained, and the need for long periods of time, such as months or years, when long-term effects are to be investigated. Many legal responsibilities that are not required in in vitro experiments and animal experiments arise in human experiments. These responsibilities include the approval of official institutions and informed consent from the patient. In dentistry, these tests, called pulp irritation tests, are performed by applying the material to be tested to the cavities opened in intact, caries-free teeth of humans or other suitable animals to be extracted for orthodontic reasons. The material to be tested is left on the teeth for a while, then the teeth are extracted and prepared for histologic examination. In histologic examination, acute or chronic inflammation and odontoblastic reactions in the pulp are examined. Periapical tissue damage that may occur due to the use of endodontic materials, which are widely used in dentistry, is tested in experimental animals. After the material to be tested is placed in the root canals of the teeth, a histologic examination is performed. Tests such as patch tests, prick tests, and radioallergosorbent tests are applied to determine the allergic potential of dental materials on humans. Allergic properties of materials in experimental animals can also be examined by skin sensitization tests before the material is used clinically.[24,31,38]

4. CYTOTOXICITY STUDIES ON RESIN-CONTAINING MATERIALS

In their experimental studies on rats, Bakır et al.[39] compared the local and systemic effects of existing pulp coating materials containing resin with traditional materials. Despite their high physical properties, low solubility, and ease of use, they reported that pulp coating materials polymerized with a light source may cause cytotoxic effects due to their resin monomer content.

Manaspon C et al.[40] examined the effects of different pulp coating materials on pulp stem cells and found that DyCal® and TheraCalTM LC were toxic to cells. Cell attachment, spreading, proliferation, and migration were compromised when cells were exposed to DyCal® or TheraCalTM LC. In contrast, ProRoot® MTA and BiodentineTM exhibited positive behavior in terms of biocompatibility and were reported to support cell activities towards regeneration potential.

The study by Kraus et al.[41] looked at how biocompatible dental resin monomers were in a lab setting. They found that BisGMA was the most toxic, followed by UDMA, TEGDMA, and finally HEMA.

Gonçalves et al.[42] examined the effects of different brands of conventional and bulk-fill composites on human fibroblasts and found that the best results were obtained in the bulk-fill composite with the highest filler content and the lowest monomer content, and polymerization of 4 mm thickness in bulk-fill composites did not cause adverse effects.

Bandarra et al.[43] evaluated the biocompatibility of glass ionomer cements, resin-modified glass ionomer cements, and resin cements by the MTT cytotoxicity evaluation method using 3T3 mouse fibroblasts and found that cell viability in the presence of glass ionomer cement was higher than that of resin-modified glass ionomer cement and resin cements.

In this research, Moussa et al.[44] found that adding an antibacterial monomer and cross-linker to a resin adhesive could make adhesive restorations last longer. However, these changes did not affect the cytotoxicity of the adhesive.

Brzovic Rajic et al.[45] evaluated the cytotoxicity and genotoxicity of six different dental nanocomposite materials, three conventional and three flowable composite resin materials, in human lymphocytes and concluded that while polymerized conventional composites showed no cytotoxic or genotoxic effects important for the clinical application of these materials, unpolymerized forms exhibited some level of cytotoxicity and genotoxicity, mainly due to the monomers in their composition.

When Gociu et al.[46] examined the biocompatibility of composite resins, they reported that Bis-GMA and TEGDMA' in the organic structure caused a decrease in cell viability by increasing reactive oxygen products.

Attik et al.[47] studied the effects of different resin materials on gingival fibroblasts and found that there was a link between the ratio of resin monomers and cytotoxicity, and that the amount of resin monomers was just as important as the ratio. They reported that TEGDMA significantly decreased vitality and was more effective on cytotoxicity compared to Bis-GMA.

In Taghizadehghalehjoughi et al.[48]'s study, in which they examined the cytotoxic effects of composite materials on gingival fibroblast cells, they concluded that factors such as the structure of the material, the filler ratio, monomer type, and filler content are effective as a whole in the cytotoxicity of a material;the presence of TEGDMA and EGDMA monomers are monomers that increase the potential toxicity of the material;and particles added to the filler content (Fluro aluminosilicate particles, iterum trifluoride particles, etc.) may affect cytotoxicity.

Bapat et al.[49] compared the cytotoxicity of conventional, resin-modified, and ceramic-modified glass ionomer cements on osteoblast cell culture and mouse fibroblasts and found that conventional glass ionomer cement showed a less cytotoxic effect.

Asdada et al.[50] evaluated the cytotoxicity and antidifferentiation effects of bulk fill composites against human dental pulp stem cells (hDPSCs) in three compartments corresponding to the depth (0-2, 2-4 and 4-6 mm) from the light source region and found that the cytotoxic effect increased with increasing depth. In order to protect the ability of dental pulp stem cells to survive and differentiate, they said that care should be taken when choosing bulk-fill resins, especially when fixing deep cavities.

Pagano et al.[51] tested how harmful different universal adhesives were to human fibroblast cells. They found that the extract method gave more accurate results and that the adhesives tested had different effects, with Optibond Solo Plus being the least harmful. FuturaBond M Plus had the most toxic effect.

Çelik et al.[52] (2019) examined the biocompatibility of composite resin, amalgam, compomer, and glass ionomer cement materials with a neutral rejection test. In the study, test specimens aged in artificial saliva for 7 days and 21 days immediately after the preparation of restorative materials were used, and finishing and polishing processes were applied to the specimens. All groups exhibited statistically significantly lower cell viability than the control group. However, the cell viability of the Dyraxt XP composite sample aged for 21 days was reported to be above 70%. It was also found that glass ionomer cement and composite resin reduced cell viability more than compomer and amalgam.

Srivastava et al.[53] evaluated the cytotoxicity of nanocomposites, flowable composites, and composite materials on human lymphocyte cells. They found that all three materials showed cytotoxic effects, and flowable composites had a higher cytotoxic effect than composites and nanocomposites. They argued that the cytotoxic effect observed was due to HEMA and TEGDMA released from the structure of the materials.

Aydin et al.[54] in animal experimental studies in which they evaluated the biocompatibility of frequently used single clinical self-etch adhesive systems histopathologically, they observed that the reinforcement formed against the material from living cells decreased over time and increased fibrocollagen development. They argued that the decrease in initial inflammatory rates against all materials may be due to the release of residual monomer and surgical trauma.

Süsgün Yıldırım et al.[55] in their experimental study in which they qualitatively and quantitatively evaluated the cytotoxic potential of five different single-stage self-etch adhesives, in the first stage, they qualitatively evaluated the cytotoxic activities of the materials in monkey kidney epithelial cell culture medium by direct contact method. As a second stage, they quantitatively evaluated the cytotoxic potential of four different dilutions of the test materials (1%, 0.1%, 0.01%, 0.001%) on L929 mouse fibroblast cells in three different time periods (24 hours, 48 hours, 72 hours). They reported that all adhesives tested showed varying degrees of cytotoxicity, which increased statistically significantly with dose.

Güngör et al.[56] in their in vitro studies, they evaluated the effect of bioactive pulp capping materials on human dental pulp stem cells (hDPSC) in terms of cell viability and bioactivity through mineralization potential. In their study, primary hDPSCs were cultured with experimental nBG, Biodentine, TheraCal LC, and ProRoot mineral trioxide aggregate (MTA) extracts. Cell viability was measured for 1, 3, and 7 days by water-soluble tetrazolium salts (WST-1) assay. Alizarin red staining was used to detect the formation of mineralized nodules, and alkaline phosphatase (ALP) activity was measured by a photometric method. As a result, the cell viability of hDPSCs decreased in all groups except nBG, and the lowest cell viability was determined in TheraCal LC in all incubation periods. They reported that nBG and MTA showed significantly higher ALP activity than the control group.

