Orthodontic tooth movement following analgesic treatment with Aspirin and Algocalmin. An experimental study

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Abstract

The objective of this study was the tracing of the effect of Aspirin and Algocalmin, two of the most frequently used analgesics after the application of orthodontic appliances, on the dental displacements, starting from the hypothesis according to whom any substance that inhibits prostaglandins’ production will have as result the inhibition of the osteoclasts’ activity and of the orthodontic tooth movements implicit.

Twenty-four male Wistar rats, separated into three groups were used. Group I (control) included eight rats in which the orthodontic device was applied, without a subsequent administration of any analgesic; Group II – eight rats in which after the device application Aspirin was administrated; and Group III – eight animals in which Algocalmin was administrated. A histological study was completed in order to establish the size of bone areola. Average mesial displacement of the first left inferior maxillary molar 28 days after applying the orthodontic device was of 3.61±0.29 mm for the control group. The average displacement in the group in which Aspirin was administrated was 0.03 mm. In the group treated with Algocalmin, the dental displacement was of 0.19±0.08 mm. Histological examination revealed the presence of large sizes bone areola in control group (244 μm), more reduced in the group treated with Aspirin (74 μm), and intermediate in that treated with Algocalmin (127 μm). Treatments with Aspirin and Algocalmin in experimental groups, immediately after the orthodontic device application, induced a decreased dental displacement rate.

Keywords: Aspirin, Algocalmin, orthodontic device, tooth movement, bone areola.

Introduction

Orthodontic treatments presume correction of various dento-maxillary anomalies with the purpose of restore the patients’ dental arches, both from a physiognomic and a functional point of view. This can be accomplished by the displacement of the malposed tooth or teeth applying a force at the level of the dental crown. This force is consequently transferred to root, periodontal ligament and alveolar bone. If the force that operates onto the teeth has appropriate characteristics, the tooth can be displaced through the subjacent alveolar bone, thus being produced its remodeling [1].

Henneman et al. [2] described a four steps theoretical model of orthodontic tooth movement. Within it, the last step presumes a joining of periodontal ligaments’ remodeling with localized resorption and apposition processes of the alveolar bone. These bone-remodeling phenomena, necessary for the teeth displacement in the subjacent alveolar bone, are always accompanied by an acute, localized inflammatory process [3, 4].

The acute inflammation progresses with discomfort sensation or pain, pursuant to stimulation of the nerve endings in the periodontium. These symptoms display large inter-individual variations. From physiological point of view, the pain is the body’s la reaction to tissue lesions [5]. It is associated with the presence of the inflammatory process, and in these conditions, a series of analgesic therapies are efficient upon the local inflammation.

According to the model of Henneman et al., osteocytes release a series of mediators during the orthodontic dental displacements; among them are prostaglandins, with role in stimulation the activity of osteoclasts and osteoblasts [2]. It is thus explicable why any substance that inhibits the production of prostaglandins will have as result the inhibition of the previous mentioned cells’ activity and of the orthodontic dental displacements implicit. Prostaglandins are produced in the human organism by the action of two isomer forms of cyclooxygenase (COX), COX-1, and COX-2 respectively, upon the arachidonic acid. In this manner, two types of prostaglandins result, depending on the isoenzyme that operates on substrate (arachidonic acid) [6]. Both types of enzymes (COX-1 and COX-2) are inhibited by non-steroid anti-inflammatory drugs such Aspirin and Algocalmin, the last one having Metamizolum natrium as active principle. They produce the irreversible acetylation of the protein and thus its inactivation [7].

Taking into consideration all these above mentioned, the objective of our study was to assess the effect of Aspirin and Algocalmin, the most frequent used analgesics following the application of orthodontic device, upon the dental displacements.

Materials and Methods

Animals

The study is a part of a bigger one, which was approved by the decision of the Ethical Commission of the “Iuliu Haţeganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania, No. 90/10.05.2010. Twenty-four male Wistar rats, grown in the Animal House of “Iuliu Haţeganu” University of Medicine and Pharmacy were used in this study. The animals, weighing
260–280 g at the beginning of the experiment, were kept in cages in a chamber with an ambient temperature ranging between 21.5–23°C, and a relative humidity of 65%. The rats were exposed to standard cycle of 12 hours light/dark.

In order to prevent the appearance of an excessive masticatory force, and implicit to reduce the risk of the device detachment during the experiment, the rats were *ad libitum* fed with a light diet (standard fine granules – “Cantacuzino” Institute, Bucharest, Romania) and water.

