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Effect of systemic anticoagulant (acetyl-salicylic acid) application on implant osseointegration in rat tibias in allogeneic bone transplantation

Efecto de la aplicación de anticoagulante sistémico (ácido acetilsalicílico) en la osteointegración de implantes en tibias de rata en trasplante óseo alogénico

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ABSTRACT

The aim of this study is to investigate the effect of systemic administration of acetylsalicylic acid, used in the treatment of coronary artery disease, on the level of osseointegration of titanium implants in the transplanted bone in the treatment of bone defects created in rat tibias using allogeneic bone transplantation. Forty-two female Sprague Dawley rats, aged 6-12 months, were used in this study. The average weight of the rats used in this experimental study was between 270 and 300 grams.To prevent harm to the animals during the experiment, temperature was constantly controlled, and a 12-hour light/12-hour dark cycle was implemented. Among the groups without allo-graft, the mean bone-implant contact value was 6.31 (Median: 6.30) in the control group, while the value was 6.40 (6.20) in the Acetylsalicylic Acid dose 1 group. No significant difference was found between these two groups. In the Ac-etylsalicylic Acid dose 2 group, the value of 6.51 (6.80) was obtained, while an increase was observed compared to the control and Acetylsalicylic Acid dose 1 groups, but no significant dif-ference was obtained. In this study the results demonstrated the beneficial effects of Acetylsalicylic Acid. Higher bone-to-implant fusion rates were achieved in the Acetylsalicylic Acid -treated groups. It is concluded that Acetylsalicylic Acid use may be beneficial in cases requiring bone augmentation.

Key words: Acetylsalicylic acid; allogeneic bone; osseointegration; bone implant connection

RESUMEN

Este estudio tuvo como objetivo investigar el efecto de la administración sistémica de ácido acetilsalicílico, utilizado en el tratamiento de la enfermedad arterial coronaria, sobre el nivel de osteointegración de implantes de titanio en el hueso trasplantado en el tratamiento de defectos óseos creados en tibias de rata mediante trasplante óseo alogénico. En este estudio se utilizaron cuarenta y dos ratas Sprague Dawley hembras, de entre 6 y 12 meses de edad. El peso promedio de las ratas fue de entre 270 y 300 gramos. Para evitar daños a los animales durante el experimento, la temperatura se controló constantemente y se implementó un ciclo de 12 horas de luz/12 horas de oscuridad. Esto indica diferencias significativas entre los grupos. En general, entre los grupos sin aloinjerto, el valor medio de contacto hueso-implante fue 6,31 (Mediana: 6,30) en el grupo control, mientras que el valor fue 6,40 (6,20) en el grupo de ácido acetilsalicílico dosis 1. No se encontraron diferencias significativas entre estos dos grupos. En el grupo de ácido acetilsalicílico dosis 2, se obtuvo el valor de 6,51 (6,80), mientras que, se observó un aumento en comparación con los grupos control y de ácido acetilsalicílico dosis 1, pero no se obtuvieron diferencias significativas. En este estudio, los resultados demostraron los efectos beneficiosos del ácido acetilsalicílico. Se lograron mayores tasas de fusión hueso-implante en los grupos tratados con ácido acetilsalicílico. Se concluye que el uso de ácido acetilsalicílico puede ser beneficioso en casos que requieren aumento óseo.

Palabras clave: : Ácido acetilsalicílico; hueso alogénico; osteointegración; conexión de implantes óseos

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INTRODUCTION

Dental implants are one of the most common methods of prosthetic treatment worldwide. Studies have highlighted that the rate of implant treatment is increasing daily and that this rate could reach 23 % by 2026 [1]. Studies have shown a rapid increase in patients receiving implants between the ages of 65-74 [1].

