Dental Journal
Majalah Kedokteran Gigi

Dental Journal
(Majalah Kedokteran Gigi)
2024 March; 57(1): 38–44

Original article

The role of continuous moderate-intensity exercise on increasing collagen density after tooth extraction

Anis Irmawati[1], Nadya Melinda[2], Tantiana[1], Yassir Ahmad Azzaim[3], Noor Faizah Balqis[4], Baher Al-Tayar[5]
[1]Department of Oral Biology, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia
[2]Graduate Student, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia
[3]Magister Student, Health of Dental Science, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia
[4]Graduate Student, Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia
[5]Department of Dental Medicine, Faculty of Medicine, Aljanad University for Science and Technology, Taiz, Yemen

ABSTRACT

Background: *The wound healing process post-extraction is expected to be quick, which can reduce the risk of complications and restore normal tissue function. A minimum oxygen supply needs to be met so that acceleration of the wound healing process can occur. Wound healing can be accelerated by continuous moderate-intensity exercise with increasing tissue oxygenation. Collagen requires oxygen in the procollagen formation process to support wound healing.* ***Purpose:*** *This study aimed to prove the role of continuous moderate-intensity exercise in increasing collagen density in the dental sockets of Wistar rats (Rattus norvegicus) after tooth extraction.* ***Methods:*** *Four groups of Wistar rats were created: control groups K1 (on day 3) and K2 (on day 7), and treatment groups K3 (on day 3) and K4 (on day 7). K1 and K2 were submerged in a bucket of water, and K3 and K4 received daily moderate-intensity exercise for a duration of two weeks. The rats' incisors were extracted on the day 15. Post-extraction collagen density was measured on day 3 (K1 and K3) and on day 7 (K2 and K4). The one-way ANOVA test and post-hoc Tukey test were used in the statistical analysis of the data.* ***Results:*** *There was a significant difference between all groups (p: 0.0001; p<0.05). Group K4 had a higher collagen density than the other groups.* ***Conclusion:*** *Continuous moderate-intensity exercise played a role in increasing the density of collagen in the rat tooth socket after tooth extraction.*

Keywords: *collagen; continuous moderate-intensity exercise; medicine; tooth extraction; wound healing*
Article history: *Received 27 December 2022; Revised 22 February 2023; Accepted 4 April 2023; Published 1 March 2024*

Correspondence: Anis Irmawati, Departement of Oral Biology, Faculty of Dental Medicine, Universitas Airlangga. Jl. Mayjen Prof. Dr. Moestopo 47 Surabaya, 60132, Indonesia. Email: anis-m@fkg.unair.ac.id

INTRODUCTION

Tooth extraction is an action that we are familiar with as dentists. Tooth extraction is the act of removing teeth that involves soft tissue and bone tissue in the oral cavity. Loss of teeth will harm the patient because it can cause malposition of teeth, interfere with the efficiency of mastication, cause problems in the temporomandibular joint, and create other problems in the oral cavity. At this time, the number of cases of tooth extraction in Indonesia is still relatively high, so it is important for the community to maintain dental and oral health.[1]

According to Basic Health Research, the prevalence of dental and oral problems in Indonesia was 23.2% in 2007 and 25.9% in 2013. Furthermore, the prevalence rate in 2018 was 57.6%. Based on data from the World Health Organization, it was found that there are about 3.5 billion people in the world experiencing health problems in the teeth and mouth.[2] A common problem is that cavities that are not treated and patients often come to ask for the tooth to be extracted.[3]

A tooth extraction is considered ideal if it does not cause excessive pain, causes minimal trauma to the supporting tissue, and the wounds created by tooth extraction can heal normally without causing interference.[4] Any tooth extraction that is not ideal can cause subsequent problems. Problems that often arise after tooth extraction are the result of a prolonged wound healing period, which can lead to various complaints in patients, including pain, bleeding, disturbances in chewing function, impaired speech function,

DOI: 10.20473/j.djmkg.v57.i1.p38–44

and, if it has been going on for a long time, infection. Improper management of wound healing can slow down the wound healing process.[5]

