

Effect of Fluoxetine Consumption on Orthodontic Tooth Movement in Rats

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Abstract

Objectives: Fluoxetine is a selective serotonin re-uptake inhibitor (SSRI) widely used for depression, bipolar disorder, anxiety and obsessive-compulsive disorder. The aim of this study was to assess the effect of fluoxetine on orthodontic tooth movement (OTM) in rats.

Materials and Methods: Forty-five male Wistar rats were randomly divided into three groups namely the control group (no medication), saline and fluoxetine dissolved in saline. In all groups, nickel titanium closed-coil spring was used between the left maxillary central incisor and first molar to exert 60g force at 2mm activation. Radiographs were taken at one and 21 days. After 21 days, the rats were sacrificed. The distance between the first and second molar teeth, optical density of bone, periodontal ligament (PDL) width, lacuna length and depth and number of osteoclasts were measured and compared among the groups.

Results: Tooth movement significantly increased in the fluoxetine group ($P=0.005$). No significant differences were found in osteoclast count ($P=0.069$). The PDL width in the mesioapical region of root was significantly different among the groups ($P=0.015$). Statistical analysis did not show significant differences in depth or length of lacunae in any examined part of the root ($P>0.05$). Bone densitometry results showed that in fluoxetine group, density of bone in all four areas (alveolar bone, hard palate, skull and mandibular bone) significantly decreased from day one to day 21 ($P<0.05$).

Conclusion: This study indicated that fluoxetine decreased bone density, which resulted in subsequently greater tooth movement in rats; however, further studies are needed on humans.

Keywords: Fluoxetine; Tooth Movement; Rats

Journal of Dentistry, Tehran University of Medical Sciences, Tehran, Iran (2015; Vol. 12, No. 12)

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Received: 17 July 2015

Accepted: 3 November 2015

INTRODUCTION

Orthodontic tooth movement is the result of alveolar bone remodeling. Bone remodeling is an inflammatory response initiated by local vascular, cellular and molecular triggering cascades of chemokines, cytokines and

prostaglandins [1,2]. The process of bone remodeling occurs by coupled interactions between resorption and deposition, which includes bone formation in the tension side and resorption in the compression side, finally resulting in tooth movement.

The prevalence of major depressive disorders in Iran has been reported to be about 4.1%, which is concerning [3]. Antidepressants are the third most commonly prescribed drugs and among them, SSRIs seem to be one of the most frequently prescribed medications [4]. Fluoxetine is a SSRI widely used for depression, bipolar disorder, anxiety and obsessive-compulsive disorder [5,6]. Administration of fluoxetine induces the inhibition of 5HT serotonin transporter receptor reuptake followed by increased serotonin concentration [7]. A reduction in macrophage, lymphocyte, neutrophil and eosinophil count has also been reported [8].

Prostaglandin E (PGE) plays a major role in events involved in tooth movement; thus, PGE inhibitors impact on tooth movement. Fluoxetine decreases PGE2 level in subcutaneous exudates and paw edema in carrageenan -induced inflammation [9]. A study by Branco-de-Almeida and colleagues about the effects of fluoxetine on inflammatory tissue destruction in rats demonstrated that in ligature-induced periodontitis, modulation of inflammatory reactions would result in reduction of inflammatory factors such as IL1 β , COX-2 and matrix metalloproteinase-9 in rat models [10]. Inhibition of 5HT serotonin transporter receptor by SSRIs may be a reason for altered function of bone cells in vitro [11]. Serotonin can increase osteoclast differentiation and direct bone turnover [11,12].

It has been shown that 5HT inhibition induced by fluoxetine consumption had a negative effect on bone accrual in growing rats. Increased rate of bone loss and fracture and decreased bone mineral density (BMD) and skeletal growth have been reported due to the administration of fluoxetine [13-15]. In contrary to these findings, some studies failed to show changes in bone formation, bone density or its geometric properties due to the administration of SSRIs [16-18]. Altered mechanical loads during orthodontic treatment result in numerous cellular-molecular changes that lead to biological adaptation to the new condition.