It is stated that this age group has more systemic drug use. Therefore, great attention should be paid to the negative situations that need to be overcome during the application. Due to long-term use of antiplatelet and oral anticoagulants, it is necessary to take precautions against thromboembolic conditions and take the necessary precautions for prophylaxis [2, 3]. The use of these drugs is common in individuals with conditions such as myocardial infarction, percutaneous coronary interventions, prosthetic heart valve placement, atrial fibrillation, pulmonary embolism, stroke and joint replacement [4].

Today, bone destruction, particularly due to periodontal disease, is a frequently researched topic in modern dentistry. The goal is to increase the volume of the alveolar bone to facilitate healing of lost bone tissue and, thus, facilitate implant placement. Bone loss, which begins after tooth extraction, can reach up to 34 % within a year, particularly in the maxillary region. Therefore, various procedures are being developed, and numerous materials and comprehensive strategies are being developed to prevent this condition [5, 6].

Acetylsalicylic acid (ASA), commonly known as aspirin, is used to reduce pain, fever, and inflammation. Systemic anti-inflammatory, analgesic, antipyretic, and antithrombotic properties of this drug are reported [7]. For individuals for whom aspirin is indicated, its use is generally oral and continuous. Aspirin's oral bioavailability is approximately 40 % [8]. ASA is one of the most prescribed medications worldwide. It is a member of the nonsteroidal anti-inflammatory drug family. ASA has a systemic effect by reducing the proliferation of cytokines due to its inhibitory properties on cyclooxygenase-1, cyclooxygenase-2, and antiplatelet aggregation. It also has effects on mesenchymal cells. This mechanism involves reducing cytokines such as interferon-γ and tumor necrosis factor-γ, thereby promoting osteogenesis and inhibiting osteoclast genesis. As a result of these events, it is reported to increase bone regeneration [9, 10].

One ASA study conducted experiments in an animal model. Osteoporosis-induced rodents were used in the experiment, and effects on the balance of absorption and resorption were observed in the rodents, and ASA was reported to play a role in bone formation [5]. Studies have reported that ASA use influences the FAS antibody, an antibody responsible for apoptosis in mesenchymal stem cells, thereby accelerating bone repair and increasing bone density. It is also said to have effects on telomerase reverse transcriptase (TERT). TERT, the terminal portion of telomeres, plays an active role in DNA repair. The absence or deficiency of TERT results in a tolerant defect in cell division, resulting in impaired bone regeneration [11, 12, 13]. Therefore, some studies report that aspirin actively regulates bone metabolism [14, 15, 16].

In the studies carried out by the researchers, it has been reported that Deproteinized bovine bone mineral has positive effects on reducing periodontal defects because it supports neovascularization, has an osteoconductive structure that has a positive effect on the growth and differentiation of cells, and protects the blood clot [17].

Allogeneic bone grafts also have these features. It is also reported in studies that it is an alternative to autografts and xenografts. It is reported that these grafts obtained from humans are available in varieties such as mineralized and demineralized bone matrix (DBM), demineralized freeze-dried bone allograft (DFDBA), freeze-dried bone allograft [18].

In addition to their osteoconductive properties, allogeneic grafts are also emphasized to have osteoinductive effects due to their presence of bone morphogenetic proteins [19]. Studies have demonstrated histological examination of DFDBA, demonstrating its ability to promote new periodontal attachment formation [20].

This study aimed to investigate the effect of systemic administration of acetylsalicylic acid, used in the treatment of coronary artery disease, on the osseointegration of titanium implants in the transplanted bone in bone defects created in rat tibias via allogeneic bone transplantation.

MATERIALS AND METHODS

Animals and study design

Since the study will be conducted on female rats (Rattus norvegicus), vaginal smears will be taken on all selected rats, and rats in the same estrus phase will be included in the study. Before starting the study, an application for study approval was made to the Fırat University Animal Experimentation Local Ethics Committee (Approval No: 2024/10-07 Dated: 22.05.2024), which approved.