**Study design**

The animals were randomly divided in three groups: Group I (control) consisted of eight rats in which the orthodontic device was applied, without a subsequent administration of any medicinal preparation. Group II consisted of eight rats treated with Aspirin (Upsarin, Bristol–Myers Squibb, France) after the device application. 1.5 mL of Aspirin solution in concentration of 20 mg/mL was administrated each two days for 10 days by gastric gavage [30 mg/body weight (b.w.)/two days], starting with the next day after the device application. Group III included eight rats in which the device was applied, and then Algocalmin (S.C. Zentiva S.A., Romania) was administrated by gastric gavage. 1.2 mL of Algocalmin solution in concentration of 5 mg/mL was administrated each two days for 10 days (6 mg/b.w./two days), starting with the next day after the device application.

**Experimental orthodontic displacement**

Before the orthodontic device application, rats were anesthetized with 2% Xylazine (Xylazine, Alfasan International B.V., Woerden, Netherlands), 0.1 mL/kg b.w. and 10% Ketamine (Vetased, S.C. Pasteur, Filipești, Romania), 0.15 mg/kg b.w.

The orthodontic device consisted in a nickel–titanium (NiTi) closed coil-spring (Dentsply International, York, Pennsylvania, U.S.A.), that generated a force of 25 g. The coil-spring was tensioned and applied between the left inferior incisor and the first left inferior molar of the rat. Force produced by the coil-spring was measured using a dynamometer (Kontaktor, Horex, Bad Homburg, Germany).

In order to ensure the orthodontic device retention, teeth were previously prepared. A perforation was performed in each tooth (mesio-distal for incisor, and buccolingual for molar) with a micromotor (Marathon N7 Dental Micro Motor, Meta Dental Corp., Elmhurst, New York, U.S.A.) having attached an efilated diamond cutter.

In order to set the tensioned coil-spring, a stainless still wire with the diameter of 0.2 mm was used. One of its ends was fixed in the previously made perforations, while the opposite end was fixed by the tensioned coil-spring.

**Measurement of dental displacement**

Twenty-eight days after the orthodontic device application, test animals were sacrificed through ether (Diethyl ether, Merck KGaA, Darmstadt, Germany) anesthesia, followed by dislocation of the cervical spine. Subsequently, their mandible was removed (area from the rats’ oral cavity at whose level the experimental study was performed).

The level of dental displacements was established using a digital micrometer (Digital Caliper, Cromwell Industrial Tools, Wigston, Leicester, U.K.). Because of the particular morphology of the teeth and alveolar bone in rodents, respectively long and vigorous root of the incisor, and short of the molar, the dental displacement secondary to the orthodontic device application was represented only by a migration of the first molar towards mesial, the incisor position remaining unchanged.

In these conditions, the total dental displacements was assessed by the measurement of the distance between the first and the second molar, taking into account that in normal physiological conditions there is a tight contact (a bridge) between them.

**Histological study**

Fixation was performed in a first step, using an ethanol–formalin–acetic acid based fixative (prepared from 20 mL concentrated formalin, 50 mL glacial acetic acid, and 785 mL 96% ethyl alcohol). Next, the alveolar bone collected from the tested rats was decalcified in 10% nitric acid, for 10–12 days, at 4°C, and then preserved in distilled water for 24 hours. Samples were subsequently included in paraffin and sectioned at 5–7 μm. Vertical and oblique sections were obtained at the level of the mesial face of the first left inferior molar, that represents a pressure area secondary appeared after the orthodontic device application. Sections were stained with Hematoxylin–Eosin (HE) and examined under the light microscope (Leica DM 750, Germany). Morphometric analysis employed the LAS EZ software (Germany) and photomicrographs were taken with Leica ICC 50 HD camera (Germany).

The histological examination evaluated the structure of the trabecular alveolar bone: the size and contour of bone areoles, and the appearance of bone matrix and cells within trabeculae.

**Statistical data analysis**

Distribution of variables involved in analysis was verified with Shapiro–Wilk test. The results proved that these did not follow a normal distribution.

Statistical comparison of rank average for three groups was performed with the Kruskal–Wallis test, while the Mann–Whitney test was employed for the statistical comparison of rank average for two groups.

The threshold of significance for the used tests was considered $\alpha=0.05$. SPSS 13.0, Microsoft Excel and Statistica 7.0 were the applications used for statistical computations.

**Results**

The orthodontic devices were well tolerated by rats of all three groups taken into study. Feeding of animals was accomplished without major problems.

