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Histological and histometric aspects of radicular dentinogenesis in upper first molars of fluoxetine treated rats

Aspectos histológicos e histométricos da dentinogênese radicular em primeiros molares superiores dos ratos tratados com fluoxetina

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ABSTRACT

Introduction: Serotonin is a neurotransmitter implicated on the control of several bodies roles including the regulation of circadian rhythm, of sleepiness, body temperature, motor and cognitive activities and of growth and development of tissues during embryogenesis. **Objective:** The aim of the present study is to assay the morphological aspects of the root dentin of upper first molars from pups of rats that were treated with fluoxetine in pregnancy. **Methodology:** For such, we conducted a random experimental study by using used 12 Wistar pregnant rats divided into three groups: C, FX and FL group. From the first to the 21 day of pregnancy, the rats received saline solution or fluoxetine hydrochloride solution, subcutaneously, according to the group to which they belonged. Subsequently, the offspring of animals was divided into subsets according to the age of tooth germ development to be studied: C20 and C45 (control group of 20 and 45 days of age); FL20 and FL45 (treated group with fluoxetine 10 mg/kg body weight of 20 and 45 days of life) and FX20 and FX45 (treated group with fluoxetine 20 mg/kg body weight of 20 and 45 days old). The thickness of root dentin, predentin thickness and length of odontoblasts were analyzed at the offspring samples. The data were tabulated and statistical values were performed with a significance level $p < 0,05$.

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Results/Conclusion: Studies have shown significant changes in dentinogenesis root of the groups treated with fluoxetine at doses of 10 and 20 mg / kg body weight during pregnancy.

Keywords: Fluoxetine; Dental Germ; Serotonin

RESUMO
Introdução: A serotonina é um neurotransmissor implicado no controle de várias funções corporais, incluindo a regulação do ritmo circadiano, da sonolência, da temperatura corporal, das atividades motoras e cognitivas e do crescimento e desenvolvimento dos tecidos durante a embriogênese. Objetivo: O objetivo do presente estudo é analisar os aspectos morfológicos da dentina radicular dos primeiros molares superiores de filhotes de ratos tratados com fluoxetina na gravidez. Metodologia: Para tanto, realizamos um estudo experimental aleatório utilizando 12 ratas Wistar usadas, divididas em três grupos: grupo C, FX e FL. Do primeiro ao 21 dia de gestação, os ratos receberam solução salina ou cloridrato de fluoxetina, por via subcutânea, de acordo com o grupo ao qual pertenciam. Posteriormente, a prole dos animais foi dividida em subconjuntos de acordo com a idade de desenvolvimento do germe dentário a ser estudado: C20 e C45 (grupo controle de 20 e 45 dias de idade); FL20 e FL45 (grupo tratado com fluoxetina 10 mg / kg de peso corporal de 20 e 45 dias de vida) e FX20 e FX45 (grupo tratado com fluoxetina 20 mg / kg de peso corporal de 20 e 45 dias de vida). A espessura da dentina radicular, a espessura da predentina e o comprimento dos odontoblastos foram analisados nas amostras da prole. Os dados foram tabulados e os valores estatísticos foram realizados com nível de significância p <0,05. Resultados / Conclusão: Estudos mostraram mudanças significativas na raiz da dentinogênese dos grupos tratados com fluoxetina nas doses de 10 e 20 mg / kg de peso corporal durante a gravidez.

Palavras chave: Fluoxetina; Germe Dentário; Serotonina

1 INTRODUCTION

Depression is currently a worldwide public health problem (Duffy et al., 2019) that affects the personal, professional, social and economic lives of its sufferers (Berle e Spigset, 2011). Its prevalence has been increasing in the last decades. Women present a high incidence rate, especially during pregnancy or postpartum (Sit et al., 2011; Pawloski et al., 2012). Depression treatment during pregnancy is important to prevent obstetric complications, such as premature birth or low birth weight babies (Hendrick and Altshuler, 2002).

As an option for depression treatment, fluoxetine, a selective serotonin reuptake inhibitor (SSRI), is the first chosen drug not only due to its efficacy, but also because of its high tolerance (Düsman et al., 2014; Dzevlan et al., 2019). The use of antidepressant drugs during pregnancy may generate some teratogenic effects that compromised the development of human and animal neonates (Morrison, Riggs e Rurak, 2005). Neonates may be exposed to fluoxetine in the womb, showing a drug level equivalent to 60% of the mother's value (Hendrick et al., 2003). Besides, pregnant women taking medication in the third trimester of pregnancy showed an increased risk for perinatal complications (Oberlander et al., 2009).