5. APPROACHES TO IMPROVE BIOCOMPATIBILITY

Strengthening the covalent bonds with the resin to prevent monomer leakage may make cytotoxicity avoidable. Zwitterionic polymer contains both cationic and anionic functional groups and is neutral. In zwitterionic polymers, a new generation material, the near-perfect biocompatibility of biocides and the antimicrobial, bactericidal, and anticariogenic effects of cationic quaternary ammonium compounds seem promising in combined use.[57]

Beyond methodological differences, the cytotoxic effects of resin-based dental materials are due to the residual monomers released. Using low-intensity light, inadequate illumination time, moisture contamination, improper handling of the material, excessive distance between light and material, and neglecting the manufacturer's instructions may increase cytotoxic effects. Therefore, all necessary precautions should be taken in clinical applications to prevent monomer release and degradation.[58]

The biocompatibility of materials is important for studies that test the properties of new biomaterials. To do this, stem cells from pulp tissue are used. This tissue has different cell populations and is very important for dentin regeneration. Propolis-containing pulp coating material has been shown to be a good alternative to calcium-phosphate-containing products due to its positive effect on increasing the antioxidant defense capacity of stem cells.[59]

Fortilin is a multifunctional protein involved in various cellular processes. Its potential as a bioactive molecule that can be incorporated into dental materials is promising. Bio-GIC (GIC supplemented with chitosan, tricalcium phosphate, and recombinant fortilin from Fenneropenaeus merguiensis) shows improved calcium deposition comparable to Biodentine. It has been stated that Bio-GIC can be further developed as a bioactive material for dentin regeneration.[60]

CONCLUSION

The application of different materials containing low- or non-toxic agents for long-term oral use in dentistry is gaining importance for both patients and staff. New materials are being added every day thanks to advances in molecular biology and tissue engineering. Before new materials are put on the market and used in patient treatments, they must be evaluated for biological compatibility, because compatibility with living tissues is a determining factor in the clinical success of the material. Following the rules established by various national and international standardization organizations is essential for these studies. Only materials that give positive results in all stages of biocompatibility testing can be accepted to be placed on the market for use by patients. When the studies conducted in recent years on this subject are examined, it is important to investigate the biological properties due to the diversification and development of the materials offered for use.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of Dental Sciences and Education

Review

DOI: 10.51271/JDSE-0021

The importance of treating dental caries in the prevention of medication related osteonecrosis of the jaw

Department of Restorative Dentistry, Faculty of Dentistry, Dicle University, Diyarbakır, Turkey

Mehmet Salık, Elif Pınar Bakır

Cite this article: Salık M, Bakır EP. The importance of treating dental caries in the prevention of medication related osteonecrosis of the Jaw. *J Dent Sci Educ.* 2023;1(4):117-122.

Corresponding Author: Mehmet Salık, mhmetsalik@gmail.com

Received: 20/12/2023 ◆ **Accepted**: 29/12/2023 ◆ **Published**: 31/12/2023

ABSTRACT

Antiresorptive agents such as bisphosphonates, denosumab and zoledronic acid may induce medication-related osteonecrosis of the jaw (MRONJ). MRONJ is a rare but serious side effect caused by medications such as bisphosphonate and denosumab, which are used as antiresorptive medications in malignancies related to bone metastases and bone metabolism diseases. Since the major predisposing factor of this side effect may be tooth extraction, our aim in this review is to show that preventing the emergence of pathology in dental hard tissues and treating it when it occurs with a preventive and therapeutic strategy, providing adequate oral hygiene, and motivating the patient for its continuity could reduce the risk of the occurrence of MRONJ by reducing the need for oral surgery in terms of restorative dental treatment.

Keywords: MRONJ, bisphosphonates, dental caries treatment, tooth extraction

INTRODUCTION

Antiresorptive agents such as bisphosphonates, denosumab and zoledronic acid may induce medication-related osteonecrosis of the jaw (MRONJ). MRONJ can occur as a side effect of high doses of agents that modify bone metabolism, such as zoledronic acid and denosumab, in patients with multiple myeloma and in cancer patients with bone metastases. Although MRONJ can occur in both jaw bones (4.5%) in the maxillofacial region, it has been observed that it is a pathological process that can be seen in the mandible (75%) rather than the maxilla (25%).[1-3] It has been reported that MRONJ, which is rarely seen, is characterized by progressive bone destruction, usually with exposed necrotic bone in the oral cavity or skin, accompanied by swelling, pain, and a fistula lasting for 8 weeks or longer.[4] Studies have suggested that invasive procedures such as tooth extraction may be a major risk factor for the onset of MRONJ, and it has been suggested that tooth extraction should be avoided in the patient group using drugs that cause MRONJ.[5-7]

In studies conducted among patients with MRONJ, it was reported that tooth extraction played a role as a predisposing factor in the occurrence of osteonecrosis, with rates ranging from 62% to 82%.[2,3,8] Although the reasons for tooth extraction include dental caries, periodontal problems, endodontic reasons, eruption failures, and part of prosthetic planning, the main reason is dental caries.[9-16] Our aim in this review is to show that preventing the occurrence of dental pathology and treating it when it occurs by using preventive and therapeutic strategies in terms of restorative and dental treatment, providing adequate oral hygiene, and motivating the patient to maintain oral hygiene can reduce the risk of MRONJ by reducing the need for oral surgery.

HISTORY

Osteonecrosis developing in the jaws due to bisphosphonates was first described by Marx and Stern in 2002 as a condition in which "bone is exposed, which does not heal with debridement and worsens and expands in area," which is the classical approach to surgery.[19] And this condition was reported to those concerned in 2003 in the "Journal of Oral and Maxillofacial Surgery" with a medical alert in which 36 cases of Pamidronate or Zoledronate-related cases were described.[20] Later, a similar condition was reported by Ruggiero et al.[21] in 2004, and by 2009, this pathologic event was reported as bisphosphonate-related osteonecrosis of the jaw bones (BRONJ) by the American Society for Maxillofacial Surgery.In 2014, upon the realization that not only bisphosphonates but also antiresorptive and antiangiogenic drugs can cause osteonecrosis, the new nomenclature was updated as drug-associated osteonecrosis

of the jaw bones (MRONJ), according to the current status report published by the American Association for Maxillofacial and Facial Surgery.[1] MRONJ is the terminology we have used throughout this review.

MEDICINES CAUSING MRONJ

The first group of drugs associated with MRONJ were the bisphosphonates pamidronate (Aredia®) and zoledronic acid (Zometa®). By blocking osteoclasts, these drugs were used to treat people whose cancer had spread to their bones. Later, new cases of MRONJ were reported after the discovery of denosumab (XGeva®), a humanized monoclonal antibody that works in a similar way on osteoclasts. Denosumab blocks RANK-RANKL binding and inhibits osteoclast function by inhibiting osteoclast inhibition. Administered subcutaneously every 6 months, it has been reported to provide a significant reduction in the risk of vertebral and hip fractures in osteoporosis patients.[22] It has also been reported that denosumab reduces bone metastases and the metastatic spread of solid tumors when administered monthly.[23-25] Romosozumab, another monoclonal antibody used subcutaneously, prevents fractures by increasing bone formation and decreasing resorption in osteoporotic women.[26]

Other drug groups, including antiangiogenic drugs, targeted therapy, and biological immunomodulators, have also been associated with MRONJ. It has been suggested that cancer patients treated with bisphosphonates and antiangiogenic drugs in combination may have an increased risk of MRONJ.[27]

Mechanism of Action of Medicines That Cause MRONJ

Drugs causing MRONJ to accumulate in the bone matrix depending on the repeated dose amount, duration, and route of administration. Since bisphosphonates are resistant to hydrolytic degradation, their half-life in the bone matrix is longer than 11 years.[28] They are stored in the bone matrix by binding to hydroxyapatites and then released and absorbed by osteoclasts.[29] This group of drugs has a toxic effect on osteoclasts, suppressing their functions and reducing their population by causing apoptosis.[30] As a result, there is a decrease in bone formation and destruction.[31] This is a human monoclonal antibody called denosumab. It works against the receptor activator of the Nuclear Factor Kappa B ligand. It inhibits RANK-RANKL binding and prevents its function by providing osteoclast inhibition.[26]

Why are MRONJ-Related Medicines Used?