The rats were produced by the Fırat University Experimental Research Center (Elazig, Türkiye) and were delivered to the academics conducting the study once the specified criteria were met. This study adhered to all recommendations of the European Declaration of Helsinki and was conducted in Elazig (Türkiye) within the animal experimentation protocol of the Ministry of Agriculture of the Republic of Türkiye. No animals were subjected to pain during the experiments, and utmost attention was paid to all ethical regulations. All recommendations in the Declaration of Helsinki for the protection of experimental animals were adhered to.

Forty-two female Sprague Dawley rats, aged 6-12 months, were used in this study. The average weight of the rats used in this experimental study was between 270 and 300 g (WL, Shimadzu, Japan). To prevent harm to the animals during the experiment, temperature was constantly controlled, and a 12-hour light/12-hour dark cycle was implemented.

Donor rats were first euthanized. Block grafts, 2.5 mm thick and 5 mm wide, were obtained from the right and left femoral bones (FIG. 1). The resulting grafts were transplanted to the rats' tibias along with the implants. Groups of 48 rats were randomly selected. The rats were divided into six groups of eight rats each.

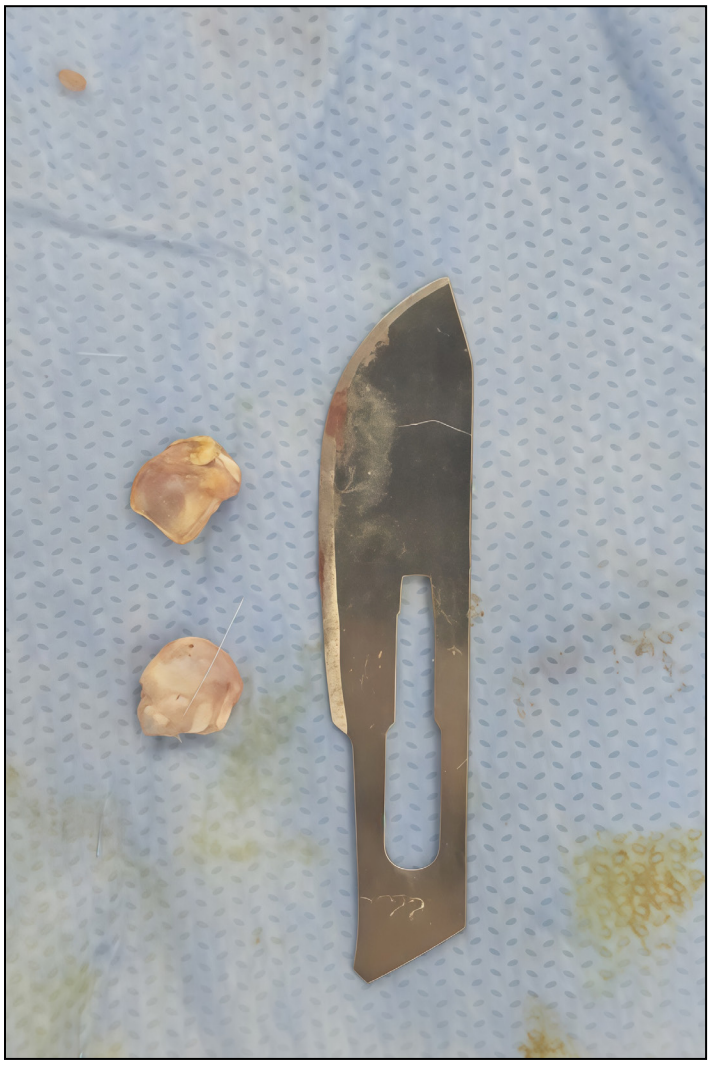

FIGURE 1. Allogeneic block grafts, 2.5 mm thick and 5 mm wide, were obtained from the right and left femoral bones of euthanized donor rats.

Allograft transplantation implant group (n = 7): In the allogeneic transplantation section, block grafts of 2,5 mm thickness and 5 mm width were obtained from the femur bones. The grafts were firmly placed in the cortico-cancellous bone part of the metaphyseal part of the right tibia bones of rats under together with 1.2 mm diameter and 4 mm long titanium implants. No additional procedures were performed.

