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Comparison of the effects of fluoxetine and venlafaxine on bone healing in a rat calvarial defect model

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ABSTRACT

Objective: The purpose of this study was to compare the effects of the selective serotonin reuptake inhibitor (SSRI) fluoxetine and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine on bone defect healing.

Materials and Methods: Wistar rats were randomly divided into three groups of eight animals each. The first received 0.1 ml/kg sterile saline solution, the second 5 mg/kg fluoxetine, and the third 5 mg/kg venlafaxine, daily by gastric gavage over 7 weeks. At week 3 of drug therapy, 5-mm diameter calvarial defects were created in the parietal bone of all of the animals. All rats were euthanized four weeks after surgery, micro-CT analysis and histomorphometric analysis were carried out to evaluate the following parameters: Bone volume fraction (BV/TV), bone surface (BS), bone surface density (BS/BV; bone surface/bone volume, 1/mm), trabecular number (Tb. N), trabecular thickness (Tb. Th), areas of new bone structure (positive areas), areas of mature bone structure (negative areas).

Results: Micro-CT analysis showed the presence of similar levels of bone formation within the defect site in all three groups ($p>0.05$). Histomorphometric analysis revealed the presence of bone-forming cells at the defect periphery, with less activity indicating bone formation at the center. No statistically significant difference was observed between the groups ($p>0.05$).

Conclusion: Based on the findings of this study, it can be said that the use of both antidepressants hasn't any effect on bone defect healing.

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Introduction

Depression is a widespread, chronic disease seen among individuals of all ages, and a debilitating psychiatric disorder resulting in significant social and economic burdens. It impacts sufferers' thoughts, behavior, emotions, and physical health. More than 320 million individuals suffer from depression worldwide, the lifetime prevalence being as high as 20% [1]. Antidepressant drugs are an essential component in the treatment of depression [1,2]. The majority of antidepressants exert their therapeutic effects through three mechanisms; the prevention of biogenic monoamine reuptake from the synaptic cleft into presynaptic neurons, the antagonization of the presynaptic receptors, and the suppression of monoamine oxidase [1]. Second-generation antidepressants, represented by selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), have become the globally most widely prescribed classes of antidepressants. Their discovery ushered in a new era in the pharmacotherapy of depression, since they are more potent and entail a lower likelihood of adverse drug reactions than first-generation antidepressants with their poor tolerability profiles [1,3]. SSRIs selectively prevent serotonin reuptake through suppression of serotonin transporters, resulting in an increase in active serotonin concentrations in the synapses. SNRIs possess the ability to specifically inhibit the neuronal reuptake, not solely of serotonin, but also norepinephrine, into presynaptic neurons, thus extending the presence of these monoamines within the synaptic cleft [1].

Bone healing, a highly regulated process, entails both osteoblast-mediated bone healing and osteoclast-mediated bone resorption. Any factor that affects these cycles may modify the rate at which bone healing occurs [4]. Previous studies reported that pharmacological agents or drugs can be highly effective in

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bone healing [4,5]. Antidepressants appear to affect bone architecture appears primarily through the serotonergic pathways. Some serotonin (5-hydroxytryptamine; 5-HT) receptor subtypes, including the serotonin transporter (5-HTT), have been detected in osteocytes, osteoblasts, and osteoclasts [6,7]. While some studies have suggested that drugs that affect serotonin, such as SSRIs, downregulate osteoblast activity, thus gradually reducing bone mineral density and increasing the risk of fractures due to falls or other factors [8], and that drugs affecting norepinephrine, such as SNRIs, may play a role in osteoblast activity and lead to a decrease in bone density by increasing bone resorption [9], other studies have proposed that they exhibit no such effects [10]. Roumestan et al. [11] demonstrated that fluoxetine exhibits anti-inflammatory activities that lower cytokine levels in such inflammatory diseases as rheumatoid arthritis, thus obviating bone loss.