Bone metastases may cause several of skeletal-related problems, including clinically defined pathologic fractures, spinal cord compression, hypercalcemia, and pain severe enough to require radiotherapy or surgery.[32] Bisphosphonates are antiresorptive drugs and are used to stabilize osteolysis, which allows the metastatic spread of malignancies associated with bone metastases such as breast cancer, prostate cancer, lung cancer, and multiple myeloma, and to reduce hypercalcemia associated with malignancies.[2]

Multiple myeloma is a pathology of plasma cells and is a rare but serious disease that leads to the uncontrolled production of these cells and their destruction by spreading to the surrounding bone tissue. It accounts for about 1% of all tumors and typically occurs in older people. These tumors can cause bones to become weaker and more susceptible to fracture. Patients affected by multiple myeloma have been found to have a higher risk of developing MRONJ due to the bisphosphonate used for treatment compared to patients treated with bisphosphonates for other diseases (for example, patients with bone metastases from advanced breast or prostate cancer).[33]

Metastatic Breast Cancer; Bone is the most common site of metastasis in patients with breast cancer. Approximately 65-75% of advanced-stage patients may develop bone metastasis. Bone-modifying bisphosphonates play an important role in the treatment of women with early and advanced metastatic breast cancer. When bisphosphonates are added to standard treatment for women with metastatic breast cancer, the risk of problems with their bones goes down by 15%. There are also delays in the start of these problems and less pain.[32] Prostate cancer, this type of cancer also metastasizes, especially to bone, with 90% of patients in the metastatic stage having bone metastases.[34] In addition, the MRONJ-related drug group is also used in the treatment of osteoporosis, osteopenia, the prevention of osteoporosis-related fractures, Paget's disease, and osteogenesis imperfecta.[35-37]

MRONJ DIAGNOSTIC CRITERIA

MRONJ is a side effect of antiresorptive drugs characterized by an exposed necrotic jawbone in the jaws in patients who have used or are using one or more of the drugs associated with the complications. The diagnosis of MRONJ is based on clinical findings rather than histopathology and radiographic data. Clinical findings and anamnesis are the most important tools for differential diagnosis. The following three criteria should be considered when diagnosing MRONJ:[38]

1. There is no history of radiotherapy to the jaws and no history of metastatic disease in the jaws.
2. The person has been or is currently being treated with bone-modifying drugs (such as bisphosphonates, denosumab, or antiangiogenics).
3. Exposed necrotic bone detected intraoral or extraoral in the maxilla or mandible for more than 8 weeks.

WHY DOES MRONJ OCCUR IN THE JAWS?

Many possible factors, such as trauma, surgical extraction, inadequate wound healing, changes in oral bacterial biofilm profile, and impaired immune response specific to the oral cavity, have been considered possible reasons for the occurrence of MRONJ, mostly in the jaws.[39] However, despite many years of research, it is still not fully understood why MRONJ occurs mostly in the jaws.[40] Nevertheless, several hypotheses have been proposed in the literature. First, it has been suggested that anti-resorptive drugs, which slow down bone metabolism, can cause necrosis. These drugs can reach higher concentrations in the jaw bones because they are used up and replaced so quickly. Secondly, anti-resorptives such as bisphosphonates administered intravenously in clinically high doses impair oral mucosal healing processes by inhibiting the proliferation of oral mucosal keratinocytes, while the jaw bones, covered by a thin mucous membrane, are particularly prone to injury during dental prosthetics or

dental treatments, In addition, it has been suggested that the antiangiogenic properties of anti-resorptives impair healing, allowing microorganisms to penetrate into the underlying bone and secondary infection to occur, and that the weakened immune response of patients undergoing chemotherapy also promotes infection.[41]

RISK FACTORS OF MRONJ

MRONJ has emerged as a complication of antiresorptive drugs, and its etiology is multifactorial.[1] Risk factors shorten the time to the onset of MRONJ and increase the rate and severity of development. Early reports on MRONJ indicated the pathologic condition as a specific side effect of high-dose, intravenous, and nitrogen-containing formulations of bisphosphonates. The risk of MRONJ in patients taking bisphosphonates was found to be significantly higher, especially in patients taking intravenous bisphosphonates such as Zoledronate. This difference has been attributed to the higher efficacy, bioavailability, and longer accumulation in bone compared to oral bisphosphonates.[42]

Invasive procedures

It has been reported that dentoalveolar operations may be the most common predisposing factor and that tooth extraction increases the susceptibility to MRONJ among patients with MRONJ at rates ranging from 62% to 82%.[2,3,8] Since invasive procedures such as tooth extraction may be a major risk factor for the onset of MRONJ, it has been shown that tooth extraction should be avoided in these patients.[5-7] However, some clinical data have shown that the risk of MRONJ goes down if the infected tooth is removed, even if antiresorptive therapy is not stopped.[43] Nevertheless, several studies have found that the risk of MRONJ occurrence is very high, with dental trauma associated with local infection, abscess, and poor oral hygiene.[44,45]

Periodontal and dentoalveolar infections

Otto et al.[33] stated that local infections rather than tooth extraction may be an important risk factor in the development of MRONJ, and dentoalveolar surgery should not be avoided in cases that cannot be treated with conservative measures.In many studies, mice with experimentally induced rheumatoid arthritis showed more severe MRONJ, with large areas of exposed bone and severe necrosis.[46]

Poor oral hygiene has been frequently emphasized as a fundamental factor in the prevention of infections in drug-treated patients at risk of osteonecrosis. Poor oral hygiene conditions may lead to various opportunistic infections. Inadequate oral hygiene has been listed among the factors affecting the occurrence of MRONJ.[47]

Trauma, excess occlusal force due to incompatible prosthesis use, and secondary trauma. Studies have revealed that the risk of jaw necrosis in naive patients using antiresorptive drugs increases due to factors such as bacterial, viral, and fungal infections, trauma, smoking, steroid use, a weakened immune system, autoimmune diseases, diabetes, and chemotherapy.[48]

CAN MRONJ DEVELOP SPONTANEOUSLY?

In a small percentage of patients on antiresorptive medication, osteonecrosis of the jaw occurs spontaneously (spontaneous). “Spontaneous” cases of MRONJ have been associated with specific anatomical sites, including the torus, exostoses, and mylohyoid ridges. The exostoses, torus, and mylohyoid ridges are particularly at risk of ulceration due to trauma because of their physical prominence, reduced circulatory ability, and thickness of overlying tissue. If “spontaneous” MRONJ is associated with anatomical sites at risk of oral trauma, perhaps the term “spontaneous” may be a misleading nomenclature, and there may in fact be a low level of trauma to the delicate oral mucosa. Given this circumstance, it might be necessary to explain to patients during patient education that oral food intake trauma can also predispose to the development of MRONJ.[49]

MRONJ STAGING SYSTEM

Stage 0

Patients without clinical evidence of necrotic bone but with vague symptoms or clinical and radiographic findings.

Stage 1

Presence of an exposed and necrotic bone or fistula in asymptomatic patients with no signs of infection/inflammation.

Stage 2

Patients with exposed and necrotic bone or bone-related fistula and signs of infection/inflammation.

Stage 3

Exposed and necrotic bone or bone-associated fistula, showing signs of infection, may include one or more of the following:

Exposed necrotic bone extending beyond the alveolar bone region (e.g., lower border and ramus of the mandible, maxillary sinus, and zygoma of the maxilla)

- Pathologic fracture
- Extraoral fistula
- Oral antral/oral-nasal communication
- Osteolysis extending to the lower border of the mandible or sinus floor[48]

HOW TO REDUCE THE RISK OF MRONJ OCCURRENCE?

The dentist should learn the patient’s medication, duration of use, frequency, and dose and be in contact with the medical oncologist with a detailed anamnesis. The dentist should be able to identify the patient who is at risk. Since MRONJ, which develops as a side effect in patients using anti-resorptives, is specific to the jaws, many procedures have been listed to potentially reduce the risk of MRONJ.[50] At the very beginning of a preventive approach to MRONJ, one should be aware that antiresorptive drugs alter the healing capacity of bone. Whether the major factor is tooth extraction or local infection, the dentist should be aware of the risk, be able to educate the patient about it, maintain oral hygiene, and conservative treatments have an important role in preventing dental caries and treating existing caries.[5-7,51] Despite being a side effect of anti-resorptives, MRONJ is a “disease” whose risk factors are treatable by the dentist just like any other disease by Marx et al.[52]

In a study conducted among patients who developed MRONJ, active periodontitis was found in 84% of patients, dental abscess in 13%, dental caries in 29%, and failed root canal treatment in 11%.[52] Failure of debridement, which is indispensable for surgical treatment in patients with MRONJ, complicates the treatment of osteonecrosis and negatively affects the patient's quality of life. Therefore, eliminating the risk factors that facilitate the occurrence of MRONJ constitutes an indispensable part of the treatment.

