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Original Article

Socket Preservation Using a Combination of Propolis Extract and Bovine Bone Graft Towards the Expression of Receptor Activator of Nuclear κB Ligand and Osteoprogerin

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Abstract

Aim: This study was undertaken to comprehend the effect of a combination of bovine bone graft (BBG) and propolis extract on the receptor activator of nuclear κB ligand (RANKL) and osteoprotegerin (OPG) expressions in post-extraction tooth sockets.

Materials and methods: Fifty-six male Cavia Cobayas were divided into eight groups each containing seven subjects. The lower left incisor of each subject was removed prior to four different materials - polyethylene glycol (PEG), propolis extract+PEG, BBG+PEG, and propolis extract+BBG+PEG (combination) being applied to the post-extraction sockets. The laboratory animals were sacrificed at three and seven days. An immunohistochemical examination was subsequently performed to observe the expression of RANKL and OPG using a light microscope at 1000× magnification.

Results: The mean expression of RANKL on the third and seventh days was the lowest in the combination group, while the mean OPG expression on those days was the highest in the combination group. The one-way ANOVA tests conducted on each group produced a p value <0.05 indicating that significant differences existed between certain groups. A Pearson's correlation test conducted on both observation day groups highlighted the opposite correlation of RANKL and OPG.

Conclusions: A combination of propolis extract and BBG effectively upregulates OPG expression and downregulates RANKL expression in the preserved post-extraction socket.

Keywords

bone graft, medicine, OPG, propolis, RANKL

INTRODUCTION

According to Indonesia's Basic Health Research (Riset Kesehatan Dasar/RISKESDAS), oral health problems in 2018 affected 57.6% of Indonesia's population.[1] Such problems often culminate in tooth extraction, while the healing process in the resulting socket induces resorption of the alveolar process, both vertically and horizontally.[2,3]

The initial phase of the healing process is characterized by blood clotting and the migration of inflamed cells which releases cytokines such as the insulin growth factor-I (IGF-I), parathyroid hormone (PTH), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6). These cytokines activate osteoblasts culminating in the expressing of

the receptor activator of the nuclear κB ligand (RANKL). RANKL binds to this receptor activator of nuclear κB (RANK) and initiates osteoclast differentiation, which subsequently resorbs the bone and, on completion of this function, undergoes an apoptotic process. In addition to RANKL, osteoblasts will express osteoprotegerin (OPG), the decoy receptor of RANKL that can inhibit the RANKL-RANK bond in osteoclastogenesis.[4]

The inflammation phase will be followed by a proliferation phase characterized by the rapid formation of new tissue. From the second week after extraction, provisional matrix deposition will be followed by the penetration of the blood vessels, bone forming cells, and projections of the woven bone over a period of several weeks. The final phases consist of bone modeling and bone remodeling. The former is characterized by changes in bone shape due to bone resorption that will affect the alveolar ridge dimension, while the latter constitutes a change, such as the remodeling of woven bone into lamellar bone that leaves the shape of the bone unaltered. Resorption of osteoclasts activities occurs in the socket.[4]

Post-extraction alveolar bone resorption occurs rapidly in the first year but at a slower rate in subsequent years. The first year sees the loss of 25% of bone width, a figure that increases to up to 40% in the third year.[5]

Alveolar bone resorption is unsuitable for prosthodontic treatments. The treatment success rate will be higher if the bone volume is adequate. Prosthodontic treatments require an adequate bone height in order for them to prove effective and have a positive aesthetic outcome. Alveolar bone loss greater than 7 mm potentially complicates prosthodontic treatment[6], which is the reason for clinicians ideally maintaining as much bone height as possible. One treatment is intended to preserve the post-extraction socket to avoid the need for clinicians to undertake more invasive bone augmentation procedures in the future.[7]

Maintaining post-extraction bone dimensions can be achieved through the application of a bone graft, with the xenograft being one of the most frequently used varieties in dentistry. This variety of graft is biocompatible with, and structurally similar to, human bone. Xenograft, the variety most frequently used being bovine xenograft[8], possesses osteoconductive properties with the result that interposition with connective tissue is rare.