One indicator of wound healing can be seen from the formation of collagen. Collagen is part of the connective tissue needed in the process of scar tissue formation and wound healing.[6] Collagen begins to form in the proliferative phase. It functions as an extracellular matrix in the wound area. This helps the process of adhesion, migration, and proliferation of cells in the matrix.[7] The wound healing process can fail if the formation of collagen does not occur. Efforts have been made to accelerate the process of wound healing in the oral cavity, including administering pharmacological or non-pharmacological drugs, maintaining oral hygiene, changing drugs that can cause allergic reactions, and reducing inflammation in wounds.[8]

In addition those mentioned above, there are other efforts that can accelerate the wound healing process, namely through exercise. [9–11] The intensity of exercise is determined based on the heart rate (HR) percentage, the maximum work capacity (MC), and the maximum oxygen volume (VO2max) of the muscles. Based on HR, MC, and VO2max, exercise intensity is classified as mild (0%–50%), moderate (50%–70%), submaximal (70%–85%) and maximal (above 85%). The time aspect refers to the duration of the exercise. The exercise times are divided into two types: continuous and interval. Continuous exercise is carried out without any rest breaks, while interval exercise is carried out according to the duration of time intensity but with the presence of rest times.[12]

In this study, moderate-intensity exercise is used. The chosen moderate-intensity exercise is swimming because it has minimal injury, moves all limbs, and the entire body weight is held by water. The goal of moderate-intensity exercise is to increase the maximum volume of oxygen in the body so that more oxygen is distributed throughout the body. This results in good tissue oxygenation. Good oxygenation of the injured tissue is one of the determinants of wound healing. [9,10]

Several studies have shown that exercise accelerates wound healing after tooth extraction. In previous studies, the wound healing process after tooth extraction was accelerated by increasing the number of fibroblasts, neovascularization, polymorphonuclear (PMN) and macrophages.[13,14] There are still shortcomings because some of the cells that are in the maturation stage of the healing process have not been studied, namely the density of collagen. Due to this, the researchers wanted to prove the role of continuous moderate-intensity exercise in increasing collagen density in the tooth sockets of Wistar rats (*Rattus norvegicus*) after tooth extraction.

MATERIALS AND METHODS

The type of research carried out is pure experimental research (true experimental) based on experimental animals. The research design used was post-test only control group design. Ethical approval was obtained from the Ethics and Law Committee of the Faculty of Dental Medicine, Airlangga University, Surabaya (434/HRECC.FODM/VII/2019).

This study used male Wistar rats (*Rattus norvegicus*) for the sample. The minimum sample size required for each group was seven rats. The total sample size in this study was 28 rats. Simple random sampling was used to select the experimental Wistar rats from the population.

Wistar rat sample inclusion criteria included: body weight of 250–300 grams, healthy and active, good condition (glossy fur, clear eyes, and non-soft textured faces), and about 8–12 weeks old before adaptation. Exclusion criteria included: more than 10% weight loss after adaptation period, anatomical abnormalities (dull hair, hair loss or baldness, inactivity, and abnormal exudate from mouth, anus and eyes), pain, and death during the study.

Before the experiment was conducted, the mice were adapted for seven days in the cage for the acclimatization process. Mice were adapted in cages made of plastic with sufficient air and light. Wood shavings were placed at the bottom of the cages to maintain cleanliness and optimal temperature. The rat cages were covered with wire gauze so that the rats did not escape and the air remained well-circulated. During the acclimation process until the end of the treatment, the rats were given food and drink with the type and dose according to the rat's body weight. Rats were fed pellets of 5 grams per day per 100 grams of body weight and given 8 ml of distilled water per day per 100 grams of body weight. If any mice died or were sick, they were excluded from the study.[13] To determine the load needed for reach rat, body weight was measured using a Torbal scale. Body weight measurements were carried out before the acclimatization process and before treatment.[13]

Measurement of maximum working capacity (MWC) in the control group and treatment group was carried out by placing each rat in a bucket filled with clean water. In the control group, the rats swam without using a load, while the rats swam with an additional weight of 3% of their body weight in the treatment group.[15] Measurement of MWC was calculated from the time the rat swam until the rat began to sink (i.e., air bubbles appeared) or stopped swimming; the time was recorded as the MWC of the observed group of rats. The purpose of measuring MWC was to determine the duration of exercise for each group. The treatment time of the control group and treatment group was 50% of the MWC. Measurement of MWC was completed before treatment in the first and second weeks.[16]

The experimental animal samples of Wistar rats were divided into four groups in this study. Group 1 (K1), a control group, was not given any exercise treatment and the collagen density was observed on the third day after tooth extraction. Group 2 (K2), a control group, was not given any exercise treatment and the collagen density was observed on the seventh day after tooth extraction.