Before Starting Medication:

Since the likelihood of MRONJ occurring after invasive dental procedures is high, medical oncologists should refer all patients with MRONJ-related drug group indications to the dentist for evaluation and consultation.[2,3,8] The dental team should prioritize practices that can prevent future tooth extractions and periodontal disease elimination, and teeth with abscesses and teeth that cannot be restored should be extracted in advance to allow time for wound healing.[17,18,51,53] Since MRONJ may develop due to mechanical trauma of large or multi-lobed lingual torus and large palatal torus with thin mucosa, it is recommended to remove them before drug treatment.[49-50,52]

DURING MEDICATION THERAPY

If the patient cannot be kept waiting due to the stage of cancer and the medical oncologist has to start drug treatment urgently, if there is no time for the treatments that the dentist should administer, the patient should be referred to the dentist for evaluation while the patient is under drug treatment since MRONJ develops depending on the repeated dose amount, duration, and route of administration of drugs.[28] Although tooth extraction is not recommended, fluoride application, supragingival scaling, restorative procedures, and root canal treatment have been recommended.[52]

The Importance of Treating Carious Teeth

Dental caries is an important health problem affecting most children and adults in many industrialized countries.[37] In the Global Burden of Disease study, in which 291 medical conditions were evaluated, untreated dental caries, affecting 3.1 billion people, was ranked as the most common among these diseases.[38-39] Although the reasons for tooth extraction include dental caries, periodontal problems, endodontic reasons, eruption failures, orthodontic treatment, and as part of prosthetic planning, the main reason is dental caries.[9-16] It has been reported that preventing the emergence of pathology in the hard tissues of the teeth with a preventive and therapeutic strategy, treating it when it occurs, providing adequate oral hygiene, and motivating the patient for its continuity will reduce the risk of MRONJ by reducing the need for oral surgery.[17,18]

In cancer patients, it has been suggested that there is a significant relationship between the condition of the oral cavity and the development of MRONJ. In MRONJ, high carious teeth, missing teeth, and filled teeth index (DMFTI) values have been associated with advanced stages of jawbone complications.[53] Advanced dental caries or periodontal disease requires invasive procedures that predispose to MRONJ.

According to a study by Kos, bisphosphonate users with MRONJ had poorer oral hygiene, more caries complications, and worse periodontal status compared to those without MRONJ.[57]

Eliminating the Effect of Reduced Saliva Flow (Hyposalivation)

Not only local drugs but also many systemic drug groups affect the condition of the oral cavity, salivary composition, and properties. In the literature, decreased salivation has been reported in patients using antiresorptive drug.[58] Saliva is not only an aid in digesting food, but also an important part of the oral cavity's innate immune system and wound healing. However, reduced salivary flow may weaken the oral cavity defense system by decreasing the number of antimicrobial peptides. Poor salivary flow can lead to reduced removal of fermentable carbohydrates from the oral cavity, making teeth more susceptible to decay. As tooth decay progresses, it can lead to infection of the jawbone. In addition, dry mouth leads to reduced bacterial clearance from oral tissues. Prolonged low oral pH levels and decreased buffer capacity can also lead to a harmful imbalance of oral microbes and disrupt the oral microbial flora.[59]

Importance of Oral Hygiene

It has been emphasized in many studies that Actinomyces species (species [spp.]) are colonizers that play an important role in oral biofilm formation, play an important role in the course of MRONJ, and are frequently detected in MRONJ lesions. When Actinomyces spp. crosses the mucosal barrier and passes into the submucosal region, only its pathogenic properties emerge, and at the same time, it can reach the anaerobic environment necessary to maintain its activity. In addition, the high distribution of Streptococcus spp. in MRONJ lesions has been frequently reported in recent studies.[60] For acute and chronic wounds, beta-hemolytic Streptococcus spp., Pseudomonas aeruginosa, and Staphylococcus aureus have been recognized as the main causes of delayed wound healing.[61] In patients with osteonecrosis, necrotic bone is painless because there is no innervation, but secondary infection and pain occur as a result of the activities of microorganisms.

Should Medication be Discontinued When MRONJ Occurs?

Drugs causing MRONJ accumulate in the bone matrix depending on the repeated dose amount, duration, and route of administration. Since bisphosphonates are resistant to hydrolytic degradation, their half-life in the bone matrix has been found to be longer than 11 years.[28] When osteonecrosis develops, it has been reported that necrosis does not regress with discontinuation of drug treatment.[5] The dentist should not intervene in the decision to terminate drug treatment, dose amount, duration, and route of administration.

CONCLUSION

MRONJ is a rare but potentially serious condition. The dentist has an important role in preventing osteonecrosis from occurring. Since treating drug-induced osteonecrosis of the jaw is hard and complicated, the dentist should be able to keep MRONJ from happening by lowering risk factors or, if that's not possible, at least make it happen later. Since most cases of MRONJ reported in the literature are associated with tooth extraction and oral surgical procedures, patient education, oral hygiene, and conservative treatment should minimize the need for invasive procedures.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of Dental Sciences and Education

Case Report

DOI: 10.51271/JDSE-0022

Management of initial and surgical management of amlodipine-induced gingival enlargement with multifactorial etiology: a case report with 6 months follow-up

Canan Akdeniz, Arzum Güler Doğru

Department of Periodontology, School od Dentistry, Dicle University, Diyarbakır, Turkey

Cite this article: Akdeniz C, Güler Doğru A. Management of initial and surgical management of amlodipine-induced gingival enlargement with multifactorial etiology: a case report with 6 months follow-up. *J Dent Sci Educ*. 2023;1(4):123-126.

Corresponding Author: Canan Akdeniz, canan.akdeniz@dicle.edu.tr

Received: 08/12/2023 ◆ **Accepted**: 28/12/2023 ◆ **Published**: 31/12/2023

ABSTRACT

Drug-induced gingival enlargement can be seen as a side effect of systemically used drugs such as calcium channel blockers, anticonvulsants, and immunosuppressants. One of these drugs is amlodipine, a dihydropyridine derivative calcium channel blocker used in the treatment of high blood pressure and coronary artery disease. Amlodipine-induced gingival overgrowth is rarely seen compared to other calcium channel blockers. The aim of this case is to present the diagnosis of gingival overgrowth due to amlodipine use and the identification of other etiologic factors such as labial frenulum, phase 1 initial, and phase 2 surgical treatment approaches. A 56-year-old female patient presented to our clinic with severe gingival overgrowth, intense bleeding, difficulty feeding, and pain. The anamnesis revealed that she had hypertension and had been taking amlodipine derivative Norvasc 10 mg once a day for 8 years. A look inside the mouth showed that there was a lot of gum tissue growing over the crowns from the labial and palatal sides, mainly in the front of the maxilla. Phase 1 treatment was initiated. As a result of the consultation with the patient's cardiologist, the hypertension medication Norvasc 10 mg was replaced with Candexil 16 mg by the medical physician. The preoperative tension and blanch test was positive, and the labial frenulum was seen to mobilize the free gingival margin of the central teeth. After the same session of gingivoplasty, the labial frenulum was removed by a frenectomy operation. After the operation, antibiotics, analgesics, and mouthwash were prescribed. The patient stated that he did not have any problems after the operation. 6-month follow-up showed uneventful healing. No recurrence of gingival growth was found in the 1st, 3rd, and 6th month follow-ups. In conclusion, this case report shows that non-surgical periodontal treatment alone isn't always enough to treat drug-induced gingival overgrowths. The gingival shape should be changed so that the patient can properly clean their teeth, and drug-induced gingival overgrowths, like the one in this case, may have more than one cause and may need additional surgery like a labial frenectomy.

Keywords: Amlodipine, gingival overgrowth, calcium channel blocker, labial frenectomy, surgical periodontal therapy

INTRODUCTION

An increase in the size of the gingival connective tissue matrix is what amlodipine-induced gingival overgrowth (AIGO) is. The connective tissue matrix is composed of many components, including collagen, fibrin, and fibronectin. Misregulation of collagen synthesis and degradation is thought to trigger drug-induced growth. Gingival fibroblasts produce more collagen when exposed to amlodipine.[1]

Amlodipine is a dihydropyridine derivative calcium channel blocker (CCB) used in the treatment of hypertension. It has structural similarities to nifedipine, which frequently causes gingival hypertrophy. Amlodipine has a long half-life of 30 to 50 hours. It has been reported that AIGO usually develops within three months after initiation of the drug at a dose of 10 mg/day.[2]

The general prevalence of gingival overgrowth due to CCB is 38%. The prevalence of AIGO is between 1.7% and 3.3%. The male-female ratio was found to be 3.3.[3] There are few cases of amlodipine-related gingival hyperplasia in the current literature.[4]

When the gums enlarge, deep pockets can form that cannot be reached with toothbrushes and dental floss, making it difficult for the patient to maintain oral hygiene. This makes the host more susceptible to oral infections, caries, and periodontitis. When AIGO is diagnosed, the first step is to change the medication in consultation with a doctor. CCB should not be discontinued to avoid complications such as stroke and angina. In addition to professional plaque cleaning, the patient should be motivated to practice oral hygiene.[2]

In this case report, our aim was to diagnose AIGO, determine the multifactorial etiologies, and present the treatment management. Non-surgical periodontal treatment may not always be sufficient in AIGO. A reliable method of treating AIGO is a combination of surgical and nonsurgical periodontal treatment with drug replacement.