In Table 1, dental displacements obtained in the case of the three groups taken into study are presented. Descriptive statistical parameters for the left inferior first molar displacement in the three groups of rats are presented in Table 2.
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Table 1 – Dental displacements obtained after 28 days for the three groups of rats (N=8)

<table>
<thead>
<tr>
<th>Group</th>
<th>1.</th>
<th>2.</th>
<th>3.</th>
<th>4.</th>
<th>5.</th>
<th>6.</th>
<th>7.</th>
<th>8.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I – control</td>
<td>3.8 mm</td>
<td>3.2 mm</td>
<td>3.5 mm</td>
<td>3.4 mm</td>
<td>4.1 mm</td>
<td>3.4 mm</td>
<td>3.6 mm</td>
<td>3.7 mm</td>
</tr>
<tr>
<td>Group II – Aspirin adm.</td>
<td>0 mm</td>
<td>0 mm</td>
<td>0 mm</td>
<td>0 mm</td>
<td>0.1 mm</td>
<td>0 mm</td>
<td>0.1 mm</td>
<td>0 mm</td>
</tr>
<tr>
<td>Group III – Algocalmin adm.</td>
<td>0.1 mm</td>
<td>0.2 mm</td>
<td>0.3 mm</td>
<td>0.1 mm</td>
<td>0.3 mm</td>
<td>0.2 mm</td>
<td>0.2 mm</td>
<td>0.1 mm</td>
</tr>
</tbody>
</table>

Table 2 – Descriptive statistical parameters of the dental displacements on groups

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Arithmetical average [mm]</th>
<th>Standard deviation</th>
<th>Standard error</th>
<th>Confidence interval of 95%</th>
<th>Minimum [mm]</th>
<th>Median [mm]</th>
<th>Maximum [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I – control</td>
<td>8</td>
<td>3.61</td>
<td>0.29</td>
<td>0.10</td>
<td>3.37 – 3.85</td>
<td>3.2</td>
<td>3.6</td>
<td>4.1</td>
</tr>
<tr>
<td>Group II – Aspirin adm.</td>
<td>8</td>
<td>0.03</td>
<td>0.05</td>
<td>0.02</td>
<td>-0.01 – 0.06</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>Group III – Algocalmin adm.</td>
<td>8</td>
<td>0.19</td>
<td>0.08</td>
<td>0.03</td>
<td>0.12 – 0.26</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
</tr>
</tbody>
</table>

From Table 2 results that the mean displacement of the first left inferior molar towards the mesial in Group I, control, after 28 days from the device application was of 3.61±0.29 mm. After the same time interval, in the group in which Aspirin was administrated by gastric gavage (Group II), the mean displacement was of only 0.03 mm (in six rats of this group any dental displacement was observed). In the group in which Algocalmin was administrated (Group III), the dental displacement after 28 days from the debut of force action was of 0.19±0.08 mm.

Comparison of the dental displacement between groups, taken two by two, is emphasized in Table 3. Thus, is pointed out a statistical significant difference between the dental displacements in control group and the groups in which were administrated Aspirin (p=0.0001), and Algocalmin (p=0.0001) respectively. A statistical significant difference was obtained by comparison of the dental displacements between the groups in which the analgesics were administrated (p=0.001).

Position of molars in Group I (control), in which was applied only the orthodontic device, after 28 days from the debut of force action, is presented in Figure 1. Displacement of the first inferior molar to the mesial is observed by the appearance of a space between the first and the second molar.

Figure 1 – Displacement of the first left inferior molar to mesial in one of the animals included in control group.

The histological study had as purpose the sizing of bone areola. They are located at the level of the alveolar bone, being produced by resorption processes by osteoclasts.

Histological preparations were obtained by collecting the alveolar bone from the level of the mesial face of the first left inferior molar that represents a pressure area secondary appeared after the orthodontic device application. At this level, bone resorption phenomena occur following to mesial traction of the molar.

Existence of certain bone areola of increased sizes presumes an intense osteoclastic activity, and the presence of certain resorption processes at the level of the alveolar bone respectively. Diminution in size of these areola indicates implicit, a reduction of bone resorption processes.

Figure 2 – Displacement of the first inferior molar to mesial with 0.1 mm in Aspirin treated group.

In the control group, the areoles had variable diameters and shapes, with irregular contours and intercommunicating with each other. Within bone trabeculae, the bone matrix was heterogeneous and lamellae had a random orientation (Figure 4). Both active and inactive osteoblasts

Figure 3 – Intermediate displacement of the first inferior molar to mesial in the Algocalmin treated group.