Mechanical stimuli induce the distortion of PDL cells, bone cells and their surrounding matrix and trigger the release of cytokines [19,20]; thus, they can all be affected by fluoxetine during the process of OTM. There are only two studies available in the literature that investigated the effect of fluoxetine on tooth movement, and they declared that this drug did not have a significant effect on OTM [21,22].

Because of the contradictory effects of fluoxetine on bone structure and small number of studies that assessed the effect of this drug on OTM and BMD simultaneously, this study aimed to assess the effect of fluoxetine consumption on OTM, PDL width, lacuna length and depth and bone density during orthodontic treatment in rats.

Table 1. Tooth movement in the three experimental groups (n=12)

Groups	Minimum(mm)	Maximum(mm)	Mean	Std. Deviation
A	0.20	0.80	0.34	0.21
B	0.23	0.45	0.32	0.079
C	0.43	1.15	0.57	0.19

Group A: Control group with no medication

Group B: Received 1mL/day normal saline

Group C: Received 10 mg/kg/day of fluoxetine dissolved in normal saline

MATERIALS AND METHODS

The present experimental study was carried out on 45 male Wistar rats with an initial weight of 200-250 g according to the US National institute of Health (publication 85-23; revised:1985). Ethical approval was obtained from the ethics committee of Tehran University of Medical Sciences. The proposal of this study was approved by the ethics committee of the University (#IR.TUMS.REC.1395.2538).

The rats were housed in transparent plastic cages under normal laboratory conditions of constant temperature (24-25°C) and %55 humidity with an artificial 12-hour light-dark cycle one week before the experiment to acclimate to the new environment. To avoid excessive chewing force, they were fed water-soaked standard rat chow. The rats were anesthetized with intraperitoneal injections of ketamine (Vetaset, 50 mg/kg) and xylazine (Dopaser, 14 mg/kg); 0.10 inch ligature wire was used to tie nickel titanium closed-coil spring (Hiek, 0.006×0.022 inch, 3M Unitek, Monrovia, CA, USA) between the left maxillary central incisor and the first molar tooth to exert 60g force at 2mm activation. A shallow cervical groove was prepared with a 0.8-inch diamond bur in the cervical portion of upper incisors and the ligature wire was fixed using light-cure composite (Transbond XT, 3M Unitek, Monrovia, CA, USA).

The rats were randomly divided into three groups as follows:

- 1) Group A served as the control group with no medication
- 2) Group B received 1 mL/day normal saline.
- 3) Group C received 10 mg/kg/day fluoxetine dissolved in normal saline.

The lower incisors were cut short about 2mm once a week during the study period to prevent appliance detachment. After 21 days, all rats were sacrificed by CO₂ asphyxiation. After cutting the maxilla from the skull, the distance between the first and second molar teeth was measured by a filler gauge (Mitutoyo, Kawasaki, Japan).

All measurements were made twice by two operators and the mean values were recorded. The maxillary sections were then immersed in 10% formalin for five days and then in 5% formic acid for seven days. Eventually, the maxillae were sectioned at the median palatal suture. Five µm sections were cut from the decalcified paraffin-embedded blocks in mesiodistal plane and stained with hematoxylin and eosin. A maximum of six sections was prepared of each sample and then one section was chosen, which included total length of the mesial root of the first molar from the cemento-enamel junction to the apex. The sections were evaluated under a light microscope (BX-51, Olympus, Tokyo, Japan) equipped with digital camera (DP25 Olympus, Tokyo, Japan) and analysis software. (DP2-BSW, Olympus, Tokyo, Japan). The number of lacunae in the mesial root (in dentin or cementum) and size of the lacunae were used as resorption indices. The depth and width of all lacunas were measured and their mean values were reported [23-26]. Lateral cephalograms with Kodak (size 2) E-speed films (Eastman Kodak, Rochester, NY, USA) were taken at 70 kV and 8 mA and exposure time of 0.3s. The focus-film distance was constant by using a box in which, rats' one and 21 were necks were fixed.