CASE

A 56-year-old woman presented to the Periodontology Clinic of Dicle University Faculty of Dentistry with complaints of severe gingival enlargement, intense bleeding, and pain (**Figure 1**). In the anamnesis, it was learned that she had hypertension and had been taking Norvasc, a 10 mg amlodipine derivative, once a day for eight years. Intraoral examination revealed a growth covering all upper teeth and increasing anteriorly. The gingival index was recorded at 3, and intense spontaneous bleeding was observed (**Figure 1**).

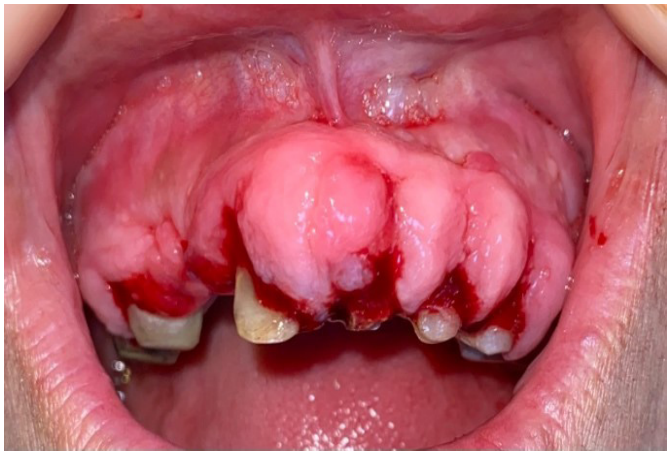

Figure 1. Phase 1 pre-treatment

It was determined that the gingival growths reached the incisal edges of the teeth. The patient was consulted by a cardiologist. The amlodipine derivative Norvasc was replaced with Candexil 16 mg, an angiotensin II receptor antagonist. Phase I treatment was initiated. During 4 sessions, scaling, root surface smoothing, and gingival curettage procedures were continued, and oral hygiene habits were reviewed (**Figure 2**).

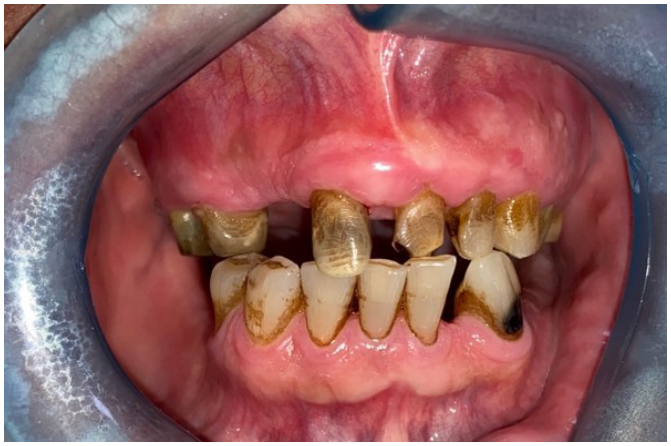

Figure 2. 2 months after drug replacement and phase 1

After 3 months, the patient was re-evaluated (**Figure 3**). Despite significant improvement in the gingival margin with nonsurgical periodontal treatment, phase 2 surgical treatment was planned to give the gingiva a knife-edge shape and prevent food retention. In the tension test, it was determined that the labial frenulum mobilized the free gingival margin of the central teeth, and a frenectomy operation was planned simultaneously with the gingivectomy operation to prevent food retention, protect the keratinized gingiva, and prevent gingival recession.

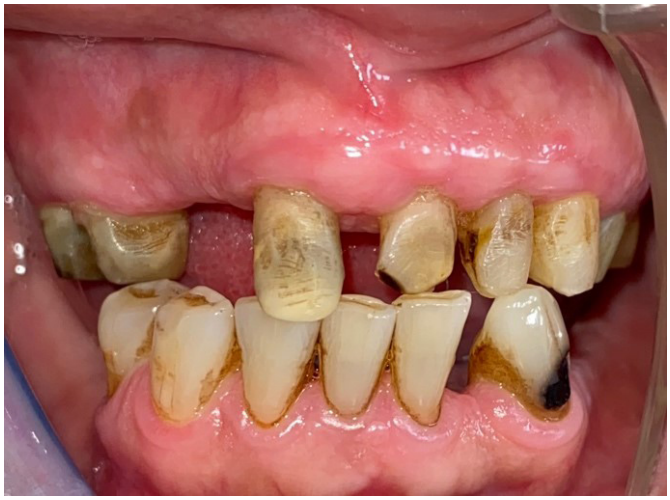

Figure 3. 3 months after drug replacement

Kirkland and Orban blades were used to give the gingiva a knife-edge shape (**Figure 4**). Then, the labial frenulum was clamped with a needle holder, and an incision was made from the posterior side with the scalpel leaning against the needle holder. On the anterior side of the needle holder, a half-thick incision was started from the most anterior part of the frenulum, two incision lines were joined at the end of the needle holder, and a lozenge-shaped piece of tissue was removed. The incision line was slightly extended to the right and left sides, the fibers that move the free gingival margin were dissected, and the periosteum was scraped with a periosteal elevator to prevent the cut fibers from re-adhering. The wound lips were dissected with tissue scissors and closed with simple sutures with 3.0 silk sutures. Since the incision line expanded in a triangular shape, a small coronal part of the wound was left for secondary healing (**Figure 4**).

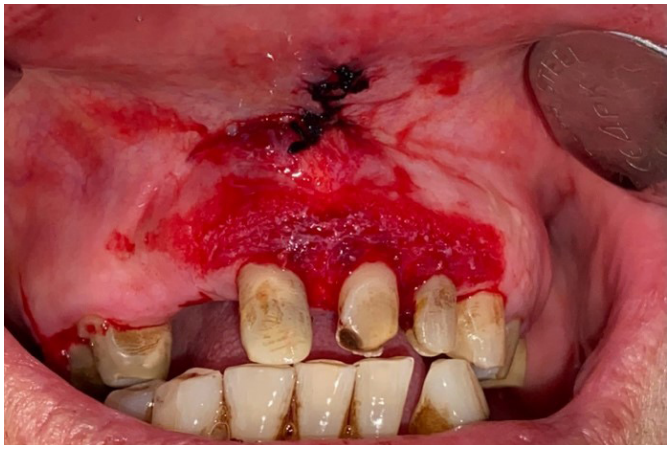

Figure 4. After operation

RESULTS

Recovery was uneventful at the 1-week postoperative follow-up. The patient reported simple postoperative symptoms such as mild pain and tightness in the frenulum area. Sutures were removed on postoperative day 14 (**Figure 5**). Mild scarring was seen in the frenulum area (**Figure 6**). One-month follow-up showed that the gingival thickness and shape were in appropriate form (**Figure 7**). Gingival overgrowth was not observed again at the six-month postoperative follow-up (**Figure 8**). The patient with AIGO was successfully followed up for a total of nine months, including three months preoperatively and six months postoperatively.