Another material used in this study was propolis extract. Propolis is a natural product in the form of a resin collected by honeybees from various plants. Bees use propolis as the material from which to build their nests and render it resistant to bacterial and fungal infection. Propolis not only acts as an anti-microorganism agent, but also as an antioxidant and anti-inflammatory agent. The antioxidant property of propolis is derived from flavonoid and polyphenol, substances that can remove free radicals from tissue, thereby supporting the regulation of RANKL and OPG. The expression of RANKL can be increased, while that of OPG can be decreased due to their sensitivity to the level of oxidative.[9] The chrysin content of propolis can reduce the expression of TNF-α, interleukin-1β (IL-1β), and IL-6. Cytokines perform specific roles in regulating RANKL expression by osteoblasts.[10,11]

Bone remodeling is highly dependent on osteoclast and osteoblast activity. These cells have numerous cell markers that can be studied. RANKL and OPG are important markers in osteoclastogenesis. A study by Arnez et al. describes how RANKL expression increases at 7 and 10 days, while that of OPG increases at 3 and 7 days. In this study, the expression of RANKL and OPG during socket preservation, using propolis extract and BBG combination, was observed on the third and seventh days.[12]

AIM

The present study aimed to comprehend the effect of a combination of BBG and propolis extract on the RANKL and OPG expressions in post-extraction tooth sockets.

MATERIALS AND METHODS

This study has been reviewed and approved by the Ethical Clearance Committee, Faculty of Dental Medicine and issued with approval number 556/HRECC.FODM/VIII/2019.

Animal characteristics

This study involved 56 male Cavia Cobayas, 300–350 grams in weight and 3–3.5 months old, which were divided into eight groups of seven subjects each.

Procedures

Before extraction of their lower left incisors, the animals were anesthetized by means of a 0.2-cc/300-g dose of ketamine. Following extraction, the sockets were filled with different materials according to the group. Suturing was performed using polyamide monofilament. These laboratory subjects were observed on the third and seventh days after application of the materials to the interior of the post-extraction sockets.

These subjects were divided as follows: groups 1 and 2 (controls), the post-extraction socket received 25 g of polyethylene glycol (PEG); groups 3 and 4, the post-extraction socket was administered with 0.5 g of propolis extract and 24.5 g of PEG; groups 5 and 6, the post-extraction socket was given 0.5 g of BBG and 24.5 gram of PEG; and groups 7 and 8, the post-extraction socket received 0.5 g of propolis extract, 0.5 g of BBG, and 24 g of PEG. Groups 1, 3, 5, and 7 were observed on the third day, while groups 2, 4, 5, and 8 were monitored on the seventh day.

Immunostaining observation

The research subjects were sacrificed, and their mandibles removed and decalcified using ethylene diamine tetra acetate (EDTA) for a period of two months. The soft mandibles were made into paraffin blocks, which were subsequently cut using a microtome (4 μ) to make immunohistochemistry slides. After deparaffinization, the slides were stained using monoclonal RANKL antibodies (12A668, Novus Biologicals, dilution 1:200) and OPG (98A1071, Novus Biologicals, dilution 1:200). The RANKL and OPG expression in the osteoblasts were observed under a light microscope at magnification 1000× and from 20 visual fields.

Statistical analysis

The data generated by this experiment were statistically analyzed using a Statistical Package for Social Science (SPSS) version 23.0 (IBM Corporation, Illinois, Chicago, United States). A One-way ANOVA and Tukey HSD were employed to analyze the RANKL and OPG expression.

RESULTS

The highest means of RANKL expression in the third- and seventh-day observation groups occurred in the control groups followed by the propolis extract groups, the BBG-groups and, finally, the propolis extract-BBG combination groups. The highest means of OPG expression in the third- and seventh-day observation groups were found in the propolis extract-BBG combination groups, followed by the BBG groups, the propolis extract groups, with the lowest means occurring in the control groups **(Fig. 1)**.

The statistical test conducted during this experiment was a Shapiro-Wilk normality test, the result of which confirmed that the data was distributed normally ($p>0.05$). A subsequent one-way ANOVA test whose significant value was <0.05 indicated significant differences between certain groups. Consequently, a Tukey HSD test was conducted to identify the significant differences between each group. The picture of OPG and RANKL expressions in this experiment was obtained using a light microscope from 20 visual fields **(Fig. 2)**.