Fluoxetine acts by potentiating serotonergic neurotransmission and, in turn, serotonin or 5-hydroxytryptamine (5-HT) participates in the regulation of mood, sleep, sexual activity, appetite, circadian rhythm, pain sensitivity, motor activity and neuroendocrine functions (Galli et al., 2013). In addition, 5-HT regulates events during embryogenesis such as neurogenesis and neuronal differentiation by also acting on epithelial-mesenchymal interaction promoting stimulation of differentiation and cell migration during neural tube and gill arches development, thus promoting the formation of different tissues (Moiseiwitsch, 2000).

Studies have shown that changes in body's 5-HT levels during embryogenesis caused changes in the growth and development of many tissues, especially in the craniofacial region (Mendes-da-Silva et al., 2002; Santiago et al., 2013; Correia-Leite de Marcelos et al, 2015; Regueira et al., 2017). Reports from Lauder et al. (2000) showed that embryos exposed to antagonists of 5-HT2 receptors exhibited different embryological malformations depending on the dose and selectivity of the used antagonist.

5-HT uptake sites are known to exist in the craniofacial region and are in sync with the major morphogenetic events in this region, including tooth development (Lauder and Zimmerman, 1988; Tecott, Shtrom and Julius, 1995).

Moisewitsch et al. (1998) demonstrated that 5-HT exerts a stimulating effect on the development of the dental germ by performing actions that are capable of inducing the formation of the enamel organ and dental papilla, originating the bell and crown stages.
Root dentinogenesis requires epithelial cells to begin the odontoblast differentiation process. All of these processes are regulated by a series of inducing mechanisms and signaling pathways, and it is possible that 5-HT influences root dentin formation, however there are few studies in the literature on root formation inducing mechanisms (Yokohama-Tamaki et al., 2006).

Thus, the aim of the present study was to histologically and histometrically analyze the root of the upper first molars in the offspring of fluoxetine-treated rats during pregnancy.

2 METHODOLOGY

The study was carried out in the Experimental Surgery Center vivarium, at the Histology and Embryology Department, and in the Histotechnical Laboratory of the Pathology Postgraduate Program of Federal University of Pernambuco, from September 2009 to March 2012. It was approved by the Animal Experimentation Bioethics Committee of the Biological Sciences Center of Federal University of Pernambuco (CBEA / CCB - UFPE), process # 23076.006899 / 2008 - 51.

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Twelve (12) Wistar albino female rats were fed with feed and water ad libitum and kept at a temperature of 23 ± 2 °C on a 12:12 h light/dark cycle. After mating and diagnosis of pregnancy by vaginal smear, the rats were divided into three groups: 4 animals for the control group (Group C), 4 animals for the group treated with fluoxetine at a dose of 10 mg/Kg of animal weight (Group FL) and 4 animals for the group treated with fluoxetine at a dose of 20 mg/Kg of animal weight (Group FX). Each group was divided into 2 subgroups according to the age of development of the dental germ (20 or 45 days of life), totaling 6 subgroups.

Two pregnant rats were used for each subgroup, and from each litter, 3 puppies of both sexes were used. The animals were obtained from mothers treated or not, from the first day of gestation.

The subgroups were named C20 and C45 (control animals with 20 and 45 days-old); FL20 and FL45: (animals of the group treated with fluoxetine at a dose of 10 mg/Kg of animal weight with 20 and 45 days-old); FX20 and FX45: (animals of the group treated with fluoxetine at a dose of 20 mg/Kg of animal weight with 20 and 45 days-old).

The pregnant rats were treated according to the study group to which they belonged from the 1st to the 21st day of pregnancy, at previously established times (between 07h and 08h in the morning). In group C, the mothers daily received a 0.9% physiological solution in subcutaneous applications at a dose of 10 µl/g. In the FL group, mothers were treated with fluoxetine at a dose of 10mg/Kg of animal weight and in the FX group, mothers were treated with fluoxetine at a dose of 20mg/Kg of animal weight, injected subcutaneously at the same times and at the established times for the control group.