DOI: 10.20473/j.djmkg.v57.i1.p38–44

Group 3 (K3) was given continuous moderate-intensity exercise treatment and collagen density was observed on the third day after tooth extraction. Group 4 (K4) was given continuous moderate-intensity exercise treatment and collagen density was observed on the seventh day after tooth extraction.

Rats in the control groups (K1 and K2) were immersed in a bucket filled with shallow clean water for a duration of 50% of the MWC, every day for 14 days. The goal was to expose the rats to water while allowing their feet to touch the bottom of the bucket so that they would not swim. Rats in the treatment groups (K3 and K4) completed continuous moderate-intensity exercise by swimming in a bucket filled with clean water with a depth of 100 cm, which was carried out every day for 14 days. Mice swam for a duration of 50% of the MWC and were given an additional load of 3% of the rat's body weight. The load was in the form of a paper clip tied with a thread and then placed on one-third of the base of the rat's tail. Exercise in the treatment group was carried out continuously (without rest).[15]

At the beginning of week 3, in all groups, rats were given anesthesia using an intramuscular injection containing ketamine with a concentration of approximately 3.6 ml and xylazine with a concentration of approximately 1.2 ml. After being given anesthesia, the rats waited until they looked weak.[17] The rats then had their mandibular incisors removed using pliers and irrigated using Aqua Dest to remove debris or remnants of tooth extraction.[13]

On the third day after the extraction, the rats in groups K1 and K3 were euthanized using sodium pentobarbital, and then the mandibles in the region of the extracted teeth were taken from the rats. The mucosal tissue around the extraction wound was taken for histological examination of collagen density. Rats that had been sacrificed were then buried.[17] On the seventh day after extraction, the process was repeated with rats in groups K2 and K4.[13]

Preparations began with cutting the lower left jaw of the rat as big as a tooth socket after tooth extraction by including the surrounding normal tissue. After cutting the left mandible of the rat, it was fixed using formalin buffer to maintain the structure and components of the cell. The decalcification process uses an ethylene diamine tetra acetic acid decalcification solution with the aim of slowly withdrawing calcium from bone specimens. The comparison between the network solution is 1:20 with an immersion time of 24 hours. Samples were processed using an auto technicon for 21 hours.

Researchers then proceeded with the network process technique using the paraffin method. Paraffin blocks containing tissue were cut to a thickness of 5 µm using a microtome. The pieces were carefully placed in a bath with a temperature below the melting point of paraffin. After that, they were placed on slides that had been smeared with egg with glycerine, which functions as an adhesive. Glass slides containing a tissue were arranged in a special rack and then put in an oven (60°C) within 30 minutes. Masson's Trichrome was used to paint tissue preparations.[17]

The collagen preparation was divided into five visual fields and counted for each visual field. The criteria for histological assessment of collagen fibers were based on the distribution and density of collagen fibers because collagen fibers in connective tissue are irregular. The assessment was converted to a score of 0 to 4 (semiquantitative) and carried out based on the following criteria: (-): 0 (no picture of collagen fibers visible), (+): 1 (collagen fibers appeared to be very thin/very small), (++): 2 (collagen fibers appeared to be thinly spread), (+++): 3 (collagen fibers looked thickly spread), and (++++): 4 (collagen fibers looked like thick clumps). The calculation of collagen density in this study was used to compare the control group with the treatment group.[18]

The data were analyzed statistically using SPSS 19. One-way ANOVA test was used for analysis between the four groups. Post Hoc Tukey test was used for different analyses between the four groups.[19]

RESULTS

Research on differences in collagen density after tooth extraction was carried out on 28 male Wistar (*Rattus norvegicus*) rats aged 8–12 weeks with a body weight of 250–300 grams. The results showed that the highest mean collagen density was in the treatment group on day 7 (K4; 3.8 ± 0.42), while the lowest mean collagen density was in the control group on day 3 (K1; 2.2 ± 0.63; Figure 1). This shows that there was an increase in the average collagen density in the treatment group that had been given continuous moderate-intensity exercise compared to the control group without exercise.

