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Development of an Animal Model for Coronectomy

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Purpose: This study aimed to develop an animal model suitable for coronectomy research. **Materials and Methods:** Eighteen Sprague-Dawley rats were divided into six groups: incisor control (InC), incisor flap (InF), incisor non-flap (InNF), molar control (MC), molar flap (MF), and molar non-flap (MNF). Coronectomy was not performed in the control groups (InC and MC). In the incisor (In) groups, coronectomy was performed on the mandibular incisors, with flap elevation in the InF group and without flap elevation in the InNF group. In the molar (M) groups, coronectomy was performed on the maxillary first molar, with flap elevation in the MF group and without flap elevation in the MNF group. The incisor groups were sacrificed on day 7, and the molar groups on days 7 and 14. Clinical healing, tooth movement, and histological and immunohistochemical analyses were performed. **Results:** InF and InNF groups showed tooth eruption similar to or the same as that before coronectomy, whereas the MF and MNF groups' roots moved slowly. In InF and InNF groups, the pulp at the maturation zone was mineralized, but apical pulp vitality was maintained. MF and MNF groups showed bacterial infection and inflammation on day 7, with mineralization on day 14; however, apical pulp vitality was maintained. The MF group showed varied healing patterns, whereas the MNF group had consistent results across individuals. **Conclusion:** Both incisors and molars are meaningful models for coronectomy. However, for consistent experimental results, coronectomy without flap elevation on the maxillary first molar is recommended. [J Korean Dent Sci. 2024;17(4):187-200]

Key Words: Animal model; Coronectomy; Osteoclastogenesis; Bone remodeling

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Introduction

The mandibular third molar is the most commonly encountered impacted tooth in clinical practice. Owing to caries, pericoronitis, adjacent tooth decay, alveolar bone loss, and the potential for cysts or tumors, it is frequently subjected to extraction[1]. Several complications can occur during the extraction of mandibular third molars. According to one study, damage to the inferior alveolar nerve (IAN) occurs at a frequency of 0.4% to 8%[2]. One study reported that 19% of patients who underwent surgical extraction of impacted third molars experience IAN damage[3]. A treatment method that can reduce the risk of nerve damage is coronectomy, which involves removing only the crown while leaving the roots close to the nerve[4]. If there are no significant complications, the remaining roots can be maintained or extracted after confirming that they have moved and separated from the mandibular canal. Coronectomy was first introduced by Ecuyer and Debien in 1984 to reduce the risk of damage to the IAN and lingual nerves. Since then, various studies have reported that it is an effective alternative treatment for the prevention of IAN injuries. Renton et al.[3] reported that coronectomy does not increase the risk of dry socket or infection, and is effective in reducing IAN damage. Leung and Cheung[2] found that coronectomy resulted in lower incidences of pain and dry sockets, although the infection rate was similar to that of total excision. Hatano et al.[5] reported that coronectomy can reduce the risk of IAN injury in high-risk patients evaluated using dental computed tomography (CT). Similarly, Cilasun et al.[6] also found that coronectomy could lower the complication rate in high-risk patients, as assessed using CT.

Coronectomy has not been recognized as a new medical technology in Korea because of the lack of sufficient research data to evaluate its safety and efficacy[7]. To evaluate the safety and efficacy of coronectomy, studies investigating the biological responses and mechanisms of the pulp and surrounding tissues in animal models are necessary. However, such research is still lacking and an appropriate animal model is yet to be established.

The incisors and molars of rats exhibit different developmental patterns. Incisors continuously erupt and can be divided into secretory and maturation zones based on the length of the tooth[8]. In contrast, molars stop erupting when their roots are fully formed[9,10]. Therefore, coronectomy is expected to exhibit different patterns in these teeth. Analysis of the tissue responses to coronectomy in these different types of teeth could provide valuable information.

This study aimed to develop an animal model that can be effectively used in future coronectomy experiments by comparing clinical healing patterns, measuring tooth movement, and conducting histological and immunohistochemical analyses of the molars and incisors in rats using various methods. The hypothesis of this study is that rat incisors, with their continuous apical tooth formation, are expected to serve as a model for coronectomy in immature human roots, while molars, which stop tooth formation after root apex development, could replicate mature root characteristics as a coronectomy animal model.

Materials and Methods

1. Study design

Eighteen 12-week-old female Sprague-Dawley rats (average weight, 290 g) were used in this study. Rats were randomly divided into six groups based on the location and method of coronectomy (Fig. 1A): 1) Incisor Control Group (InC), 2) Incisor Flap Group (InF), 3) Incisor Non-Flap Group (InNF), 4) Molar Control Group (MC), 5) Molar Flap Group (MF), and 6) Molar Non-Flap Group (MNF). The protocol was approved by the Institutional Animal Care and Use Committee of Yonsei Medical Center, Seoul, Korea, and the animals were selected, managed, and operated in accordance with their guidelines (AICUC 2020-0278). The animals were housed in a room with

a 12-hour light-dark cycle, maintained at a temperature of 20°C±5°C and humidity of 50%±10%, with access to standard food and water.