The statistical analysis of RANKL and OPG correlation shows that there are significant correlations between these two markers in both the third and the seventh day observation groups (Sig. (2-tailed) <0.05). The third day observation group sig. (2-tailed) value was 0.010, while the seventh day observation group sig. (2-tailed) value was 0.000. A negative Pearson's correlation value means that the subjects have an inverse relation. On the third observation day, the Pearson's correlation value (r) was −0.480, signifying a moderate significant inverse correlation between RANKL and OPG. On the seventh observation day, the Pearson's correlation value (r) was −0.665, which means that there was a strong significant inverse correlation between RANKL and OPG.

DISCUSSION

The majority of tooth extractions will lead to significant resorption of the alveolar bone, which occurs because of the post-trauma healing process. Fifty percent of ridge width will be loss.[4,13] Excessive amounts of bone loss will complicate prosthodontic treatment with the result that clinicians must invest considerable effort in preserving the alveolar bone. Socket preservation can be undertaken using bone graft to maintain bone dimension and avoid future invasive bone augmentation.[7]

In this study, bone graft was combined with propolis extract as the socket preservation material. BBG is a type

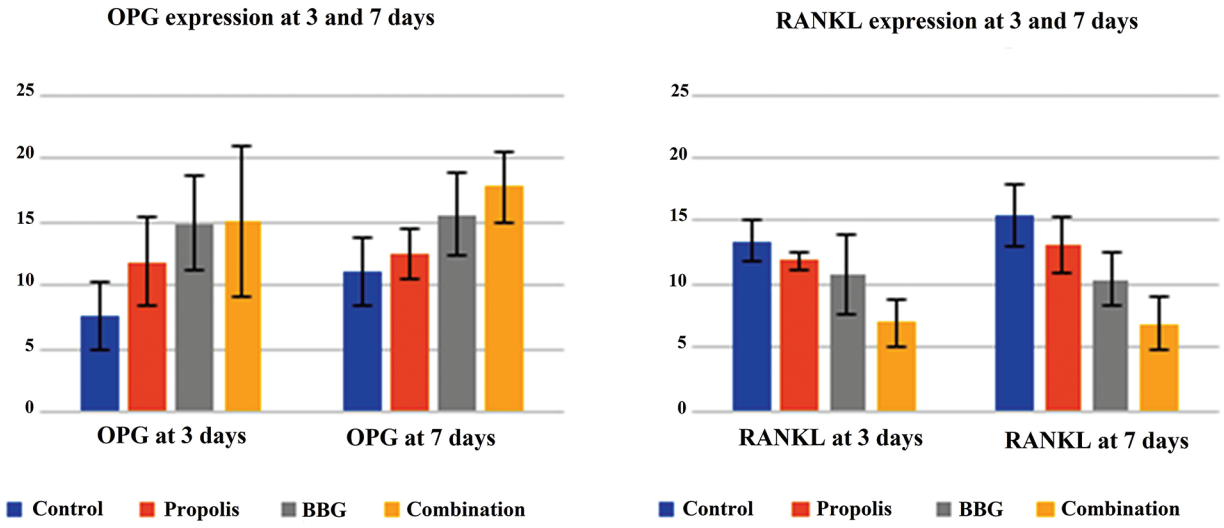

Figure 1. Chart describing mean numbers and standard deviations of RANKL and OPG expressions on the third and seventh days of study.