Implant- allograft transplant- acetylsalicylic acid dose 1 group (n = 7): In this group, in addition to the application of the allograft bone block transplantation, 200 mg/kg ASA was administered via oral gavage three times a week for a four-week study.

Implant- allograft transplant- acetylsalicylic acid dose 2 groups (n = 7): In this group, in addition to the application of the allograft bone block transplantation, 400 mg/kg ASA was administered via oral gavage three times a week for a four-week study.

Control implant group (n = 7): 1.2 mm diameter, 4 mm long titanium implants were firmly implanted into the cortico-cancellous bone of the metaphyseal portion of the right tibia of the rats. No additional procedures were performed.

Implant Acetylsalicylic Acid dose 1 (n = 7): 1.2 mm diameter, 4 mm long titanium implants were firmly implanted into the cortico-cancellous bone of the metaphyseal portion of the right tibia of the rats. Additionally, 200 mg/kg ASA was administered via oral gavage three times per week throughout the four-week study.

Implant Acetylsalicylic Acid dose 2 (n = 7): 1.2 mm diameter, 4 mm long titanium implants were firmly implanted into the cortico-cancellous bone of the metaphyseal portion of the right tibia of the rats. Additionally, 400 mg/kg ASA was administered via oral gavage three times per week throughout the four-week study.

Surgical procedures

Surgical procedures were performed under sterile conditions. General anesthesia was achieved with 10 mg/kg xylazine (Rompun, Bayer, Germany) and 50 mg/kg ketamine (Ketasol, Richter Pharma, Austria) administered intraperitoneally. After shaving, the surgical site was washed with povidone-iodine and then covered with sterile drapes. An approximately 15-mm incision was made over the tibial crest using a number 22 scalpel, after which the skin, soft tissues, and periosteum were dissected. Harvested allogeneic bone grafts, along with milled titanium implants, were placed in the subjects' tibias to provide initial firmness (FIGS. 1 and 2).

The implant cavities were created using a rotary instrument (NSK, Japan) at 500 rpm, cooled with sterile saline. After implant placement, the surgical site was closed with 4-0 absorbable suture. All rats in all study groups received antibiotics (Cefazolin sodium 40 mg·kg-1, iespor 250, I.E. Ulagay, Türkiye) and analgesic (Tramadol hydrochloride 0.1 mg·kg-1, Contramal, Abdi Ibrahim, Türkiye) were injected intramuscularly for 3 days (d) after the operations to prevent infection and pain. After a four-week osseointegration period, the subjects were euthanized and were prepared for biomechanical analysis (FIG. 3).

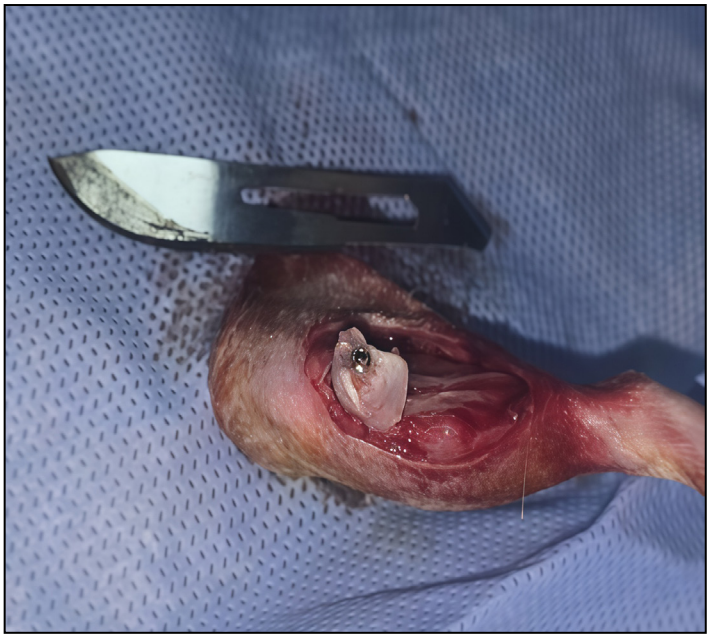

FIGURE 2.Application of allogeneic graft with implant to the application area.