Concern that antidepressant use may adversely affect the recovery period following an injury or iatrogenic orthopedic surgery heightens the importance of future studies on this subject. Understanding this effect is of clinical significance for dentists and orthopedic surgeons, due to its implications for the treatment of very large numbers of patients using SSRIs or SNRIs undergoing surgical and dental procedures. We think that the findings from this study may be important for patients who use antidepressants such as fluoxetine and venlafaxine due to depression and other affective disorders, especially children and young adults whose growth and development are continuing, and the elderly who may be at risk of osteoporosis. To the best of our knowledge, no previous animal studies have compared the effects of SSRIs and SNRIs on bone healing. Therefore, the purpose of this study was to compare the effects of SSRI fluoxetine and SNRI venlafaxine on bone healing.

Materials and methods

Animals

Twenty-four healthy, aged 2 to 3 months, male Wistar rats weighing 200 to 250 g were used in this study. All animals were purchased from The Akdeniz University Animal Experiments Application and Research Center. The rats were placed into polycarbonate cages containing two animals each and were allowed to acclimatize to this environment for one week before the study began. Ad libitum access was permitted to a standard laboratory diet (rodent chow and tap water). All rats were housed at 22 ± 2 °C, at a humidity of 40–60%, in constant clean, warm air, and in 12 h on/12 h off light/ dark cycle. All rats were monitored daily by a veterinarian in the animal facility.

Approval for the research was granted by the Akdeniz University Animal Ethics Committee, Turkey (B.30.2.AKD.0.05.07.00/105). All procedures and the reporting thereof were conducted following the Animal Research: Reporting in Vivo Experiments (ARRIVE) guideline [12].

Drug administration

The drug treatment plan lasted seven weeks and the administration of sterile saline (0.9% isotonic sodium chloride solution) or fluoxetine (Prozac®, Lilly, Turkey) or venlafaxine (Sulinex XR®, Abdi İbrahim, Turkey) was performed daily by gastric gavage. To simulate chronic antidepressant use, rats received drug treatment for 3 weeks before the surgical procedures [13], and their treatment was continued until euthanasia.

Experimental groups

A stratified randomization procedure was performed in Microsoft Excel taking the rats' body weight as a reference. The data were entered into a spreadsheet following a sequence from the lightest to the heaviest animal, and then random numbers were generated by the program for each rat, followed by a random allocation into three groups. The lightest and heaviest animals were homogeneously distributed into the following groups:

1 The control group ($n = 8$), received 0,1 ml/day sterile saline solution
2 The fluoxetine group ($n = 8$), received 5 mg/kg/day fluoxetine HCL
3 The venlafaxine group ($n = 8$), received 5 mg/kg/day venlafaxine Hcl tablets dissolved in 0.9% isotonic sodium chloride solution (Sulinex XR®).

Fluoxetine and venlafaxine dosages in humans range between 50 and 150 mg/d and between 37.5 and 225 mg/d, respectively [14]. The equivalent of approximately 0.83 to 2.5 and 0.63 to 3.75 mg/kg/d, respectively. Higher doses are usually employed in animals due to their faster metabolism compared to that of humans [7]. The rats were weighed weekly to ensure dosage standardization.

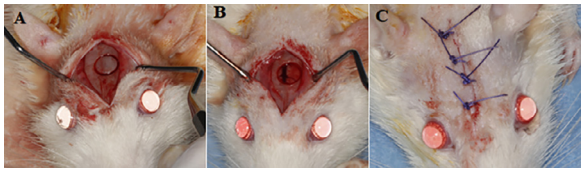


Fig. 1. A-C. Operation of creating a calvarial defect. A, 5 mm-diameter circular bicortical cut was made by trephine burr in the parietal bone. B, Parietal bone defect after removal of the external and internal cortical with exposure of the dura mater membrane, which is preserved. C, Simple interrupted suture with a synthetic thread.