Animals with 20 and 45 days-old were anesthetized with xylazine at 20 mg/Kg of animal weight (i.m.) and ketamine at 50 mg/Kg of animal weight (i.m.). The animals were beheaded, their jaws were removed and the upper jaw with the right and left dental germs were sectioned tangentially to the mesial face of the first molar. Dental germs were fixed in 10% buffered formalin solution for 24 hours at room temperature. The specimens were then decalcified in an aqueous solution of 10% nitric acid. The conventional histological technique for paraffin embedding was followed. Histological sections were obtained at approximately 4µm each, stained with hematoxylin-eosin (HE), mounted on Entellan® (Merck KGaA, Darmstadt, Germany), observed and photographed under an ECLYPSE 51® light microscope (Nikon, Tokyo, Japan).

For morphological analysis, an ECLYPSE 51® light microscope (Nikon, Tokyo, Japan) was used. The root of each dental germ was divided into three thirds to facilitate analysis:

cervical, middle and apical thirds. In these regions, the histological characteristics of the dentin, pre-dentin and odontoblastic layer regions were observed and described.

For histometric analysis, an ECLYPSE 51® light microscope (Nikon, Tokyo, Japan) coupled to a microcamera was connected to a computer containing the image capture plate (ATI) and the IMAGE J® histometric software (National Institute of Mental Health, Bethesda, MD, USA). The three thirds of the root were analyzed, and from each studied tissue, 10 fields were selected, from which dentin and pre-dentin thickness and odontoblasts height were measured. From these data the means and standard deviations were obtained for the statistical analysis.

Data were tabulated and submitted to ANOVA Oneway statistical test. In case of significant difference, Tukey comparisons were performed when the hypothesis of equality of variances was verified or Tamhane when the hypothesis of equality of variance was rejected. Statistical tests were performed with a margin of error of 5.0%.

3 RESULTS

3.1 20-DAYS-OLD ANIMALS

At this age, only the cervical and middle thirds of the root are fully formed.

Histologically, the presence of thicker dentin in the cervical third, with the thickness gradually decreasing in the apical direction was observed in both control and experimental groups. This layer presented homogeneous and acidophilic matrix cut by the dentinal tubules containing the odontoblast cell processes inside. It was also observed the presence of a thin pre-dentin layer, with a weakly acidophilic shade between the dentin and the odontoblastic layer. Odontoblasts, located peripherally in the pulp region, were high prismatic, distributed in palisade and single layer; in the middle portion of the root they acquire a cuboid aspect. In the center of the pulp region, fibroblasts were identified as the most abundant cells, undifferentiated mesenchymal cells, blood vessels, all immersed in collagen matrix. Regarding the most apical portion, the beginning of the root apex formation was evidenced (Figure 1).

Figure 1. Photomicrographs of the root of the dental germ root of the upper first molars of 20-day-old rats. Images A, B and C represent, respectively, the cervical, middle and apical portions of the root of Group C. Images D, E and F represent, respectively, the cervical, middle and apical portions of the root of Group FL. Images G, H and I represent, respectively, the cervical, middle and apical portions of the root of Group FX. D, Dentin. PD, Pre-dentin. O, Odontoblasts. Bar equivalent to 56µm. HE staining.

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Regarding dentin thickness (Graphic 1A), the variability expressed by the coefficient of variation was not high, given that the highest value of this measure was a maximum of 39.79% (<50.0%). For the fixed margin of error, the only significant difference between the groups was observed in the cervical third ($p < 0.05$) and Tukey's paired comparisons tests showed a significant difference between the Group FX and Groups C and FL.

Regarding the pre-dentin thickness (Graphic 1B), no significant differences were recorded between groups for any of the measured thirds ($p > 0.05$).

Variability in odontoblasts data (Graphic 1C) was reduced since the highest coefficient value was 21.15% (<30%). In each third, odontoblasts length averages were correspondingly higher in Group C and lower in Group FX. Statistically significant differences were recorded between the groups in each third ($p < 0.05$) and Tukey's comparative tests show significant differences between Group FX and Group C in the cervical third and in the apical region, as well as between Group FX and Groups C and FL in the middle third.

Graphic 1. Graphic of the Mean and Standard Deviation of Dentin Thickness (1A), Pre-Dentin Thickness (1B) and Odontoblast Length (1C) in 20-day-old animals in micrometers (µm) in Groups C, FL and FX in the cervical, middle and apical thirds.