In this study, collagen density was observed through histopathological anatomy (HPA; Figure 2). HPA images show different collagen densities in each group. The control group on day 3 (K1) showed thin collagen fibers, the control group on day 7 (K2) showed collagen fibers that seemed to spread thinly, the treatment group on day 3 (K3)

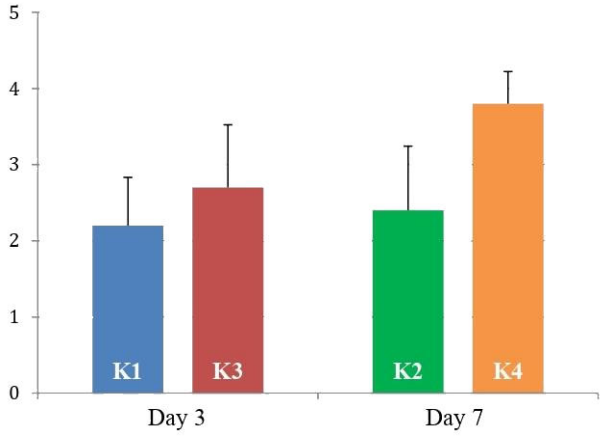

Figure 1. The mean of collagen density in the control and treatment groups on days 3 and 7.

DOI: 10.20473/j.djmkg.v57.i1.p38–44

showed collagen fibers that seemed to spread thickly, and the treatment group on day 7 (K4) showed collagen fibers that were thickly clumped together.

The one-way ANOVA test results showed a significant difference for each group (p = 0.000; Table 1). Using the Post Hoc Tukey test, the results showed a significant difference between the control group on day 3 (K1) and the treatment group on day 7 (K4; p = 0.000), the control group on day 7 (K2) and the treatment group on day 7 (K4; p = 0.000), and the treatment group on day 3 (K3) and the treatment group on day 7 (K4; p = 0.001; Table 2).

DISCUSSION

The prevalence of dental and oral problems in Indonesia has increased every year, and a problem that often occurs is that cavities are not treated and patients ask for the tooth to be extracted. Any tooth extraction that is not ideal can cause subsequent problems, one of which is a lengthy wound healing period. A long wound healing period can result in various complaints from the patient, so efforts are needed to accelerate wound healing.[5] Efforts were made in this study to accelerate wound healing in the oral cavity, namely