Surgery

A critical-size calvarial bone defect was created as previously described [15]. Briefly, all rats received 20 mg/kg xylazine HCl (Alfazyne 2% ®, Ege-Vet, Turkey) as a pre-anesthetic agent by intraperitoneal injection and 90 mg/kg ketamine HCl (Ketalar®, Pfizer, Turkey) as a general anesthetic agent. The animal's head was first shaved and washed using a disinfectant. Lidocaine (Jetokain simplex®, Adeka, Turkey) was employed as infiltration anesthesia at the surgical site. An incision was made along the midsagittal suture to expose the parietal bones. Under surgical loupes, a 5-mm in diameter skull defect was created in the middle of the skull bone with a 5-mm diameter trephine (slow-speed hand drill) by removing both external and internal cortical. Care was taken to avoid damage to the dura during the procedure. Once bleeding had been brought under control, the incision was closed primarily with a 5–0 synthetic suture (Pegalak®, Doğsan, Turkey) (Fig. 1). There was no evidence of local or systemic infection in any of the rats throughout the perioperative period.

In the postoperative period, rats received a 40 mg/kg/day dose of the antibiotic cephalosporin (Seftivet®, Deva, Turkey) for five days. All animals were monitored daily for any indications of pain, restricted movement, dehiscence, infection, loss of appetite, or weight loss until euthanization. The euthanasia was performed 4 weeks after surgery, using intraperitoneal administration of a lethal dose (200 mg/kg) of thiopental sodium (Pental®, IE Ulagay, Turkey). The calvaria was then harvested for radiological and histomorphometric investigation.

Micro–CT analysis

A micro-CT (SkyScan-1272, Bruker, Kontich, Belgium) device was used in this study. The features of the device were an X-

ray source; 40–100 kV, 10 W (< 5 μm spot size at 4 W), X-ray camera; 16 MP, 4096 × 4096- pixel size at maximum magnification. The expression was < 0.35 μm for the 16 MP camera. NRecon v.1.6.3 software (Bruker-microCT, Belgium) was used to transform the data obtained from the scanned samples, while analysis was performed on CTAn v.1.12 software (Bruker-micro-CT, Belgium). Variables such as bone volume fraction (BV/TV; bone volume/tissue volume, mm^3), bone surface (BS), bone surface density (BS/BV; bone surface/bone volume, 1/mm), Tb. N (trabecular number, 1/mm), and trabecular thickness (Tb. Th) were measured in micro-CT.

Histomorphometric analysis

Defect area specimens collected from the rat calvaria were fixed in 10% buffered formalin solution for at least 24 h, decalcified in 5% nitric acid solution, and subjected to closed system tissue processing procedures. The specimens were then embedded in paraffin blocks, from which 4-micron thick sections were taken, stained with hematoxylin and eosin, and placed under a light microscope. Areas of new bone structure exhibiting cellular and osteoblastic activity (positive areas), together with areas of a mature bone structure consisting of hypocellular, compact bone (negative areas) were detected at light microscopic examination [16].

Positive and negative areas from each animal were marked in a digital setting, and these positive and negative areas required separate calculations. Due to the lack of software and a device (whole slide scanner) capable of meeting these needs within the university, a new system suited to the study method was developed. Images captured using a single-lens reflex camera mounted on the microscope were transferred to the system and grouped on a case basis. These images were marked by the pathologist, area calculations were performed and reported in line with the statistical analysis stage. The system developed consists of three distinct software modules (Angular SPA, NET Core REST API, and Python REST API) and an MSSQL relational database system. The Angular SPA web interface project is responsible for user interactions, the NET Core web service project for database operations, and the Python web service project for image processing procedures.

Statistical analysis

Descriptive statistics were generated and the Kolmogorov–Smirnov test was used for normality testing of continuous data. Then, data were analyzed using the Kruskal–Wallis nonparametric test, followed by posthoc group comparisons with the Bonferroni-adjusted Mann–Whitney U test. P values lower than 0.05 were regarded as statistically significant. Statistical analysis was carried out using a commercial software program (IBM SPSS Statistics 22.0, SPSS Inc., USA).