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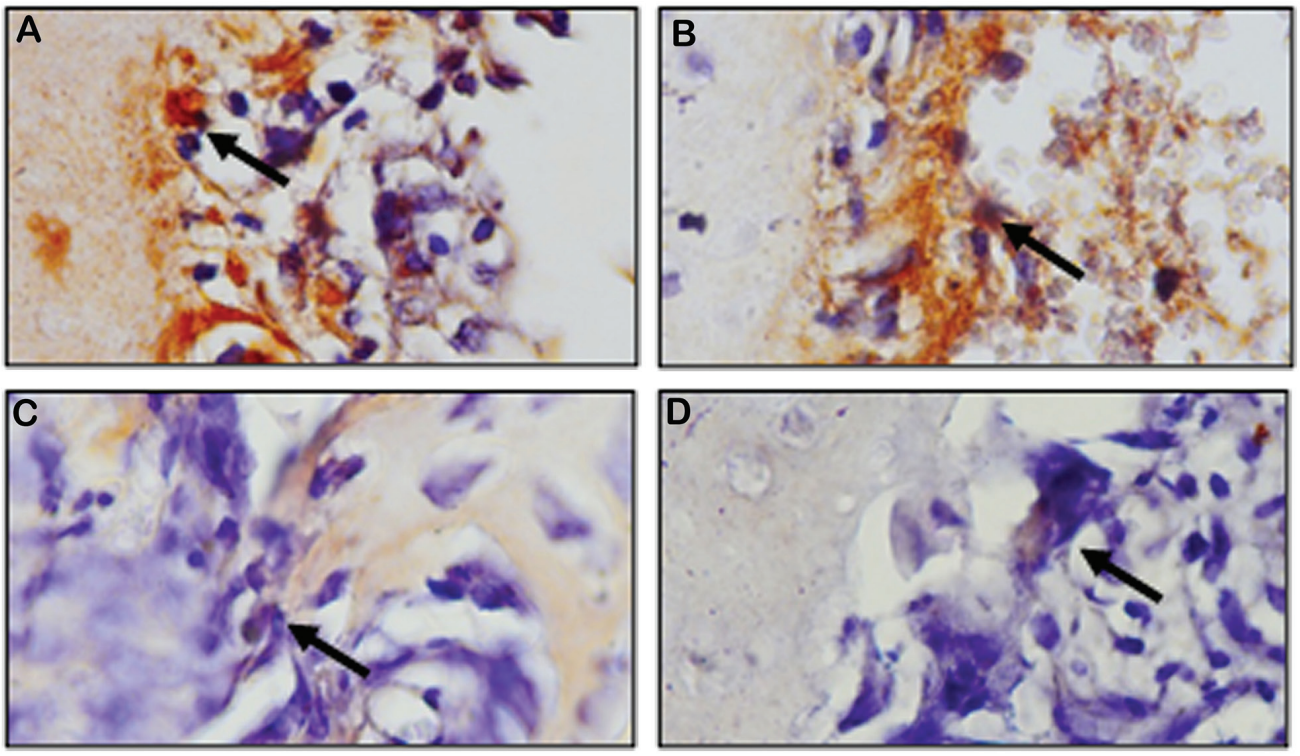

Figure 2. (**A**) RANKL expression on the third day; (**B**) OPG expression on the third day; (**C**) RANKL expression on the seventh day; (**D**) OPG expression on the seventh day. The black arrows indicate the expression of RANKL in (**A**) and (**C**); expression of OPG in (**B**) and (**D**).

of xenograft often used in dentistry due to its relatively greater availability and promotes osteoconductive activities[8,14], while propolis extract has anti-inflammation, anti-microorganisms, antioxidant, and immunomodulator properties.[15] This combination is expected to accelerate the bone healing process.

RANKL and OPG are important factors in bone healing which play essential roles in osteoclastogenesis. RANKL will bind to RANK, thereby inducing the osteoclastogenic process. The RANK-RANKL bond will initiate osteoclast precursor differentiation to become mature osteoclast, stimulate bone resorption capacity, and reduce osteoclast apoptosis. In this process, OPG acts as an inhibitor, preventing RANKL from binding to RANK by binding to RANKL.[16]

The mean values of RANKL and OPG were observed on the third and seventh days. On each occasion, the lowest mean of RANKL occurred in the propolis extract-BBG combination groups, followed by the BBG groups, then the propolis extract groups, while the highest mean was in the control group. The mean values of OPG were the opposite of those of RANKL. The lowest number occurred in the control groups, followed by the propolis extract group, while the highest number was in the group where a combination of propolis extract and BBG was applied to the post-extraction socket.

Bone graft is a material often employed to substitute for lost bone mass. Bone tissue demonstrates regenerative capability and can grow into the site provided by the graft. There are various types of bone graft such as autograft, allograft, xenograft and alloplast, although autograft is the gold standard in the field of dentistry. However, autograft requires an additional surgical site in order for the graft material to be obtained. Consequently, xenograft is used in this study due to its greater accessibility, osteoconductive properties, and structural similarity to human bone. Osteoconductivity in xenograft can support new bone growth inside the graft, with the result that interposition of connective tissue rarely occurs. Bovine bone graft is the most widely employed type of xenograft in dentistry.[8,14,17]