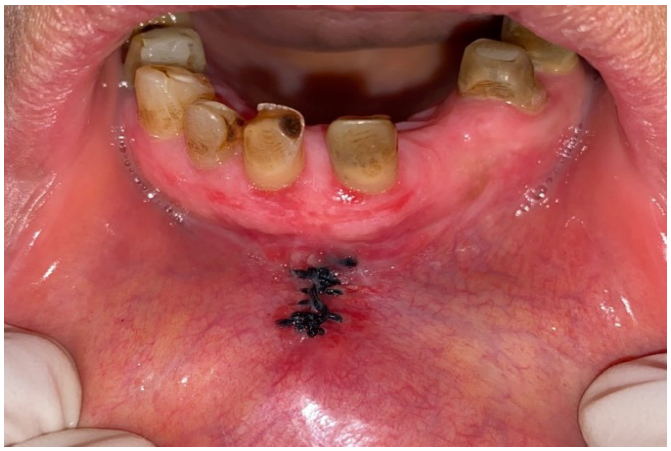

Figure 5. 2 weeks after operation

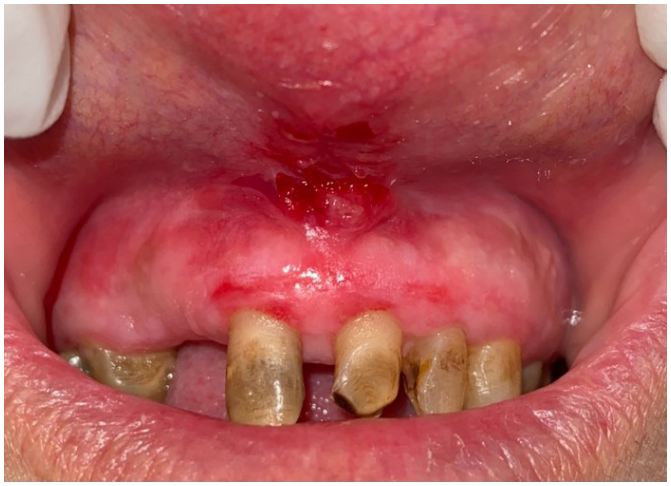

Figure 6. After sutures are removed

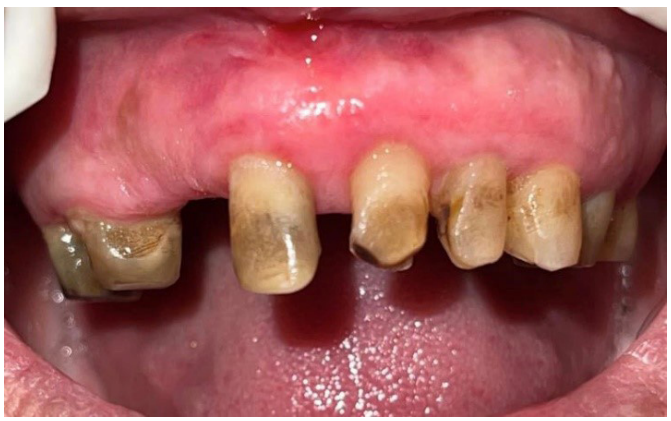

Figure 7. 1 month after operation

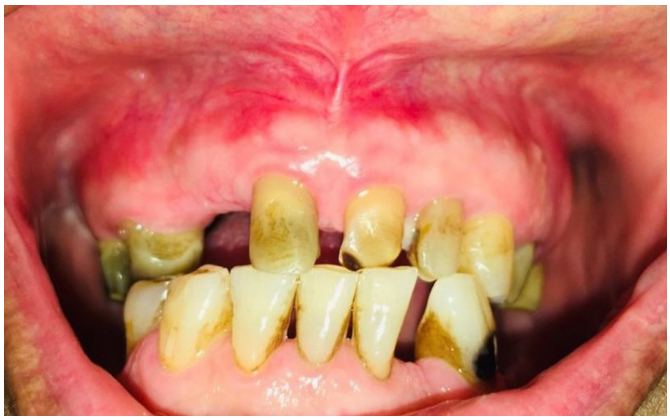

Figure 8. 6 months after operation

DISCUSSION

Gingival overgrowths cause speech and chewing difficulties, poor oral hygiene, and an unaesthetic appearance. Gingival overgrowth is also a serious concern for clinicians, as it provides a favorable environment for the growth of microorganisms.[5]

A study of 150 cardiac patients found that amlodipine at a dose of 5 mg/day did not cause AIGO, even when used for more than 6 months. On the contrary, Seymour et al. reported three patients with poor oral hygiene who developed gingival enlargement due to amlodipine use for at least three months.[4] AIGO is now considered to be not uncommon.[2]

Age is not a valid risk factor for gingival overgrowth associated with the use of CCBs, as CCB medications are generally suitable for middle-aged and older adults.[6] This is supported by a study of more than 800 patients treated with calcium channel blockers, in which age was not identified as a significant risk factor.[7]

Gingival overgrowth only happens in some people who take the same medication at the same dose or frequency. Because of this, some doctors think that drug-induced gingival overgrowth (DIGO) may be linked to a genetic tendency, but the exact genetic link has not been found.[8] The only genetic marker investigated in relation to DIGO is human lymphocyte antigen expression (HLA). Since HLA phenotypes are determined before transplantation, investigation of this marker has been limited to organ transplant patients. Several studies have reported the relationship between HLA expression and the incidence of drug-induced gingival overgrowth, but the results were not found to be significant.[6]

Many etiopathogenetic mechanisms have been proposed for DIGO; however, the exact cause is not known. Since many drugs with variable pharmacodynamics may cause DIGO, it may have a multifactorial pathogenesis.[8] One hypothesis state that anticonvulsants, immunosuppressants, and CCBs all cause cation flux inhibition.[9] Folic acid is actively transported to gingival fibroblasts, but there is less cation flow. This means that fewer cells take in folate, which in turn lowers the production and activation of matrix metalloproteinases. These are enzymes that break down collagen. This decreases collagenase activity, leading to decreased collagen degradation and thus connective tissue accumulation, which eventually manifests as DIGO.[10]

Folic acid has been added to food sources for more than 20 years to help prevent neural tube birth defects and other congenital anomalies. As the amount of folate in food sources has increased over the past 20 years, the prevalence of DIGO has decreased. However, there is currently insufficient evidence to prove a cause-and-effect relationship between increased folate intake for public health and a progressive decline in the incidence of DIGO over the years.[10]

The etiology of DIGO is multifactorial. Bacterial plaque is an important factor, and the severity of gingival overgrowth is directly proportional to the degree of plaque accumulation and plaque-induced inflammation.[11]

Surgical treatment of DIGO involves reorganization of the gingiva with a scalpel, blades, or laser. Successful therapeutic management of DIGO includes plaque control, topical folic acid, and topical azithromycin.[10]

CONCLUSION

In this report, we present the treatment of a patient with AIGO treated with surgical and non-surgical methods following drug exchange and a six-month follow-up after surgery. Different periodontal surgeries may also be needed to prevent the recurrence of DIGO. Although our 6-month results are stable, long-term follow-up studies are needed.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of Dental Sciences and Education

Case Report

DOI: 10.51271/JDSE-0023

Creating smile aesthetics by using crown lengthening and upper lip repositioning surgical operations together in a gingival smile case: a case report

Canan Akdeniz, Arzum Güler Doğru

Department of Periodontology, Faculty of Dentistry, Dicle University, Diyarbakır, Turkey

Cite this article: Akdeniz C, Güler Doğru A. Creating smile aesthetics by using crown lengthening and upper lip repositioning surgical operations together in a gingival smile case: a case report. *J Dent Sci Educ*. 2023;1(4):127-130.

Corresponding Author: Canan Akdeniz, canan.akdeniz@dicle.edu.tr

Received: 08/12/2023 ◆ **Accepted**: 28/12/2023 ◆ **Published**: 31/12/2023

ABSTRACT

When the distance between the gingival margin and the lower border of the upper lip is more than 3 mm while smiling, it is called a gummy smile. The etiology of excessive gingival visibility is varied: delayed passive eruption, anterior dento-alveolar extrusion, vertical maxillary overhang, short upper lip, hypermobile upper lip, or a combination of multiple factors. The aim of our study is to diagnose gingival smile and explain the treatment of excessive gingival appearance due to vertical maxillary excess and hypermobile upper lip with crown lengthening and upper lip repositioning surgeries. A 27-year-old female patient presented to our clinic with the complaint of excessive gingival exposure while smiling. In the intraoral examination, it was determined that the patient had good oral hygiene, the upper lip was hypermobile, and the crown lengths of the upper central teeth were shorter than normal due to passive eruption. Gingivectomy, crown lengthening, and lip repositioning operations were planned for gummy smile treatment. For lip repositioning, the first incision was made from the mucogingival line of teeth numbered 14-24, the second incision was made 8-10 mm apically; and the tissue in between was excised. The wound edges were closed with 5.0 nylon mono sutures. Postoperative antibiotics, analgesics, and mouthwash were prescribed. The patient stated that he did not have any postoperative problems. The 6-month follow-up showed an uneventful recovery. In this case, the excessive gingival appearance was reduced by restricting the muscle traction of the elevator lip muscles, and the tooth length was increased with the crown length operation, providing aesthetic satisfaction for both the patient and the physician. As a result of our study, this procedure is safe for patients, less invasive, has minimal side effects, and may be an alternative to orthognathic surgery in appropriate cases for the correction of gingival smiles.