3.2 45-DAYS-OLD ANIMALS

Histologically, thicker dentin was observed in the cervical third, progressively decreasing its thickness in the apical direction. Compared to the 20-days-old animals, dentin showed more developed, with a more acidophilic matrix. It was also found the presence of a thin pre-dentin layer, thinner than in 20-days-old animals, situated between the dentin and the odontoblastic layer. This layer, located peripherally in the pulp region, is formed by cells distributed in palisade and single layer, with morphology similar to the described for the 20-days-old animals. In the center of the pulp it was observed the presence of fibroblasts, undifferentiated cells, blood vessels, all immersed in the amorphous intercellular matrix. In the apical third, the apex was open, without concluding its closure (Figure 2).

Figure 2. Photomicrographs of the root of the dental germ root of the upper first molars of 45-day-old rats. Images A, B and C represent, respectively, the cervical, middle and apical portions of the root of Group C. Images D, E and F represent, respectively, the cervical, middle and apical portions of the root of Group FL. Images G, H and I represent, respectively, the cervical, middle and apical portions of the root of Group FX. D, Dentin. PD, Pre-dentin. O, Odontoblasts. Bar equivalent to 123µm. HE staining.

Regarding dentin thickness (Graphic 2A), statistical data showed no significant differences between the thirds in the 45-days-old studied animals.

Regarding the pre-dentin thickness (Graphic 2B) there was a significant difference in the middle third for the Group FX, which is smaller than in the other groups.

In each third, the odontoblast length averages (Graphic 2C) were correspondingly higher in Group C and lower in Group FX.

Graphic 4. Graphic of the Mean and Standard Deviation of Dentin Thickness (4A), Pre-Dentin Thickness (4B) and Odontoblast Length (4C) in 45-day-old animals in micrometers (µm) in Groups C, FL and FX in the cervical, middle and apical thirds.

Statistically significant differences were recorded between the groups in each third ($p < 0.05$), and Tukey's comparison tests showed significant differences between the FL and FX groups and Group C in the cervical third, and between the FX group with Groups C and FL in the middle and apical thirds.

4 DISCUSSION

It is known that growth and development events are observed throughout the body and can be modified by exogenous factors such as nutritional changes (Vilela et al., 2001) or by pharmacological manipulations in the neurotransmitter system. Tetracycline, ciprofloxacin, anticonvulsants, diuretics are examples of drugs that promote proven deleterious effects on teeth (Tredwin et al., 2005). In addition, psychoactive drugs that can overcome the placenta, such as fluoxetine, can potentially interfere fetal development (Jacques-Belik, 2008).

In the present study, for both 20 and 45-days-old animals, it was observed that the development of dentin, pre-dentin and root odontoblasts layer in thickness and extension are compatible with dentinogenesis phase. These data corroborate those described by Losso in 2003, in which the chronology of the rhizogenesis of the first upper molars of rats indicated that on the twenty-first day of life the root is approximately two to three thirds; at forty days old the root is almost completely formed and from 60 days the root is already fully formed.

Regarding root histology at the analyzed ages, Kameyama in 1973 described that at three weeks of life, mesial and distal root growth have already occurred and Hertwig's epithelial sheath is short. About the root apex at this age, the author described it as broadly open. These data corroborate the histological report observed in the 20-days-old group. They are also in agreement with the histological findings of Imai et al. (2007) that in 20-days-old rats, tooth morphogenesis is almost complete and tooth eruption occurs.

From histometric analysis, in the 20-days-old group, the highest dentin thickness synthesized in the cervical third of the group FX may have been occurred due to greater root angulation. Since the roots of rat molars are very curved and divergent, it is possible that a more curved region had been sectioned at an angle that may induce misinterpretation of this greater thickness. However, overall (although not significant), both dentin and pre-dentin synthesis were higher in Group FX in all measured thirds.

Odontoblasts, on the other hand, presented their lengths decreased in group FX among the third thirds, which may portray a reduction in the synthesis organelles in the two analyzed ages. The hypothesis that fluoxetine may change the morphology of odontoblasts is plausible since several studies have already shown the influence of other substances on their differentiation and/or function, showing the sensitivity of these cells (Sakakura et al., 1989). However, this data is incompatible with the increase in dentin thickness. Excluding possible failures in the processing technique, one hypothesis to explain the increase in dentin thickness with reduced odontoblastic volume would be that this cell is rapidly synthesizing and apically degranulating its synthesis content, which may be of greater proportion for a given component in detriment of the other.