2. Study protocol (Fig. 1, Fig. 2)

All experiments were conducted after administering an intraperitoneal injection of a combination of Zoletil® (tiletamine and zolazepam, 50 mg/ml, 0.6 ml/kg body mass; Virbac lab., Carros, France) and Rompun® (zylazine, 23.32 mg/ml, 0.4 ml/kg body mass; Bayer, Leverkusen, Germany). In the InF group, a crevicular incision was made in the mandibular incisors using a #12 blade. The flap was elevated with a periosteal elevator and coronectomy was performed on both mandibular incisors up to the buccal alveolar crest height using a 016 carbide fissure bur (Komet, Brasseler, Lemgo,

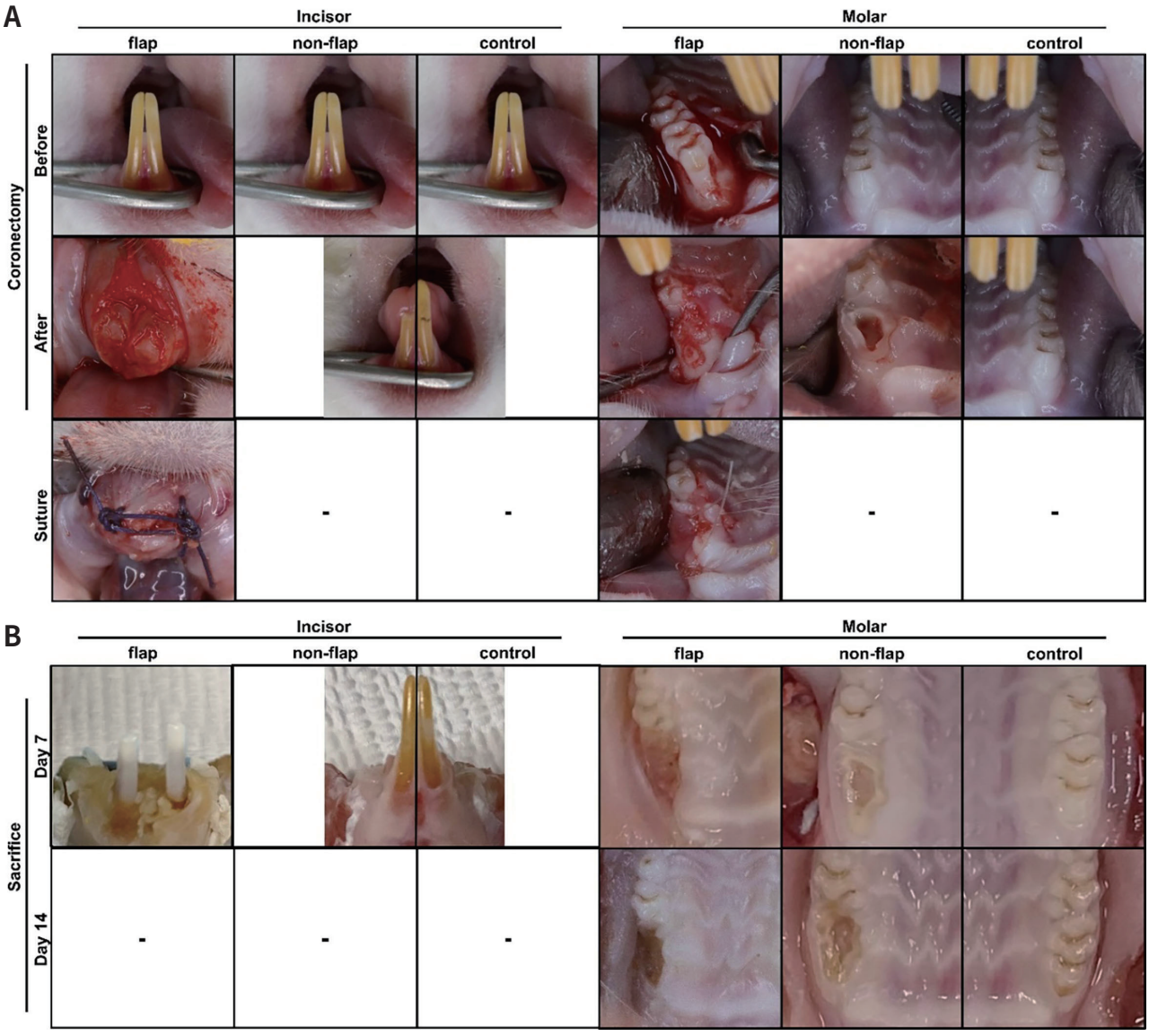

Fig. 1. Procedures of coronectomy in the incisor and molar groups. (A) Photograph of applied coronectomy. (B) Photographs 7 and 14 days after coronectomy.