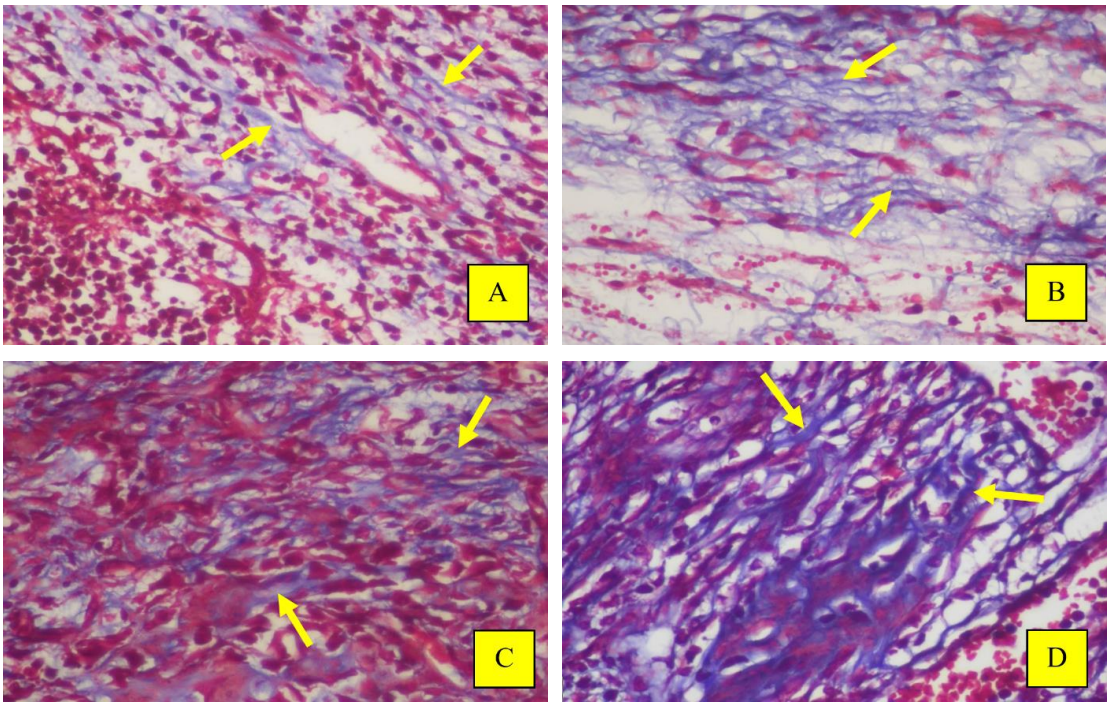

Figure 2. Collagen fibers in the socket of the excised mandibular incisor of Wistar rats with Masson's Trichrome staining with 400x magnification in the control group. (A) third day of control, (B) seventh day of control, (C) third day of treatment, (D) seventh day of treatment.

Table 1. Results of the one-way ANOVA test

Group	n	Mean ± SD	Significance (p)
Day 3 control (K1)	7	2.2 ± 0.63	0.000*
Day 7 control (K2)	7	2.4 ± 0.84	
Day 3 treatment (K3)	7	2.7 ± 0.82	
Day 7 treatment (K4)	7	3.8 ± 0.42	

Note: * significant

Table 2. Results of the Post Hoc Tukey test

Group	K1	K2	K3	K4
K1		0.528	0.120	0.000*
K2			0.345	0.000*
K3				0.001*
K4				

Note: * significant

DOI: 10.20473/j.djmkg.v57.i1.p38–44

through exercise. One determinant of the speed of the wound healing process is tissue oxygenation, which must be sufficient so that, through exercise, the maximum amount of oxygen volume in the body can be increased.[9,10]

There are many factors that can affect wound healing. Wound healing begins when the tissue is injured. Healing time depends on several factors in the wound healing process, with angiogenesis being one of the most important. The growth factor that stimulates angiogenesis and vasculogenesis is vascular endothelial growth factor (VEGF). In hemostasis and inflammation phases, some cells will produce VEGF, which can accelerate the wound healing process.[16] Wound healing occurs in the proliferation phase, and several vital processes are related to studying the number of fibroblasts and neovascularization. Macrophage cells found in the inflammation phase secrete matrices and growth factors to stimulate angiogenesis and fibroplasia. The processes of angiogenesis and fibroplasia go hand-in-hand and synergize to form a layer of epithelium and collagen, which is a sign of the final phase of wound healing or remodeling.[11]

Wound healing can be inhibited by several factors. Malnutrition and vitamin C deficiency can interfere with collagen synthesis and protein deficiency.[20] Aging can decrease liver function so that the synthesis of clotting factors is disrupted, the inflammatory response is slow, circulation to the wound area is impaired, there is a decrease in the formation of lymphocytes and antibodies, and less elastic scar tissue is formed. Low oxygen pressure in the arteries can cause disruption of collagen synthesis and epithelial formation so the necessary level of oxygen in tissues is not met.[21] Poor blood supply to the wound area can inhibit the delivery of oxygen, vitamins, minerals, and amino acids to the wound area. Hypoxia can inhibit mitosis in migrating epithelial cells and fibroblasts, collagen synthesis, and the ability of macrophages to play a role in destroying ingested bacteria.[20] Sudden unexpected stress on the wound can inhibit the formation of endothelial cells and collagen tissue.[21]

Wound healing is generally categorized into four stages: hemostasis, inflammation, proliferation, and maturation (remodeling).[11] It begins with the hemostatic stage, where bleeding occurs, which can trigger the formation of clotting by platelet cells. It is followed by the inflammatory stage, characterized by PMN migration to the wound site, which is facilitated by transforming growth factor-β (TGF-β) to clean wounds contaminated with bacteria and dead tissue. Macrophages continue the process of cleaning wounds contaminated with bacteria and produce several growth factors (Interlukin-1 (IL-1), Interlukin-6 (IL-6), Tumor necrosis factor-α (TNF-α), TGF, and Platelet-derived growth factor (PDGF)). Next is the proliferation stage (fibroblast), which aims to establish a balance between scar tissue formation and tissue regeneration. Cytokine response and growth factors released by inflammatory cells cause matrix-producing fibroblasts to migrate to the wound area. Fibroblasts synthesize a new extracellular matrix and immature type III collagen. Stimulated fibroblasts also produce growth factors. Last is the maturation (remodeling) stage of the granulation tissue, which forms a new epithelial layer and strengthens the wound surface. Fibroblasts and capillary tissue begin to disappear, and then molecular cross-linking degrades, resynthesizes, and reorganizes the collagen matrix into scar tissue. Type III collagen is then replaced by type I collagen. Serine proteases and matrix metalloproteinases, under the control of regulatory cytokines, regulate scar tissue collagen homeostasis.[22–25] This study included the proliferative stage.