Keywords: Lip reposition, gummy smile, gingivectomy

This case was presented as a poster at the international Turkish Periodontology association in 2023.

INTRODUCTION

Smiling is a powerful communication method that expresses happiness and joy regardless of the language and race of the person. For this reason, it is a serious concern for individuals that their smile is not aesthetic. In order to have an aesthetic smile, all anatomical structures, such as the lips, gums, teeth, and jaws, must be in harmony.

Gummy smile, also known as "gummy smile" is defined as a non-pathologic condition in which more than 3 to 4 mm of gum tissue is visible when smiling, causing aesthetic disharmony. The etiology of a gummy smile includes short lip length, hypermobile/hyperactive lip activity, a short clinical crown, dentoalveolar extrusion, delayed passive eruption, impaired active eruption, vertical maxillary overhang, and gingival overgrowth.[1] The worldwide prevalence of gummy smiles ranges from 10.5% to 29% and is more common in women, with a ratio of 2:1.[2]

Before treating the gummy smile, the etiology should be accurately determined, and it should be kept in mind that more than one etiologic factor may coexist because the treatment of the gummy smile may vary according to the type and number of etiologic factors. Many different techniques have been used in the treatment of gingival smiles. Some of these methods are inserting maxillary teeth, crown lengthening, orthodontically leveling the gum margins of the upper teeth, lip repositioning surgery, orthognathic surgery, and non-surgical methods like botulinum toxin use.[3] In addition, hyaluronic acid (HA)-structured fillers have started to be used in the treatment of gummy smiles as a current therapeutic approach, with the idea that they increase the resistance of soft tissues and limit muscle movements.[4]

In 1973, the lip repositioning procedure to treat gingival smiles was described by Rubinstein and Kostianovsky, followed by case reports by Litton and Fournier, Miskinyar, and Robbins.[2] Shreyas et al.[5] found that a total of 105 articles on the subject were published in a 10-year literature review on the use of lip repositioning surgery in the treatment of gummy smiles. As can be seen, more studies on lip repositioning surgery are needed.

The aim of this study is to describe the surgical technique of lip repositioning as an adjunct to crown lengthening in the following case report and to evaluate the 6-month efficacy of postoperative hypermobility of the upper lip.

CASE

A 27-year-old female patient was admitted to Dicle University Faculty of Dentistry, Periodontology Clinic, with the complaint of excessive gingival exposure while laughing (**Figure 1**).

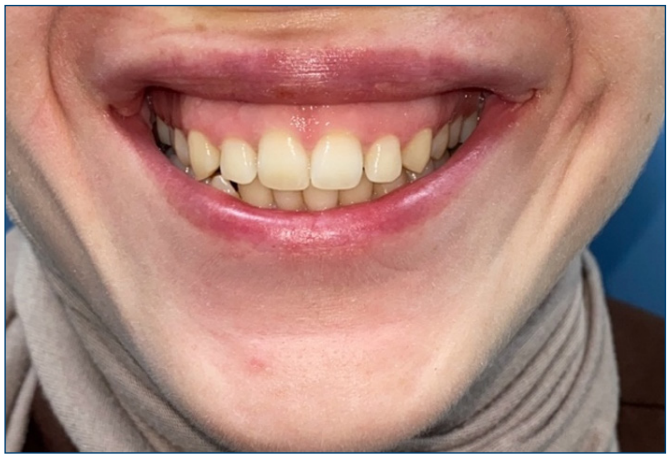

Figure 1. Pre-operative spontaneous smile

Our patient stated that she covers her mouth with her hand while laughing in social environments. No obstacle to surgery was found in her medical history. No bone loss and clinical attachment loss were found in the intraoral and radiographic examinations, and no clinical inflammation was detected clinically (**Figure 2**).

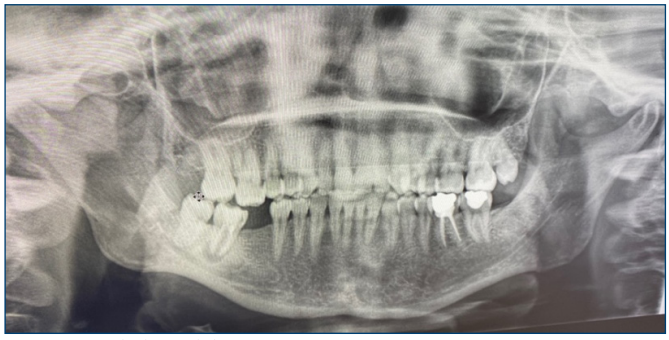

Figure 2. Radiological data

According to the 2017 World Periodontology Workshop, she was classified as clinically gingival healthy in healthy periodontium. The clinical crown lengths of the anterior teeth of the maxilla were shorter than normal; the crown length of teeth 11 and 21 was measured at 8-8.5 mm (**Figure 3**). However, incisors, which are the center of the aesthetic smile, usually have crowns with a height of 9.5 to 11 mm.[6] The patient's smile arc was close to the ideal configuration; it was seen to be in the form of a convex arc. When the gingival levels were examined, it was determined that the gingival levels of the right and left lateral teeth were not symmetrical, and the gingival margin of the right canine tooth was below the right central tooth. According to the ideal red aesthetic criteria, the central gingival margin and the canine gingival margin should coincide, and the lateral gingival margin should be slightly below this line.[6]

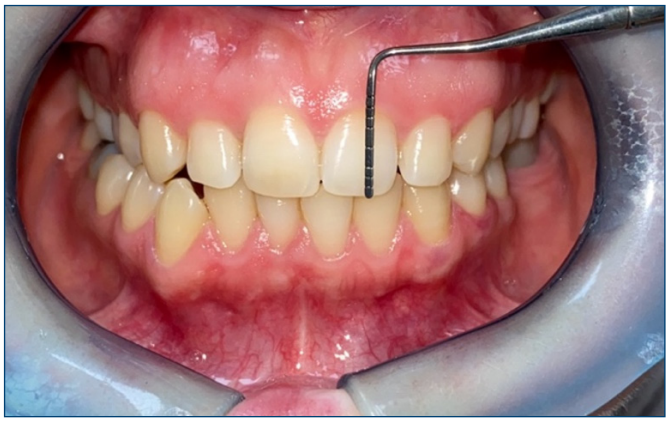

Figure 3. Pre-operative maxillary central tooth length

When the patient's smile was evaluated, it was observed that the upper lip was thrown towards the base of the nose while laughing spontaneously, the gingiva appeared around 4 mm at this time, and the upper lip was hypermobile. After a detailed clinical examination, it was decided to perform crown lengthening and lip repositioning surgeries together. A gingivectomy was first performed to increase the visibility of the anterior teeth and to level the gingival margins (**Figure 4**).

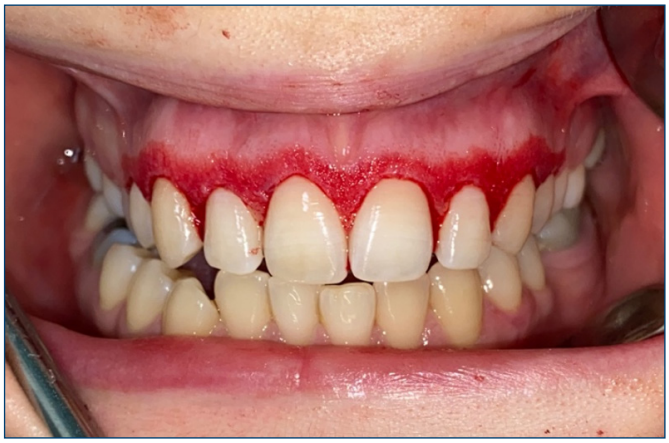

Figure 4. After crown lengthening operation

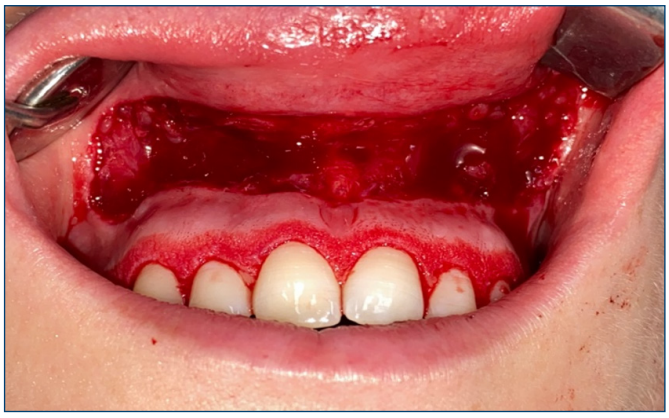

Figure 5. Exposed connective tissue after incision

Lip repositioning surgery was performed to reduce the traction of the lip elevator muscles. Incision points were marked with a sterile surgical marking pen. The first incision was made horizontally from the mucogingival line of teeth

14-24. The second incision was made 6-8 mm apical to the first incision, with twice the amount of visible gingiva (**Figure 5**). After removing the tissue in between as half thickness, the connective tissue was exposed (**Figure 5**). The incision line on the lip side was dissected with blunt-tipped curved scissors to facilitate suturing. In order to ensure symmetry, first the midline, then the right and left most distal areas were joined with a simple suture, and then the remaining areas were sutured with a locked continuous suture (**Figure 6**).