Table 2. Descriptive data of PDL width (micrometers)

Groups	Group A	Group B	Group C
Mesioapical	0.97	0.15	0.13
Distoapical	0.99	0.13	0.12
Mesio coronal	0.84	0.12	0.12
Disto coronal	0.11	0.13	0.13

Group A: Control group with no medication

Group B: Received 1mL/day normal saline

Group C: Received 10 mg/kg/day of fluoxetine dissolved in normal saline

Radiographs taken on days processed by an automatic film processor (Velopex, Extra X, Medivance, London, UK). A digital densitometer (Tobias TBX, Ivyland, PA, USA) was applied to measure the optical density in 1mm perimeter around four points:

(1) Point 1 (on the alveolar bone): Superior to Bu point (a point on the premaxilla between the jawbone and the lingual surface of the upper incisors).

(2) Point 2 (on the hard palate): Anterior to Mu point (a point on the intersection between the maxillary bone and the mesial surface of the upper first molar).

(3) Point 3 (on the skull): Po point (The most posterior point on the cranium).

(4) Point 4 (on the mandibular bone): K Point (The intersection between the Go-Mn (Gonion to Menton) line and the line perpendicular to the Go-Mn (Gonion to Menton) through GN (Gnathion) [27]. Post hoc test after one-way ANOVA was used for multiple comparisons. SPSS version 22 was used for statistical analysis and processing of data (SPSS Inc., IL, USA). The Probability value less than 0.05 was considered significant.

RESULTS

Table 1 shows the descriptive data of OTM in the three experimental groups. The amount of OTM significantly increased in group with fluoxetine administration compared to the other two groups ($P=0.005$). No significant differences were observed between the two groups of no drugs and saline ($P=0.125$).

In histological evaluation of sections, no significant differences were found in osteoclast counts in the bone adjacent to the mesial roots of rat molars in fluoxetine, saline and control groups ($P=0.069$). Table 2 shows descriptive data of PDL width. It was analyzed separately for each location including the mesiocoronal, mesioapical, distocoronal and distoapical, and the P-value was 0.215, 0.015, 0.159 and 0.223, respectively. It was shown that only PDL width in the mesioapical area of the root was significantly different among the groups. Table 3 displays descriptive data of lacunae length and depth. Statistical analysis did not show significant differences in depth and length of lacunae in any examined part of the root. P-value for depth in the mesial, depth in the distal, length in the mesial and length in the distal area was 0.185, 0.58, 0.52 and 0.55, respectively.

In data analysis of bone densitometry, density of bone in all four areas (alveolar bone, hard palate, skull and mandibular bone) in the fluoxetine group decreased from day one to day 21 and the difference was statistically significant (Table 4). P-value for alveolar bone, hard palate, skull and mandibular bone was 0.002, 0.005, 0 and 0, respectively.

DISCUSSION

Depression is a common disease, which may be a cause of disability in the future. Due to their favorable efficacy and insignificant side effects, SSRIs, particularly fluoxetine, are the most commonly used and first line drugs for depression treatment [28,29].

Table 3. Descriptive data of lacunae length and depth (micrometers)

Groups		Depth	Width
A	Mesial	0.07	0.11
	Distal	0.16	0.32
B	Mesial	0.15	0.51
	Distal	0.16	0.37
C	Mesial	0.18	0.79
	Distal	0.23	0.57

Group A: Control group with no medication

Group B: Received 1mL/day normal saline

Group C: Received 10 mg/kg/day of fluoxetine dissolved in normal saline

Fluoxetine eliminates depression symptoms by inhibiting 5HT reuptake followed by serotonin concentration enhancement in synaptic cleft [7]. Also, this drug causes a reduction in cytokines [10] and affects bone cell function [30], which play basic roles in OTM. Thus, we assessed the effects of fluoxetine on OTM in our study. In the current study, we found that OTM increased in the fluoxetine group. Also, bone density in alveolar bone, hard palate, skull and mandibular bone decreased in fluoxetine group compared to the control group.

The effect of fluoxetine on bone is due to the active pathway of serotonin [11] since serotonin signaling pathway has been shown to affect bone cells in addition to central nervous system [11,31]. Serotonin transporter (5HTT) is found in all types of bone cells [15]; thus, 5HT inhibition by SSRIs seems to result in altered function of these cells [11]. The 5HTT gene disruption had adverse effects on bone mass and bone strength in mice [32]. Also, SSRI consumption seems to have a high correlation with the rate of fracture among antidepressant drugs [33]. Some studies have investigated the effects of these drugs on bone density. Diem et al. stated that use of SSRIs was associated with an increased rate of bone loss in the hip [14]. Tsapakis et al. declared that SSRIs had an adverse effect on bone at the therapeutic dose levels used for treatment of depression [15].