Moderate-intensity exercise can increase the activity of the sympathetic system so that heart muscle contractions increase over time. This results in an increase in the rate of blood flow to all cells of the body, including the extraction socket. The blood carries nutrients, electrolytes, and oxygen, and, therefore, moderate-intensity exercise can increase the uptake of oxygen by the tissues due to an increase in blood capacity. The main role of the cardiovascular system during exercise is to distribute oxygen and nutrients to the muscles that contract during exercise. This is what causes blood flow to the muscles to increase dramatically during exercise.[26,27]

If there is a wound, the increased blood flow can help deliver oxygen, vitamins, minerals, and amino acids to the wound area, with the aim of accelerating wound healing. If the blood flow is disrupted, it will cause the supply of oxygen that is channeled through the bloodstream to decrease, resulting in hypoxia in the tissue, which will interfere with the wound healing process. Tissue hypoxia will further inhibit mitosis in migrating epithelial cells and fibroblasts, collagen synthesis, and the ability of macrophages to play a role in destroying ingested bacteria.[28]

Collagen is important for wound healing. Collagen is the main protein in the components of the extracellular matrix. The synthesis of collagen and fibroblasts in wound healing requires oxygen. Oxygen is an important co-factor during the hydroxylation of proline and lysine in the process of procollagen formation. The formation of collagen in the wound healing process is influenced by pressure, infection, stress, pain, nutrition, the process of phagocytosis, oxygen diffusion, oxygen in the tissues around the wound, and genetic factors in each individual (host factors). Adequate oxygen supply to the wound area will help the process of collagen synthesis in wound healing.[29,30]

Eighteen varieties of collagen are known, each with a specific function. The primary structural protein in tendons and skin is type I collagen, which also comprises more than 90% of the protein in the bone matrix.[26] Type II collagen functions to form fibrillar tissue and is necessary for the hypertrophy and differentiation of chondrocytes. In cartilage tissue, type III collagen controls the biomechanics and fibril structure of collagen.[31] Collagen type IV is arranged into a mesh-like network, one example being the basal lamina of the epithelium.[32] Through stimulation of chondrocyte proliferation, functions of collagen type VI increase cartilage regeneration. The fibrillar collagen

DOI: 10.20473/j.djmkg.v57.i1.p38–44

tissue in cartilage is stabilized and regulated by type IX collagen. Endochondral ossification and mesenchymal stem cell cartilage depend on type X collagen, which controls matrix mineralization in endochondral ossification. Type XI collagen helps to create a network that offers mechanical resistance, homeostasis, and stabilization of the cartilage matrix.[31]

The main collagens in wound healing are types I and III.[24] Collagen functions as an extracellular matrix in the wound area. This helps the process of adhesion, migration, and proliferation of cells in the matrix. Fibroblasts are important in the collagen synthesis process. Collagen begins to form in the proliferative phase. At the beginning of healing, fibroblasts will synthesize collagen types III and V, which are found in connective tissue and blood vessels, but in the remodeling phase (maturation), collagen types III and V are replaced with type I collagen, which is stronger in resisting pressure.[7 19]

The Post Hoc Tukey test results (Table 2) showed that the collagen density in the wound healing process in rats in groups K1 and K2, groups K1 and K3, and groups K2 and K3 were not significantly different. There was an insignificant difference between the K1 and K2 groups because they were not given treatment (exercise), so there was no increase in oxygen supplied to the tissues. Because there is not enough oxygen in the wound area, the process of collagen synthesis in wound healing cannot run quickly. This causes collagen synthesis to run normally without any stimulation that accelerates the process of collagen synthesis. There was no difference in the two groups because of the disruption of the factors that affect collagen formation.