The propolis extract used in this study was obtained from Lawang, East Java. It contained caffeic acid (2.56%), apigenin (1.05%), flavonoid (1.28%), saponin (0.82%), quercetin (1.03%), and terpenoid (1.15%) which account for its anti-microorganism, anti-tumor, anti-oxidant, immunomodulatory, and anti-inflammatory properties.[10,15,18] Apigenin and quercetin constitute flavonoid derivatives. Each constituent element within the Lawang propolis extract possessed the ability to downregulate proinflammatory cytokines such as IL-1β, IL-6, and TNF-α, while also upregulating anti-inflammatory cytokines. Apigenin and caffeic acid also demonstrate the ability to inhibit osteoclastogenesis by deactivating nuclear factor kappa light chain enhancement.[19,20]

The healing process is initiated by the hemostatic phase followed by the inflammation phase during which numerous proinflammatory cytokines are produced. This phase happens on the second and third days after extraction and

is characterized by inflammatory cell migration. The residual cells and the product of the inflamed cell-induced apoptotic process will be phagocyted by macrophages. Proinflammatory cytokines such as IL-1β, IL-6, and TNF-α will be produced by macrophages and mast cells. Macrophages emerge in the late inflammation phase 48-72 hours after extraction and will be retracted to the wound area by chemoattractant agents such as cytokines.[4]

In osteoclastogenesis, proinflammatory cytokines execute important roles. For example, TNF-α, IL-6, and IL-1 can upregulate osteoclasts formation by upregulating the production of RANKL and M-CSF and increasing the responsivity of osteoclast precursors to RANKL. RANKL plays the role of stimulating preosteoclast differentiation, the attachment of osteoclasts to bone tissue, and, subsequently, the activation and longevity of osteoclasts. The TNF-α that is released by activated macrophages can upregulate the production of proinflammatory cytokine and also RANKL by osteoblasts.[16,21]

In addition to RANKL, osteoblasts regulate OPG expression. The analysis conducted in this study shows that RANKL expression had a significant negative correlation with OPG expression in the third- and seventh-day observation groups. Negative correlation means that RANKL and OPG have an inverse relation to each other. Similar to the results of other studies, this research found that when RANKL expression increases OPG expression will decrease relatively or, at least, OPG induction will be reduced, and vice versa. These processes can cause changes in the RANKL/OPG ratio during osteoclastogenesis.[21]

Proinflammatory cytokines (TNF-α, IL-1β, and IL-6) are ones that can induce osteoblasts to upregulate RANKL expression. If the expression of these cytokines is suppressed by the characteristics in propolis extract, RANKL expression by osteoblast will decrease. Most of the factors that induce RANKL expression by osteoblasts will also regulate OPG. The upregulation of RANKL expression with the help of cytokines will also downregulate OPG expression.[22] Therefore, the decreasing degree of RANKL expression by osteoblasts in this study will also be followed by an increase in OPG expression.

This study not only observed the mean number but, in addition, compared each group using the Tukey HSD test by means of which the significant differences in each group were located. RANKL expression on the third observation day showed that there were significant differences between the combination (propolis extract-BBG) group and the other three groups. This indicated that BBG, with its osteoconductive properties, and propolis extract, with its anti-inflammatory and antioxidant properties, worked together and decreased the number of RANKL expression on the third observation day, which was the first peak of RANKL expression.[23]

The OPG expression in the third day observation group showed significant differences between the control group and the BBG group; the control group and the combination (propolis extract and BBG) group. A nonsignificant difference was found between the combination (propolis extract and BBG) group and the BBG group; as well as the combination group and the propolis extract group. This might be because the peak OPG expression occurred on the first and seventh days after the bones had been injured. Therefore, the result for the third day observation group showed some insignificant differences.[23] The peaks of RANKL expressions occurred on the third and fourteenth days, while those relating to OPG expressions manifested themselves on the first and seventh days after the wound had occurred. This study was conducted to observe RANKL and OPG expressions on the third and seventh days in order that they could be observed at their peak times.[12,23]

RANKL and OPG expressions observed on the seventh day demonstrated the same results in terms of which groups had significant differences compared with other groups. The significant differences occurred between the control groups and the BBG groups; the control groups and the combination groups; as well as the propolis extract groups and the combination groups. Apart from these groups, the results indicated no significant differences between the combination groups and the BBG groups; the propolis extract groups and the control groups; or the propolis extract groups and the BBG groups. There were no significant differences between the BBG groups and the combination groups in terms of RANKL expression on the seventh day, which may have been due to the fact that it was not supposed to be the peak of RANKL expression day. Moreover, the process may have happened earlier because the anti-inflammation effect of the propolis extract can accelerate the inflammation process. That is why the result was significant on the third observation day. OPG expression also demonstrated an insignificant difference on the seventh day possibly because it constitutes the second peak of OPG production. Therefore, there is a possibility that the peak of OPG expression in this study happened on the first day with the result that it produced an insignificant result on the seventh day.[23,24]