Results

No unexpected events were encountered in the perioperative or postoperative periods. No complications that might result in animals being excluded (such as wound site infections or damage to the dura) occurred during the study.

Micro–CT analysis

Micro-CT images of the decalcified bone samples from the treatment groups are shown in Fig. 2. Analysis revealed that new bone formed within the defect site in all groups and that the amount of newly formed bone was similar between them. Neither drug resulted in any significant change in terms of bone healing. Levels of bone healing at four weeks, calculated in terms of BV/TV, were similar in all the study groups ($p = 0.55$). No significant difference was also determined between the three groups in terms of BS, BS/BV, Tb. N, and Tb. Th ($p = 0.65$, 0.09, 0.51, and 0.42 respectively).

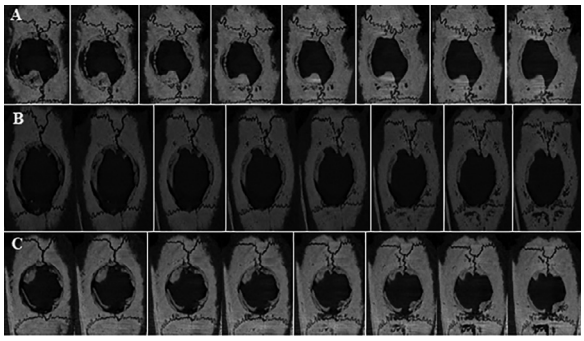


Fig. 2. A-C. Micro-CT image of critical-sized rat calvarial defect. A, Control group. B, Fluoxetine group. C, Venlafaxine group.

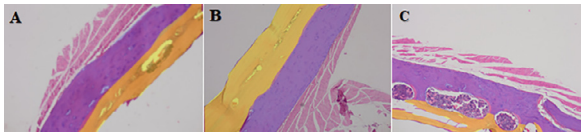


Fig. 3. A-C. Histological observations (H&E, X40). Newly formed bone tissue is marked in blue and mature bone tissue is marked in yellow in the defect margin at 4 weeks after the operation. A, Control group. B, Fluoxetine group. C, Venlafaxine group.

Histomorphometric analysis

Histological images of the decalcified bone samples from the treatment groups are shown in Fig. 3. Analysis revealed the presence of similar levels of new bone formation in the defect site in all groups ($p = 0.28$). Additionally, the degrees of old (mature) bone formation in the defect regions were similar across all groups ($p = 0.47$). Bone growth largely occurred within the periphery of the defects, with gradual progression toward the central parts.

Discussion

Treatment of bone defects remains a major challenge in the fields of cranial, maxillo-facial, and orthopedic surgery. Even in bone defects where autografts, known as the gold standard [17,18], are applied the pharmacological agents or drugs used can adversely affect healing, which may prevent the desired success from being achieved. Therefore, it is of great importance to know the potential effects of drugs that are widely used worldwide, such as SSRI and SNRI, on bone healing. To the best of our knowledge, this is the first pre-clinical study comparing the effects of SSRI fluoxetine and SNRI venlafaxine on bone healing. We think that our findings represent an important contribution to the subject due to the current lack of consensus regarding the association between their use and bone healing. While some clinical studies have implicated SSRIs or SNRIs use in bone loss [6,8,19], others have reported no effect [10]. Some clinical studies have reported that SSRIs and SNRIs are associated with an increased risk of bone fracture. Wang et al. [20] suggested that this risk increased in patients with osteoporosis and a history of falling.