In the K1 and K3 groups, there was an insignificant difference because the formation of type III collagen fibers synthesized by fibroblasts began on the third day. On the third day, the collagen density showed inflammatory cells and erythrocytes that were still scattered around the wound area due to overlapping between the inflammatory phase and the proliferative phase of wound healing. Thus, there was an insignificant difference between the control and treatment groups on the third day. In the K2 and K3 groups, there were no significant differences. In the K2 group, there was no treatment in the form of exercise, so there was not enough oxygen supply to accelerate the process of collagen synthesis in wound healing. In the K3 group, treatment was carried out but observed on the third day; since the formation of type III collagen fibers began on the third day, the collagen fibers were still in the form of inflammatory cells and erythrocytes that were scattered around the wound area.

In this study, the treatment group with continuous moderate-intensity swimming and observation of collagen density on day 7 (K4) had the best wound healing effectiveness when compared to the other groups because it showed the highest collagen density. Furthermore, there was a greater effectiveness of wound healing in the group that was given exercise than the group that was not given exercise. This proves that exercise can increase collagen density and indirectly make the wound healing process more effective. This is in accordance with previous research, which has shown that exercise provides greater benefits for wound healing when compared to those who do not exercise.[32] In conclusion, there was a difference in post-tooth extraction collagen density in rats after continuous moderate-intensity exercise, so continuous moderate-intensity exercise played a role in increasing the density of collagen in the rat tooth socket after tooth extraction.

REFERENCES

1. Ngangi RS, Mariati NW, Hutagalung BSP. Gambaran Pencabutan Gigi Di Balai Pengobatan Rumah Sakit Gigi Dan Mulut Universitas Sam Ratulangi Tahun 2012. e-GIGI. 2013; 1(2): 1–7.
2. World Health Organization. Oral health. 2022. Available from: https://www.who.int/news-room/fact-sheets/detail/oral-health. Accessed 2022 Sep 30.
3. FDI World Dental Federation. The challenge of oral disease – A call for global action. The oral health atlas. 2nd ed. Geneva: FDI World Dental Federation; 2015. p. 17.
4. Karalis M, Pavlidis TE, Psarras K, Ballas K, Zaraboukas T, Rafailidis S, Symeonidis N, Marakis GN, Sakantamis AK. Effect of experimentally induced liver cirrhosis on wound healing of the post-extraction tooth socket in rats. Eur Surg Res. 2008; 40(2): 190–6.
5. Shafer WG, Hine MK, Levy BM. Shafer's textbook of oral pathology. 7th ed. Rajendran A, Sivapathasundharam B, editors. Elsevier; 2012. p. 567–70.
6. Afiyah LL, Medawati A. Efektifitas gel ekstrak Pithecellobium lobatum Benth. pada proses kesembuhan luka pascapencabutan gigi: Studi pada Cavia cobaya dengan pengamatan histologis. Mutiara Med J Kedokt dan Kesehat. 2017; 17(2): 86–91.
7. Xue M, Jackson CJ. Extracellular matrix reorganization during wound healing and its impact on abnormal scarring. Adv wound care. 2015; 4(3): 119–36.
8. Sunarjo L, Hendari R, Rimbyastuti H. Manfaat xanthone terhadap kesembuhan ulkus rongga mulut dilihat dari jumlah sel PMN dan fibroblast. ODONTO Dent J. 2015; 2(2): 17–24.
9. Sen CK. Wound healing essentials: Let there be oxygen. Wound Repair Regen. 2009; 17(1): 1–18.
10. Babalola TK, Abasi UU. Effects of exercise on plasma lactic acid and body temperature in man, following a standardized meal. Bangladesh J Med Sci. 2018; 17(2): 270–4.
11. Oki AS, Alviansyah MF, Khoswanto C, Rahayu RP, Luthfi M. Acceleration of post-tooth extraction socket healing after continuous aerobic and anaerobic physical exercise in Wistar rats (Rattus norvegicus). Dent J. 2020; 53(4): 196–200.
12. Irmawati A, Rachma LA, Sidarningsih S, Hatta MN, Arundina I, Aljunaid M. Exercise as a method to reduce the risk of oral cancer: A narrative review. Dent J. 2022; 55(1): 56–61.
13. Oki AS, Bimarahmanda ME, Rahardjo MB. Increased number of fibroblasts and neovascularization after tooth extraction in wistar rats with moderate-intensity continuous exercise. J Int Dent Med Res. 2018; 11(3): 840–5.
14. Setyadewi W, Oki AS, Sunariani J. Moderate intensity physical exercise effect on PMN and macrophage expression in Rattus norvegicus post tooth extraction. J Int Dent Med Res. 2017; 10(2): 364–7.
15. Irmawati A, Jasmin N, Sidarningsih. The effect of moderate exercise on the elevation of Bax/Bcl-2 ratio in oral squamous epithelial cells induced by benzopyrene. Vet world. 2018; 11(2): 177–80.
16. Irmawati A, Giffari FZ, Oki AS. The effect of moderate exercise on vascular endothelial growth factor expression during tooth socket wound healing after tooth extraction. J Postgrad Med Inst. 2018; 32(1): 19–23.