In a cross sectional study on 83 patients, it was shown that SSRIs may be the cause of BMD decrease in radius and lumbar spine [34].

In a study on a population of women, Williams et al, also reported the same results in femoral neck, trochanter and mid forearm in individuals under treatment with SSRIs [35]. These findings are also in agreement with the radiographic results of the present study, in which fluoxetine group showed reduced bone density compared to the control group. It may be concluded that fluoxetine increases the rate of tooth movement through a reduction in bone density. In contrast, some studies did not support the negative effects of SSRIs on bone [16,36]. Spangler et al, in a three-year longitudinal study showed no association between SSRI drugs and BMD changes [37]. Mortazavi and colleagues reported increased bone regeneration in calvarial defects of animal models due to the use of SSRIs [38]. Reduction of bone loss in ligature-induced periodontitis due to the anti-inflammatory properties of fluoxetine was also reported [10]. There are only two studies that assessed the effect of fluoxetine on tooth movement. Franzon Frigotto et al. investigated the effect of fluoxetine administration on the tooth movement rate, bone remodeling, and trabecular bone microarchitecture during induced tooth movement in rats. They evaluated the microarchitecture of trabecular

Table 4. Descriptive data of densitometry shown as optical density (standard deviation)

Groups	Day	Alveolar bone	Hard palate	Skull	Mandibular bone
A	1	1.65(0.16)	1.32(0.19)	1.61(0.13)	1.60(0.13)
	21	1.86(0.14)	1.41(0.16)	1.82(0.12)	1.84(0.15)
B	1	1.70(0.11)	1.39(0.23)	1.64(0.15)	1.67(0.17)
	21	1.87(0.11)	1.38(0.14)	1.76(0.15)	1.75(0.24)
C	1	1.70(0.17)	1.30(0.93)	1.65(0.98)	1.66(0.11)
	21	1.48(0.22)	1.16(0.18)	1.42(0.17)	1.43(0.17)

Group A: Control group with no medication

Group B: Received 1mL/day normal saline

Group C: Received 10 mg/kg/day of fluoxetine dissolved in normal saline

bone by micro-computed tomography of rats' femur and concluded that fluoxetine administration in rats did not change the tooth movement rate and it had no effect on bone resorption either [21]. Rafiei et al. evaluated the effect of fluoxetine on tooth movement, root resorption and alveolar bone in lab rats; they only used histological evaluation to study alveolar bone and showed that fluoxetine did not cause significant changes in tooth movement or root resorption rate in rats [22].

In the current study, we performed bone densitometry in four regions of rats' head including alveolar bone, hard palate, skull and mandibular bone in order to evaluate the bones that are directly related to tooth movement. These bony regions were not investigated in previous studies and the differences in the results may be related to this issue.

Histological analysis did not show significant differences in the number of osteoclasts among the fluoxetine, saline and control groups. In some in-vitro studies, increased differentiation of osteoclast-like cells was noted [11,21,39] but in this study there was no increase in the number of osteoclasts. This finding may be in agreement with the results of some studies, which claimed that SSRI consumption might alter osteoclast functions [11]. In our study, PDL width in the mesioapical ($P=0.015$) portion of the root was significantly wider than that in the control group. Increased PDL width may be the result of increased tooth movement in the fluoxetine group. Finally, it should be mentioned that the results of animal studies cannot be completely generalized to humans because the dosage, duration of force application, bone structure and force level are not similar in humans and rats [22].

CONCLUSION

This study indicated that fluoxetine decreased bone density, which resulted in subsequently greater tooth movement in rats. Thus, clinicians may see higher rate of tooth movement in patients under treatment with fluoxetine

compared to those not using it, but more investigations through clinical trials for evaluation of its exact effects on humans are recommended.

ACKNOWLEDGEMENT

This research was founded and supported by a grant from Dental Research Center, Dentistry Research Institute, Tehran University of Medical Sciences (Grant No: 93/469/86). The authors would like to thank Dr. Mohammad Javad Kharazi Fard for his contribution in performing the statistical analysis of this study.

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