Table 3 – Comparison of the dental displacements of the first molars in the three groups, taken two by two

<table>
<thead>
<tr>
<th></th>
<th>Ranks average</th>
<th>Ranks average</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I – Group II</td>
<td>12.50</td>
<td>4.50</td>
<td>0.0001</td>
</tr>
<tr>
<td>Group I – Group III</td>
<td>12.50</td>
<td>4.50</td>
<td>0.0001</td>
</tr>
<tr>
<td>Group II – Group III</td>
<td>4.88</td>
<td>12.13</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Position of molars in the group in which after the orthodontic device application Aspirin was administrated (Group II) is emphasized in Figure 2, where is presented one of the two animals in which a displacement of the first inferior molar to mesial with 0.1 mm existed.

Dental displacements in the group in which, after the application of the coil-spring, Algocalmin was administrated (Group III) are emphasized in Figure 3. These are intermediate as compared to those obtained in the other two groups, being statistical significant more reduced than in the group in which no analgesics preparation was administrated, and significantly increased than in the Aspirin treated group respectively.

Figure 4 – Example of bone areola at the level of the alveolar bone in control group.
lined the areoles. Osteocytes at the periphery of the trabeculae, in the proximity of the areoles showed signs of deformation, were irregular in shape and with pyknotic nuclei (Figure 5).

In Group II, areoles were smaller compared with the control, approximately equal in size and had a regular contour; no communication could be seen between areoles. Bone trabeculae were thick, composed of regularly arranged lamellae (Figure 6). Bone matrix appeared homogenous and osteocytes had a normal aspect; inactive osteoblasts lined the areoles surface (Figure 7).

In Group III, areoles were intercommunicating with each other and irregular in shape, but smaller compared with the control. Bone trabeculae were composed of homogenous bone matrix and irregularly oriented lamellae (Figure 8). Both active and inactive osteoblasts lined the surface of bone trabeculae; in some zones, degenerating osteocytes were identified (Figure 9).

Figure 4 – Photomicrograph of the trabecular alveolar bone in the control group. HE staining, ×200.

Figure 5 – Photomicrograph of the bone areoles and trabeculae in the control group. HE staining, ×400.

Figure 6 – Photomicrograph of the trabecular alveolar bone in Group II. HE staining, ×200.

Figure 7 – Photomicrograph of the areoles and bone trabeculae in Group II. HE staining, ×400.

Figure 8 – Photomicrograph of the trabecular alveolar bone in Group III. HE staining, ×200.

Figure 9 – Photomicrograph of the areoles and bone trabeculae in Group III. HE staining, ×400.
Discussion

Immediately after applying the orthodontic force upon the tooth that needed to be displaced, resorption of the alveolar bone and de-tensioning of periodontal ligaments occurred in the pressure area, while in the traction area bone apposition and tensioning of periodontal ligaments were present. Tensioning of the collagen fibers that bind the tooth to bone, secondary to the force application, will also determine a tensioning of the alveolar bone at the level of traction area [1].

An important theory describing the mechanism of bone reaction in the moment of its tensioning involves the effect of capillary pressure upon the bone cells [8]. It was presumed that at the level of surfaces where the intracanalicular plasmatic flux is reduced, the apoptosis of osteocytes is produced, with a secondary appearance of osteoclasts at this level [9]. In the following step, a deformation of cells from the tooth adjacent tissues occurs. This is accomplished both through a direct mechanism, that presumes their tensioning secondary to periodontal ligaments tensioning, and an indirect one, induced by the increase of the capillary blood pressure [10].

It is necessary that the cells of the periodontal ligament to display an increased sensibility to mechanical stimuli in order to achieve the previously mentioned phenomena. This fact was proved by a series of in vitro studies [11], in which fibroblasts from the periodontal ligament structure were reacting to the mechanical deformation by production of cytokines and matrix metalloproteinases with role in the collagen degradation. However, osteoblasts too, not only the fibroblasts display an increased sensitivity to the mechanical stimuli. They have released a series of signal molecules, such as prostaglandins, after their direct and indirect deformation [12].

The tensioning of osteocytes in the alveolar bone structure appears as consequence of plasma exit at the level of the bone canaliculi, secondary to application of an orthodontic force. This is transmitted to the cell via some specific receptors or via cytoskeleton. The in vitro answer of the osteocytes to the increase of the capillary blood pressure consists in the production of mediators, such as nitric oxide (NO) and prostaglandins [13, 14].

Remodeling is the last step in the process of tooth displacement secondary to an orthodontic force application. The rhythm of the dental displacements is diminished or they may even be completely blocked under the presence of certain factors, which interfere in the different steps of this mechanism, delaying its normal evolution. Thus is delayed the achievement of the essential objective of the orthodontic treatment: that of correction of the malpositioned tooth/teeth position, in the purpose of their alignment on the arch.