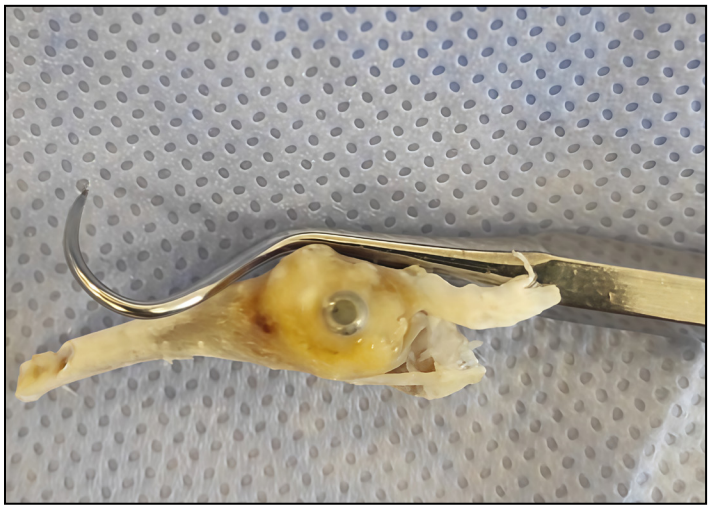

FIGURE 3. The implant and surrounding bone tissue after healing. The transplanted bone is fully integrated with the recipient site.

Biochemical analysis

The study period was set at 4 weeks. At the end of this period, the euthanized rats were prepared for biomechanical analysis. The reverse torque method was used as the analysis method. Samples were preserved in 10 % formalin until analysis. Analyses were performed without delay to prevent dehydration. All samples were placed in polymethylmethacrylate blocks for analysis. A Mark-10 (Cap Torque Tester, Model MTT01-12, NY, USA) device was used during analysis.

A controlled manual force was applied in a counterclockwise direction, and the maximum value (N/cm) was recorded when the force was stopped. The implants and surrounding bone tissue were removed for analysis. The implants were subjected to reverse torque testing with a torque device (Mak 10, USA) (FIG. 4). The rotational movement and force values when the implant first moved within the socket were recorded. Data were obtained in N/cm and statistically evaluated for skewness and kurtosis.

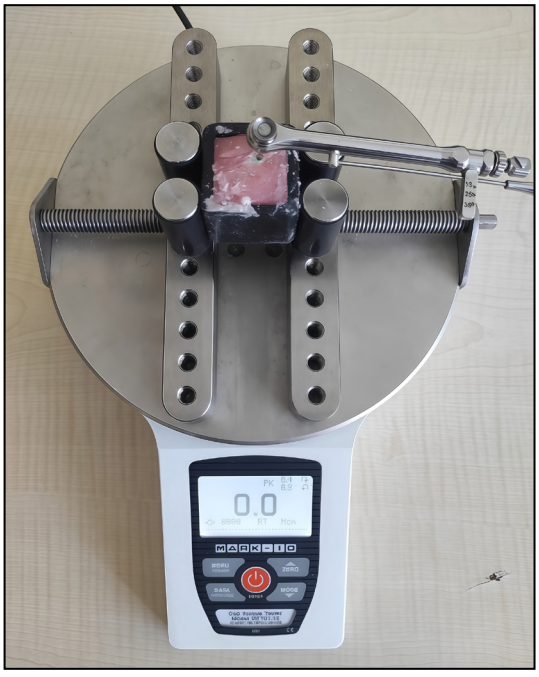

FIGURE 4. Biomechanical reverse torque analysis (Mark 10, NY, USA).