Although in vitro studies by Moisewitsch and Lauder (1996) state that serotonin has a strong stimulating role in the development of dental germs and that the use of fluoxetine was able to inhibit these same processes, the data from the present study did not suggest the same ability, since, histologically, all germs evolved according to the odontogenesis pattern pertinent to each age. It is possible that this divergence is due to the different dosage of the used drug or even to methodological procedures.

Other oral structures were also previously analyzed regarding the effect of using fluoxetine. Cavalcanti et al. (2009) analyzed the influence of fluoxetine on the temporomandibular joint of rats and Silva et al. (2010) analyzed the influence of fluoxetine on the amelogenesis of rats, both found no changes in the development of these studied craniofacial regions. Battaglino et al. (2007), in their study, administered systemic fluoxetine daily for 6 weeks in mice to find out the action of this drug on bone mass. The results were not significant for the cortical bone; however, major changes in the architecture of the trabecular component, increased volume and bone surface were observed when comparing control and treated animals. Recently, Koura et al. (2019) demonstrated that fluoxetine inhibited progenitor bone cell proliferation, differentiation and mineralization in a dose-dependent manner. The study proposed that fluoxetine induced apoptosis during bone cell differentiation and reduced

osteoblast proliferation, reduced bone cell mineralization and the formation of new healthy cells. Fluoxetine is not only capable of inhibiting serotonin activity, but also directly affects cell proliferation and apoptosis of body tissues.

The statistically significant histometric findings obtained in this research, alone, are not sufficient to affirm the occurrence of interference in the root dentinogenesis process. In addition, histological aspects of the analyzed samples maintained the same morphological pattern between the groups, also presented in other studies.

The literature remains scarce on this subject, which requires more research in order to clarify questions about the influence of fluoxetine on the development of root dentinogenesis.

5 CONCLUSION

Fluoxetine use, especially at a dose of 20 mg/Kg, decreases the size of odontoblasts and increases dentin synthesis in animals with 20 and 45-days-old. However, the present study alone is not sufficient to conclude the exact role of fluoxetine in dentinogenesis. Nevertheless, histometric data suggest that its application may interfere in root dentinogenesis of rats whose mothers were treated with fluoxetine during pregnancy.

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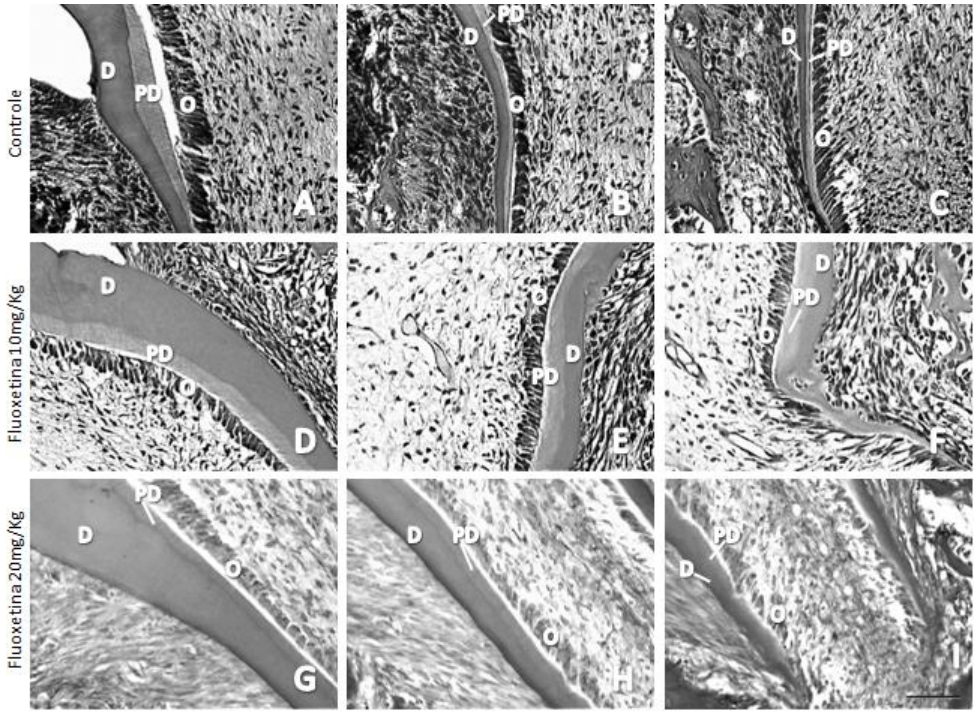

Figura 1. Fotomicrografias da raiz do germe dental de primeiros molares superiores de ratos com 20 dias de vida. As imagens A, B e C representam respectivamente as porções cervical, média e apical da raiz do Grupo C; as imagens D, E e F do Grupo FL; e, as imagens G, H e I do Grupo FX. D, Dentina. PD, Pré-dentina. O, Odontoblastos. Barra equivalente a 56µm. Coloração HE.