DOI: 10.20473/j.djmkg.v57.i1.p38–44

17. Rüegg MA, Meinen S. Histopathology in Masson Trichrome stained muscle sections. TREAT-NMD Neuromuscular Network; 2014. p. 1–9.
18. Permatasari N, Handayani MP. Efek jus belimbing (averrhoa carambola linn.) Dalam meningkatkan pembentukan kolagen pada soket pasca pencabutan gigi tikus wistar. Prodenta J Dent. 2013; 1(1): 7–14.
19. Purnomo W, Bramantoro T. Pengantar metodologi penelitian bidang kesehatan. Https://catalog.aup.unair.ac.id/Kedokteran/298-pengantar-metodologi-penelitian-bidang-kesehatan.html, editor. Surabaya: Airlangga University Press; 2018. p. 98–100.
20. Zhafirah R, Nur Aida A, Hirawan H, Wardana T. Wound healing induces VEGF expression stimulated by forest honey in palatoplasty Sprague Dawley. Dent J. 2023; 56(1): 48–52.
21. Potter PA, Perry AG. Buku ajar: Fundamental keperawatan - Konsep, proses, dan praktik. Volume 2. 4th ed. Jakarta: EGC; 2005. p. 1153.
22. Fauzia M, Dewanti AP. The effect of lime (Citrus Aurantifola Swingle) peel extract in periodontal dressings on the number of fibroblasts in the gingival wound healing process. Dent J. 2022; 55(2): 81–7.
23. Primadina N, Basori A, Perdanakusuma DS. Proses penyembuhan luka ditinjau dari aspek mekanisme seluler dan molekuler. Qanun Med. 2019; 3(1): 31–43.
24. Purnama H, Sriwidodo, Ratnawulan S. Proses penyembuhan dan perawatan luka: Review sistematik. Farmaka. 2017; 15(2): 251–8.
25. Hanafiah OA, Hanafiah DS, Syaflida R. The effect of 3% binahong leaf extract gel on the wound healing process of post tooth extraction. Dent J. 2021; 54(2): 57–62.
26. Barrett K, Brooks H, Boitano S, Barman S. Ganong's review of medical physiology. 23rd ed. New York: McGraw Hill Medical; 2010. p. 261–72.
27. Kumarudin A. Pengaruh latihan aerobik terhadap peningkatan volume oksigen maksimal (VO2 Maks) pada remaja usia 18-20 tahun. 2013. p. 1–11.
28. Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE. Schwartz's principles of surgery. 10th ed. New York: McGraw-Hill Medical; 2016. p. 242–6.
29. Prahasanti C, Arini NL, Wulan KD, Hendro OV, Wijaksana IKE, Ulfah N, Kusumawardani B, Hari P, Abullais SS. The expression of BMP4 and FGF2 in Wistar rats (Rattus norvegicus) post application of gourami fish (Osphronemus goramy) collagen. Dent J. 2023; 56(2): 115–21.
30. Wu Z, Korntner SH, Mullen AM, Zeugolis DI. Collagen type II: From biosynthesis to advanced biomaterials for cartilage engineering. Biomater Biosyst. 2021; 4: 100030.
31. Preston RR, Wilson TE. Lippincott's illustrated reviews: Physiology. Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012. p. 48.
32. Patel H, Alkhawam H, Madanieh R, Shah N, Kosmas CE, Vittorio TJ. Aerobic vs anaerobic exercise training effects on the cardiovascular system. World J Cardiol. 2017; 9(2): 134–8.

DOI: 10.20473/j.djmkg.v57.i1.p38–44