Statistical analysis

IBM SPSS Statistics 22 was used for statistical analysis of the data in the study. In this evaluation, the conformity of the parameters to the normal distribution was evaluated with the Kolmogorov–Smirnov test. In addition, the Kruskal–Wallis's test was used to compare the non-normally distributed parameters between groups, and the Mann–Whitney U-test was used to determine the group that caused the difference. Significance was evaluated at the $P < 0.05$ level.

RESULTS AND DISCUSSION

In the analyses performed, a P value of 0.027 was obtained for all groups. This indicates significant differences between the groups. Overall, among the groups without allograft, the mean bone-implant contact value (N/cm) was 6.31 (Median: 6.30) in the control group, while the value was 6.40/6.20 in the ASA dose 1 group. No significant difference was found between these two groups. In the ASA dose 2 group, the value of 6.51/6.80 was obtained, while an increase was observed compared to the control and ASA dose 1 groups, but no significant difference was obtained.

However, the situation is slightly different in the groups where we applied for a bone allograft transplant. In the allograft-only group, the bone-implant union value was obtained as 5.27/5.20, and statistically significant differences were obtained with the ASA dose 1 group (P = 0.021). Similarly, in the allograft-treated group and systemically applied ASA dose 1, the bone-implant union value was obtained as 5.40/5.30. (P = 0.034) statistically significant differences were also obtained with the ASA dose 1 group.

In the allograft-treated ASA dose 2 group, the bone-implant union value was obtained as 5.29/5.40 (N/cm), and statistically significant differences were obtained with the ASA dose 1 group. (P = 0.025). In the analyses, significant differences were also obtained between the control group and the group that received only allograft (P = 0.041) (TABLE I).

TABLE I
Bone implant contact biomechanical measurement values

Groups	BIC (N/cm) (Mean/ Median)	Min.	Max	P*
Control (n = 7)	6.31/6.30	5.10	7.80	
ASA Dosage 1(n = 7)	6.40/6.20	5.70	7.60	
ASA Dosage 2(n = 7)	6.51/6.80	4.70	7.90	
Allograft^{a1,b}(n = 7)	5.27/5.20	4.30	6.70	< 0.05
Allograft ASA Dosage 1^{a2} (n = 7)	5.40/5.30	4.70	6.20	= 0.027
Allograft ASA Dosage 2^{a3} (n=7)	5.29/5.40	4.10	6.20	

*Krusskal Wallis Test, P = 0,027. ^{a1,2,3}: Statistically significantly different compared with ASA Dosage 1. a^1: 0,021 a^2: 0,034 a^3: 0,025. ^{b} Statistically significantly different compared with the controls. ^{b}: 0,041. ^{a} and b: Mann Whitney U Test. BIC: Bone implant contact. ASA: Acetylsalicylic Acid

Various procedures are being tested to achieve bone regeneration. These procedures; use of biomaterials, blood concentrates, mesenchymal cell acquisition and use, drugs that will facilitate extra healing can be given as examples. In addition, its use in biologic agents such as clopidogrel and simvastatin is specifically increasing [21, 22, 23, 24, 25, 26].

The use of ASA in conjunction with certain biomaterials and derivatives has yielded positive results in bone tissue

regeneration. Positive results have been obtained especially in local applications. In the studies, the amount of new bone formation was between 6.42 and 78.67 % in the groups without ASA, while this value was observed between 20 and 88 % higher in the groups where ASA was applied. Statistically significant differences were also observed in these studies. In studies whose data were carefully examined, statistically high new bone formation was observed in the ASA group in terms of new bone formation evaluated as mm3 [27, 28, 29, 30, 31].

In a study conducted by Subramanian *et al*. [32], ASA was used to investigate the effects of grafts containing BMP-2 and it was reported that it prevented ectopic bone formation in the research used in membranes. Similar results were obtained in this study. Higher bone-implant fusion rates were achieved in the ASA-treated groups. This suggests that the use of ASA may be encouraged in cases requiring bone augmentation.