The patient was prescribed antibiotics, analgesics, and mouthwash containing 0.12% chlorhexidine after surgery.

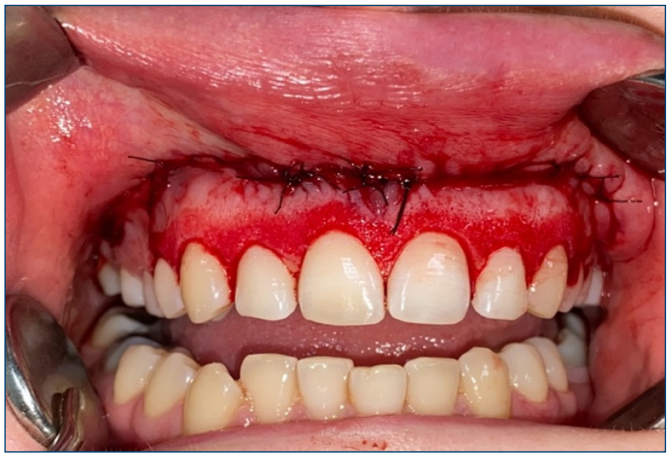

Figure 6. After suturation

RESULTS

An uneventful recovery was seen one week after surgery. The patient reported tension in her upper lip when she smiled 1 week after surgery. Two weeks later, the sutures were removed (**Figure 7**).

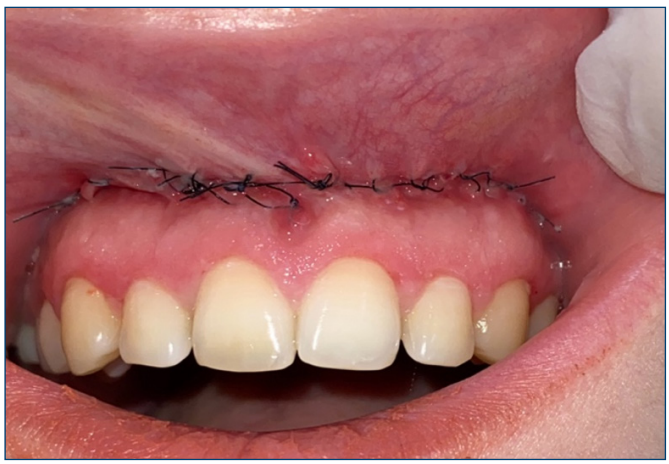

Figure 7. 2 weeks after the operation

Postoperative healing occurred with minimal discomfort. Since the suture line was hidden in the upper lip mucosa, uneventful healing was seen with a scar that was not visible when the patient smiled. Two weeks later, the patient's excessive gingival appearance was reduced (**Figure 8**). A stable result was obtained after 6 months of follow-up (**Figure 9**).

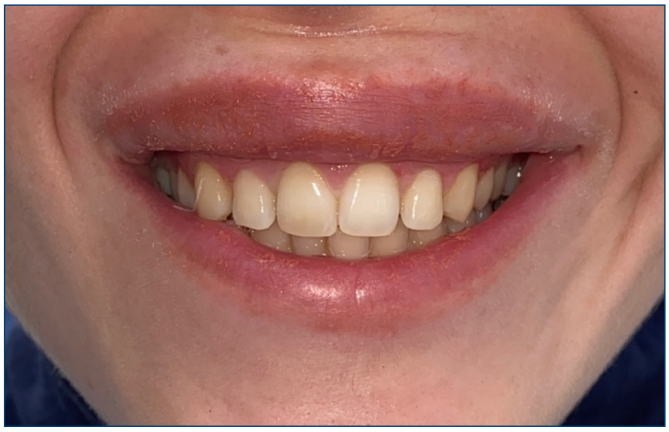

Figure 8. Spontaneous smile 2 weeks after the operation

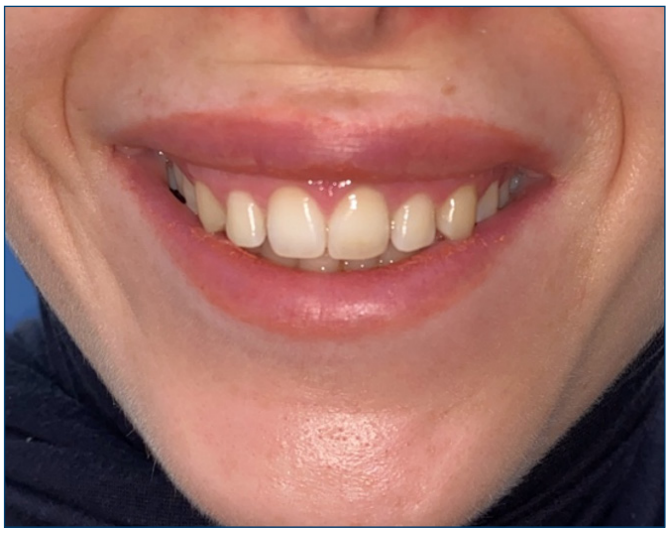

Figure 9. Post-operative 6-month follow-up

DISCUSSION

This clinical report describes lip repositioning to reduce the appearance of excessive gingiva and crown lengthening surgery for aesthetic periodontal reasons. To achieve satisfactory results, the etiology must be accurately determined, and the lip repositioning procedure should be used alone or in combination in the right case. Contraindications to lip repositioning include the presence of a minimal area of adherent gingiva and severe vertical maxillary redundancy. A minimal area of adherent gingiva may pose difficulty in suturing, flap design, and stabilization.[7] According to the vertical maxillary excess classification, orthognathic surgery is preferred for grade II (excessive gingival appearance 4-8 mm) and grade III (excessive gingival appearance ≥ 8mm).[8] However, lip repositioning can be used as an alternative treatment for patients who do not want orthognathic surgery.[7]

The advantage of the lip repositioning technique over other gummy smile correction treatments is that it is simple, safe, and effective and provides stable and satisfactory treatment results after healing.[9]

Combining the lip repositioning technique with other approaches such as periodontal plastic surgeries, restorative procedures, or Botox injections has been suggested to achieve more predictable and consistent results.[10] Modifications of surgical lip repositioning have been reported in the medical literature. Several articles advocate

smile muscle disconnection to prevent the smile muscle from returning to its original position and to minimize flap tension during suturation. Another method to prevent reattachment of the smile muscles is to use an alloplastic or autogenous spacer. This spacer is inserted through the nose between the elevator muscles of the lip and the anterior nasal spina (ANS), restricting the upward movement of the lip. Lip repositioning has also been performed in combination with rhinoplasty. There are case reports of lip repositioning performed in combination with depigmentation and crown lengthening, frenectomy, and crown lengthening. There are also studies in the literature where crown lengthening and lip repositioning procedures were performed with lasers in the same session.[11]

In literature studies, the most common postoperative complications were reported as decreased comfort, scar formation, and pain. In modified lip repositioning surgeries, swelling, ecchymosis, edema in the upper lip and perioral region, minor bleeding, and mucocele formation were reported.[10]

CONCLUSION

This case report demonstrates the successful treatment of gingival smiles with lip repositioning and crown lengthening procedures. At 6-month follow-up, our results appear to be stable. Appropriate case selection is considered to be critical to the success of the surgical procedure. Long-term follow-up studies and randomized controlled trials are needed to evaluate the stability and efficacy of this method.

ETHICAL DECLARATIONS

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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