Bias and confounding factors may occur when establishing populations in human studies [7]. Pre-clinical studies investigating and comparing the effects of SSRIs and SNRIs on bone regeneration/healing in greater depth are therefore now needed. A rat calvarial bone defect model was employed in the present study to

produce a representative model of patients receiving SSRI or SNRI therapy and undergoing bone surgery due to the similarities in bone biology between humans and rats [21]. A limited number of animal studies have investigated the effects of SSRIs and SNRIs on bone healing. There is also no consensus on this subject in animal studies, like clinical studies. While some animal studies have reported that SSRIs and SNRIs exert a positive effect on healing and bone architecture [4], others have reported a negative impact [7,22,23]. Moreover, the results of other investigations have shown neither positive nor negative effects [24,25].

Mortazavi et al. [4] investigated the effects of two different doses of fluoxetine (7.5 or 15 mg/kg/day) on bone healing in a rat calvarial defect model. Those authors reported a dose-dependent increase in bone formation with fluoxetine administration for eight weeks. Battaglino et al. [26] reported that the intraperitoneal administration of fluoxetine (10 mg/kg/day) in mice for six weeks increased bone mass in the fixed vertebrae, femur, and calvarium. However, Ortuño et al. [27] reported that although fluoxetine (20/mg/day) administration for three weeks in a mouse model produced a decrease in bone resorption, the effect of the drug changed when the treatment period was increased (six weeks), and that the effect of the drug on bone formation decreased. In another study showing that long-term SNRI administration resulted in adverse effects on bone structure, Fekete et al. [22] reported that prolonged (12-week) SNRI (12 mg/25 g of diet) administration caused a decrease in osteoid synthesis and an increase in bone resorption in rats subjected to orchidectomy. In contrast to Howie et al. [28], who suggested that sertraline administered at a dose of 10 $mg.kg^{-1}$ in drinking water for six weeks in a mouse model interrupted the repair and healing of calvarial bone defects and negatively affected healing and Abu Nada et al. [7], who suggested that sertraline administered subcutaneously (5 mg/kg/day) adversely impacted on bone healing and implant osseointegration in a rat model, we found no evidence that the use of SSRI or SNRI has any positive or adverse effect on bone healing**.** The results of the present study are compatible with those of Westbroek et al. [25], who showed that long-term (six months) fluoxetine (5 mg/kg/day) administration causes no major changes in bone architecture or strength in growing rats. Similarly, Warden et al. [29] administered intraperitoneal fluoxetine (5 mg/kg/day or 20 mg/kg/day) for four weeks in a growing mouse model and reported that the application caused no difference in postnatal cranial dimensions. Additionally, Gold et al. [24] reported that eight-week intraperitoneal fluoxetine (1 mg/kg/day) administration resulted in no change in the structure of rat femoral bone. The discrepancy in findings among previous reports may be due to the types of animals used, the bone types investigated, and the treatment protocols (therapeutic dose, type, and duration of application). Further studies in which different doses, types, and administration times are investigated together are now needed to form a consensus on this issue and to serve as a guide to clinical applications.

The fact that no statistically significant difference was determined between the drug and control groups in the present research raises the question, also mentioned by Gold et al. [24], of whether depression has a greater effect than antidepressants on bone structure and healing. This is because although the underlying mechanism by which depression exacerbates the risk of bone loss and fracture has not been fully elucidated, it has been linked to an increased risk of bone loss and fracture [30]. Depression has been reported to be capable of altering the concentrations of several hormones that affect bone formation and/or resorption [30,31], and of leading to a chronic low-grade inflammatory response [31]. Depression has also been linked to decreased mobility and weight loss, both of which exhibit significant effects on bone [19].

The present study has several limitations. First, the treatment protocol has not included different therapeutic doses, types, and duration of application. Second, this study had a relatively small sample size, and therefore its outcome cannot be applied directly to clinical practice.

Conclusion

In conclusion, based on the findings of the present study, it can be said that the use of both drug groups hasn't any effect on the healing of defects in the calvarium of rats. However, further preclinical and clinical studies need to be designed to overcome the limitations of this study.

Declaration of Competing Interests

None of the authors have any commercial associations that might create a conflict of interest nor do any of the authors have any financial interests or personal relationships with other people or organizations that would represent a conflict of interest.

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