Previous studies [3, 15, 16] proved a statistically significant increase of pro-inflammatory interleukin levels in the gingival fluid of orthodontic tractioned teeth 24 hours after the beginning of the treatment, which denotes initiation of a localized inflammatory process vital for dental displacement. And, as any inflammatory process is accompanied by pain, this sensation is only natural in the initial stages of the orthodontic treatment.

Taking into consideration all the above-mentioned factors, a whole range of analgesics are massively prescribed for diminishing the pain accused by patients under orthodontic treatment. Among them, Aspirin and Algocalmin (having as active substance water-free Metamizolum natrium) are the most frequently used in order to reduce the pain sensation in these patients.

During dental orthodontic displacements, osteocytes release a series of mediators, among which prostaglandins that stimulate osteoclasts’ activity [14]. If prostaglandin production is inhibited (by the use of non-steroidal anti-inflammatory substances, for example), this diminishes the osteoclastic activity and dental orthodontic displacement. Thus, we investigated the effects of Aspirin and Algocalmin, the analgesics most frequent utilized after the application of the orthodontic devices, upon the dental displacements.

A multitude of species have been utilized for the measurement of the dental displacements in experimental animals, i.e., rats [17], rabbits [18], dogs [19], cats [20], and even monkeys [21]. In the present study, rats were used as experimental animals, because of their accessibility. The number of experimental animals included into study was of 24, randomly divided into three groups.

A high number of systems, generators of forces have been utilized in studies of the experimental dental displacements in animals; among these may be mentioned elastics, orthodontic arcs and rings, springs with various designs and the coil-springs. Some of these mechanisms generators of forces have adverse secondary effects upon the experimental animals’ periodontal tissue (i.e., rings) [22], and other request laboratory and complex surgical techniques [22].

Application of the coil-spring in our study necessitated an accessible laboratory technique, and its retention with the wire introduced in orifices previously prepared on the experimental animals’ teeth was very good; none of the devices detached during the study. Moreover, any affection of the periodontal tissues was observed in the groups of animals taken into study.

In the control group, the morphology of the alveolar bone reflected the intense bone remodeling associated with orthodontic movement. The irregular contour of the areoles and the heterogeneous aspect of the bone matrix suggest that in some zones the trabeculae underwent resorption, whereas in other zones, formation of new bone matrix occurred. Active osteoblasts were located on the bone surface where new bone was formed, whereas inactive osteoblasts were associated with bone resorption. Osteocytes adjacent to the areoles showed signs of degeneration due to the pressure exerted by the orthodontic device and transmitted by the canaliculi interconnecting the peripheral lacunae to the areoles.

In Group II, no signs of bone remodeling could be seen.

In Group III, features common to both control and Group II could be seen. Bone remodeling is present, but at a slower rate compared with the control.

Clinical and histological data in our study confirms the initial hypothesis. Thus, the non-steroid anti-inflammatory, such as Aspirin and Algocalmin (water-free Metamizolum natrium), secondary administrated to orthodontic devices with the purpose of pain sensation reduction,
diminish the dental displacement through the subjacent alveolar bone to disappearance.

By Aspirin and Algocalmin administration is thus delayed the deployment of the orthodontic treatment in good conditions, and the displacement through the subjacent alveolar bone of the ectopic teeth respectively, in the purpose of their alignment on the arch.

An interesting result of our study was the presence of a statistical significant difference between the level of the dental displacements in the group in which Aspirin was administrated as compared to that treated with Algocalmin (\(p=0.001\)). A possible explanation would be the mechanism of COX-1 and COX-2 inhibition, less intense of Algocalmin as compared to that of Aspirin, but this must be proved by further studies.

The results of this study suggest that in the orthodontic-treated patients, for attenuation of the pain sensation appeared during the treatment, is indicated the use of analgesics whose mechanism of action does not involve the cyclooxygenase inhibition, as it happens in the case of Aspirin and Algocalmin.

Conclusions

This study proved the existence of a statistical significant decrease of the dental displacements in the groups in which Aspirin and Algocalmin was administrated as compared to the control one (\(p=0.0001\)). A statistical significant difference also resulted by comparison of dental displacements recorded between the groups in which the analgesics were administrated (\(p=0.001\)), the displacement being more reduced in the Aspirin treated group. The histological proved that in the control group, the morphology of the alveolar bone reflected the intense bone remodeling associated with orthodontic movement, while in the group in which Aspirin was administrated, no signs of bone remodeling could be seen. In the group in which Algocalmin was administrated, features common to both groups could be seen. Bone remodeling is present, but in a slower rate compared with the control.

Conflict of interests

The authors declare that they have no conflict of interests.

References


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