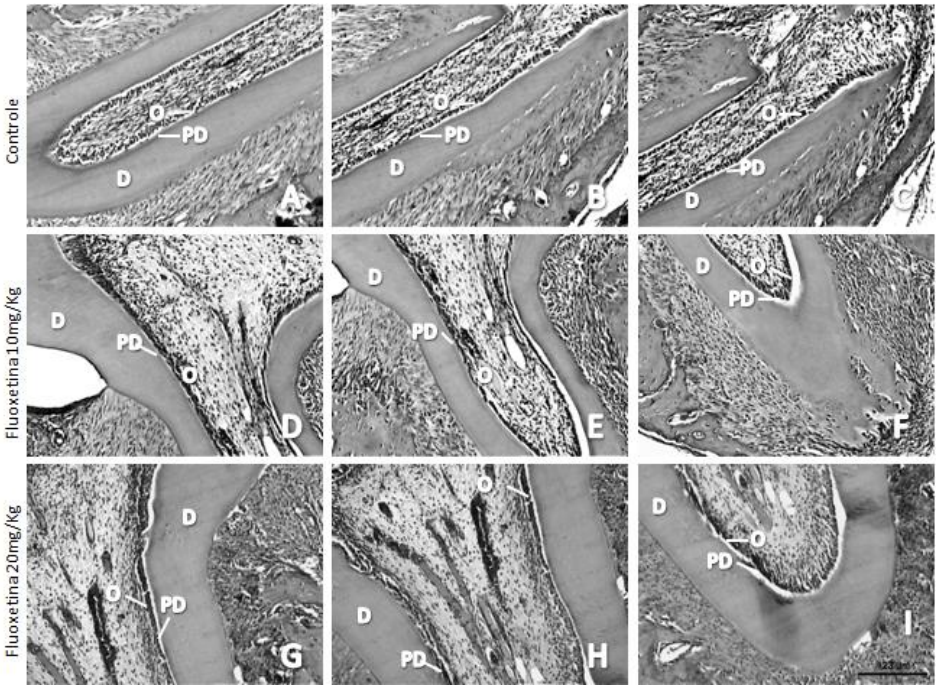

Figura 2. Fotomicrografias da raiz do germe dental de primeiros molares superiores de ratos com 45 dias de vida. As imagens A, B e C representam respectivamente as porções cervical, média e apical da raiz do Grupo C; A imagens D, E e F do Grupo FL; e, as imagens G, H e I do Grupo FX. D, Dentina. PD, Pré-dentina. O, Odontoblastos. Barra equivalente a 123µm. Coloração HE.

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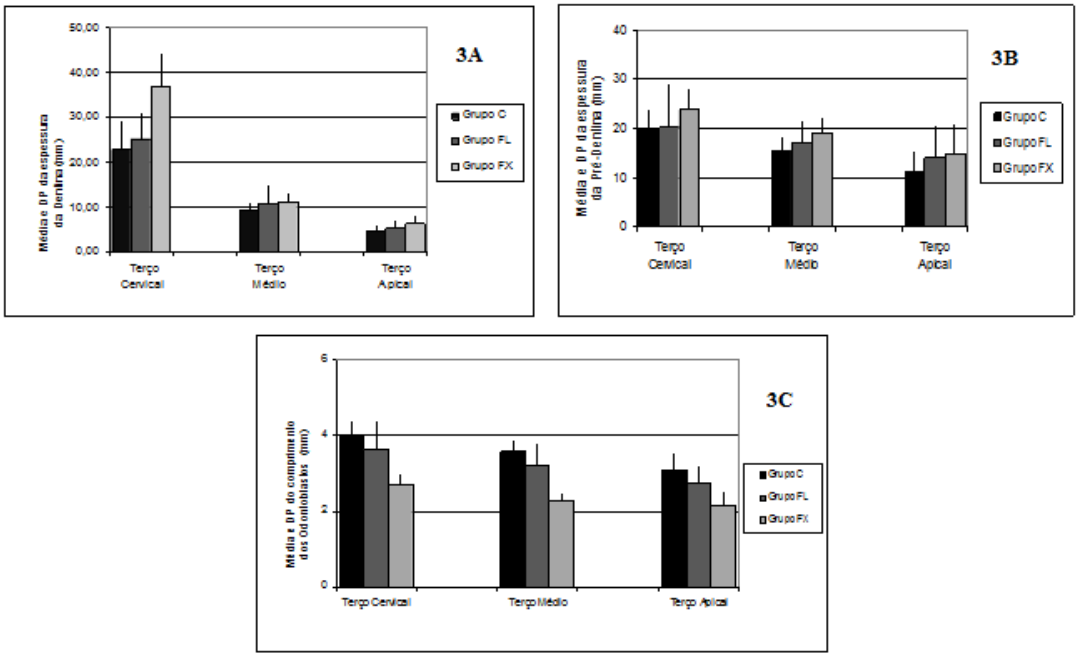