Today, autogenous grafts, which combine osteogenic, osteoinductive, and osteoconductive properties, are widely used as the gold standard in bone augmentation. However, due to the difficulty of obtaining this graft group, complications that arise during its acquisition, and undesirable outcomes, alternative methods are being sought. Furthermore, because no other material has osteogenic properties, autogenous grafts are the most reliable materials [33, 34].

Different methods are being tried when evaluating graft procedures. One of these is materials containing hydroxyapatite. Furthermore, alternative methods for augmentation are being explored. One of these is the option of using shorter implants in areas with insufficient bone [35, 36]. When evaluating allogeneic grafts, they offer benefits due to their combined osteoinductive and osteoconductive properties. However, these grafts have drawbacks such as the potential for immunologically unfavorable burns, the risk of host-to-host disease transmission, and their short lifespan [37, 38]

Due to the negative characteristics of allografts, various storage techniques have been developed to eliminate these undesirable conditions. These methods have resulted in clinically usable derivatives such as DBM, Autolyzed, Antigen-Extracted, Allogeneic (AAA) bone, and Bone Decellularized Extracellular Matrix (dECM, bone dECM) [39, 40, 41].

In this study, it was preferred allogeneic grafts because they are easy to obtain, minimize the risk of complications, and maximize postoperative patient comfort. The procedure were performed by placing the grafts obtained from donor animals as a block into the surgical site without any additional intervention. The aim of this study was to increase the effectiveness of vertical bone augmentation, particularly in patients with horizontal bone loss, and to improve implant survival rates. The primary goal was to achieve a surgical procedure that minimized patient trauma and increased success. The results demonstrated that cases were used ASA had higher bone-to-implant fusion rates.

In one study, mice were ovariectomized and osteoporosis was induced. The aim of this study was to target telomerase activity and inhibit osteoclast activity. Results showed improved bone formation and suggested that bone resorption could be prevented [42]. Studies have investigated the immunological basis of ASA's effects. ASA's local effects on IFN-γ and TNF-α were detected, resulting in local reductions in these levels. As a result, the osteogenic deficiency caused by proinflammatory cytokines affecting bone marrow mesenchymal stem cell (BMMSCs) was eliminated, and positive results were obtained in BMMSC-based bone regeneration [43].

Zhang *et al*. [44] and Li *et al*. [45] reported that ASA upregulated Treg cells and downregulated Th17 cells in an experimental colitis study, supporting the immune modulatory properties of BMMSCs. Zhang *et al*. [46] reported that the composite gel-ASA treatment resulted in greater new bone formation in the ASA group compared to the non-ASA group, regardless of whether periodontal ligament stem cells were included. Furthermore, in an experiment conducted on mouse calvarium, ASA was identified as an independent factor stimulating bone regeneration [46].

Bone augmentation is generally a critically important and challenging treatment in periodontics. This aimed to provide the most beneficial treatment to the patient in this challenging and demanding situation. When we evaluated the results, positive results were obtained. Similar to other studies demonstrating a cause-and-effect relationship, we believe this is due to ASA's direct positive effect on inflammatory cytokines. Inflammation is the most important cause of bone loss. We believe that eliminating and reducing the negative and chronic problems associated with inflammation contributes to bone healing.

CONCLUSIONS

This study evaluated allogeneic grafts, which are widely used today due to their non-traumatic and comfortable application. An experimental study was conducted using ASA, a biological substance that has a positive effect on bone healing with allogeneic grafts. In this study, the beneficial effects of ASA were statistically demonstrated. Higher bone-implant fusion rates were obtained in the groups treated with ASA.

In conclusion, it was determined that the use of ASA may be effective in conditions requiring bone augmentation. However, more detailed and specific studies are needed for more conclusive results.

Conflict of interests

The authors of this study declare that there is no conflict of interest with the publication of this manuscript.

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