In accordance with a number of earlier studies, the application of immunomodulatory and anti-inflammatory agents from the propolis extract in this study can decrease the magnitude and duration of inflammation. In cases of the overactivation of inflammatory cells, the healing process will be compromised. Proinflammatory cytokines released by macrophages can exacerbate the inflammatory reaction. Therefore, they need to be temporarily suppressed in order to promote more rapid healing.[24]

Certain results indicate that there are insignificant differences between the combination group and the BBG group. However, the means may show a contrasting situation. For example, the means still indicate that BBG groups have a lower level of RANKL expression and a higher degree of OPG expression when compared to the combination groups. Bone remodeling is a complex process influenced by various factors. Osteoclastogenesis, in which RANKL and OPG play important roles, is only one of the factors that influence it. For this reason, observation

of other factors and markers is required in order to understand the entire bone remodeling process.[4]

The results of this study concur with those of the research conducted by Kresnoadi et al. in 2020 and Lunardhi et al. in 2019, which stated that the combination group (BBG and propolis extract) show the highest mean number of osteoblasts and lowest mean number of osteoclasts on the third and seventh days. Kresnoadi et al. asserted that the combination of natural propolis extract and BBG can increase HSP70 expression, osteocalcin, as well as the number of osteoblasts, while decreasing the number of osteoclasts.[25] The RANKL and OPG values obtained in this study parallel the number of osteoblasts and osteoclasts resulting from previous studies. The decreasing expression of RANKL and increasing expression of OPG after application of BBG-propolis extract combination as a socket preservation material will help OPG bind to RANKL with the result that RANKL cannot bind to RANK. This will inhibit the initiation of osteoclast precursor differentiation.[25,26] By impeding the process of osteoclastogenesis, it is anticipated that the healing process may occur more rapidly resulting in minimal bone resorption.

CONCLUSIONS

Based on the experiment conducted during this study, it can be concluded that the combination of propolis extract and BBG effectively upregulates OPG expression and downregulates RANKL expression in the preserved post-extraction-socket.

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Competing interests

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Сохранение лунки с использованием комбинации экстракта прополиса и бычьего костного трансплантата для экспрессии рецепторного активатора ядерного κB-лиганда и остеопрогерина

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Резюме

Цель: Это исследование было предпринято, чтобы понять влияние комбинации бычьего костного трансплантата (BBG) и экстракта прополиса на экспрессию рецептора-активатора ядерного лиганда κB (RANKL) и остеопротегерина (OPG) в лунках зубов после удаления.

Материалы и методы: Пятьдесят шесть самцов морской свинки Cavia Cobayas были разделены на восемь групп, в каждой из которых было по семь субъектов. Нижний левый резец каждого субъекта был удалён перед тем, как на лунки после экстракции были нанесены четыре различных материала – полиэтиленгликоль (PEG), экстракт прополиса + PEG, BBG + PEG и экстракт прополиса + BBG + PEG (комбинация). Лабораторных животных умерщвляли через три и семь дней. Впоследствии было проведено иммуногистохимическое исследование для наблюдения за экспрессией RANKL и OPG с использованием светового микроскопа при 1000-кратном увеличении.

Результаты: Средняя экспрессия RANKL на третий и седьмой дни была самой низкой в группе комбинации, тогда как средняя экспрессия OPG в эти дни была самой высокой в группе комбинации. Односторонние тесты ANOVA, проведенные в каждой группе, дали значение $p<0.05$, что указывает на наличие значительных различий между определёнными группами. Корреляционный тест Пирсона, проведённый в обеих группах обсервационного исследования, выявил противоположную корреляцию RANKL и OPG.

Заключение: Комбинация экстракта прополиса и BBG эффективно усиливает экспрессию OPG и подавляет экспрессию RANKL в сохранившейся лунке после экстракции.

Ключевые слова

костный трансплантат, лекарство, OPG, прополис, RANKL