Figura 3. Gráfico da Média e Desvio Padrão da espessura da Dentina (3A), da espessura da Pré-Dentina (3B) e do comprimento dos Odontoblastos (3C) em animais com 20 dias de vida em micrometros (µm) nos Grupos C, FL e FX nos terços cervical, médio e apical

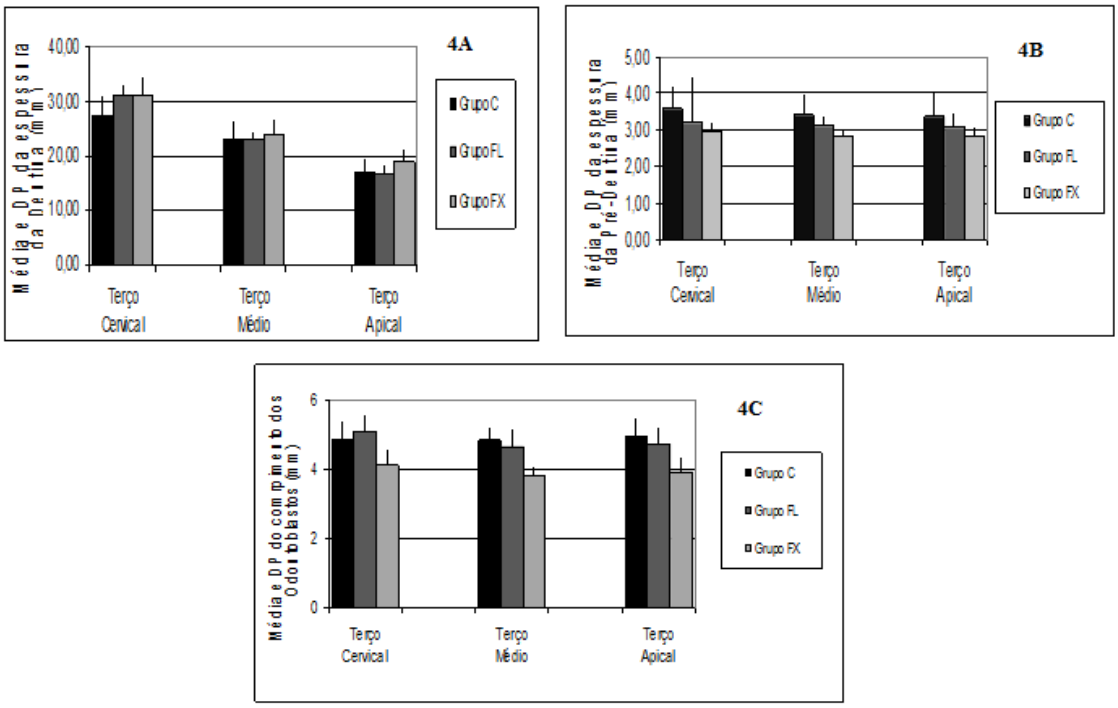

Figura 4. Gráfico da Média e Desvio Padrão da espessura da Dentina (4A), da espessura da Pré- dentina (4B) e do comprimento dos Odontoblastos (4C) em animais com 45 dias de vida em micrometros (µm) nos Grupos C, FL e FX nos terços cervical, médio e apical