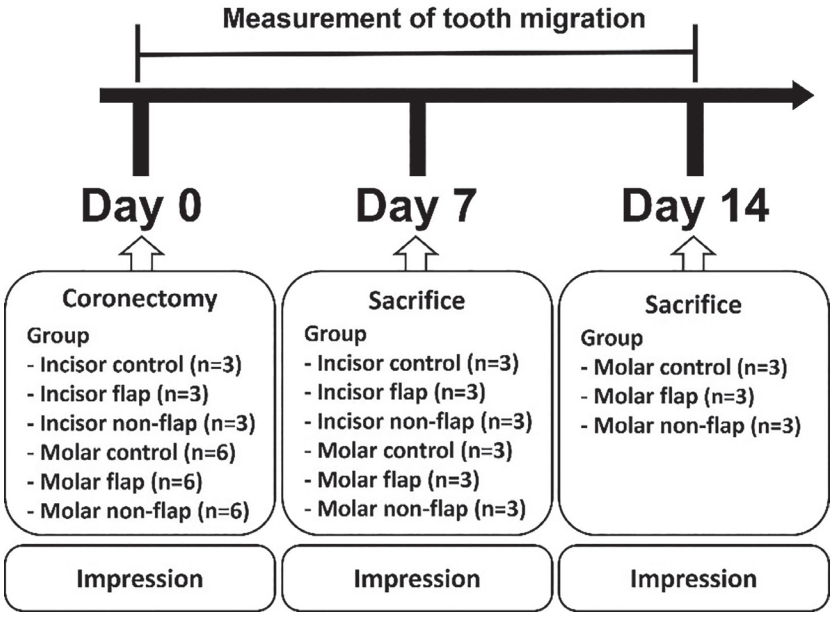

Fig. 2. Experimental protocol.

Germany). The remaining roots were covered with buccal and lingual flaps and sutured with 6-0 absorbable surgical sutures (Monosyn, Braun, Germany). In the InNF group, coronectomy was performed on the right mandibular incisor up to the level of the mesial interdental papillary tip using a diamond disk (Komet, Brasseler, Lemgo, Germany) and a carbide bur, with the left mandibular incisor serving as the InC. For the MF group, horizontal incisions were made on the mesial side of the left maxillary first molar using blades #12 and #15, followed by a crevicular incision around the entire first molar and the mesial half of the second molar. The flap was elevated with a periosteal elevator and coronectomy was performed up to the buccal and lingual alveolar crest heights using a 016 carbide fissure bur. The remaining roots were covered with an extended buccal flap and sutured using 6-0 absorbable surgical sutures. In the MNF group, coronectomy was performed on the left maxillary first molar up to the gingival margin height using a 016 carbide fissure bur, with the right maxillary first molar serving as the MC. Rats in the incisor groups were sacrificed on day 7, and those in the molar groups were sacrificed on days 7 and 14. Sacrifice was performed by intraperitoneal administration of a combination of zoletil and rompun under general anesthesia, followed by perfusion with 10% formalin. Maxillary and mandibular specimens were extracted and fixed in 10% formalin.

3. Measurement of tooth movement

For all groups, impressions were taken using polyvinylsiloxane impression material (Aquasil Ultra XLV, Dentsply DeTrey GmbH, Konstanz, Germany) after coronectomy and just before sacrifice. The impressions were scanned using an Identica hybrid 3D dental laser scanner (MEDIT T510, Seoul, Korea) and the amount of tooth movement between the two periods was measured using 3-matic software (Materialise, Leuven, Belgium). The amount of tooth migration was measured by calculating the straight-line distance using scan data provided in standard tessellation language (STL) file format, which was used to create 3-dimensional models. The measurement was obtained by subtracting the distance before the procedure from the distance after the procedure. In the InC and InNF groups, the reference point was from the labial gingival margin to

the middle of the incisal edge. In the InF group, the reference point was from the labial alveolar crest to the middle of the incisal edge. For the molar groups, tooth movement was measured by determining the distance from the defined plane to the cusps or bottom of the pulp chamber. The plane was defined by three points: the mesial cusps of the left and right maxillary second molars, and the mesial cusp of the right maxillary third molar. The distance to the mesial cusp of the first molar was measured in the MC group. In the MF and MNF groups, the distance to the bottom of the pulp chamber of the remaining root was measured to determine the amount of tooth movement. One rat in the MF group was excluded on day 14 because the gingiva covered the pulp chamber.

4. Histological observation

All the samples were decalcified with EDTA, dehydrated, and embedded in paraffin. For both molar and incisor groups, a sagittal section that showed the entire root canal from the crown to the apex was selected and cut into continuous 3 μm thick sections. The sections were stained with hematoxylin and eosin and subjected to immunohistochemistry (IHC). The pulp was examined for signs of mineralization, inflammation, and necrosis. Additionally, the periodontal ligament and the presence of inflammatory cells or alveolar bone resorption at the root apex were assessed. In the incisor groups, the first and second mandibular molars were used as a reference line to divide the incisors into secretory and maturation zones (Fig. 3). For the molar groups, the regions of interest were set at the root apex and cervical third of the mesial root canal. These regions were observed under high magnification.

All histologically stained slides were scanned using the Aperio AT2 image-capturing device (Leica Biosystems, Wetzlar, Germany) and evaluated using Imagescope software 12.3 (Aperio Technologies, Vista, CA, USA). Stained slides were assessed by a single researcher.

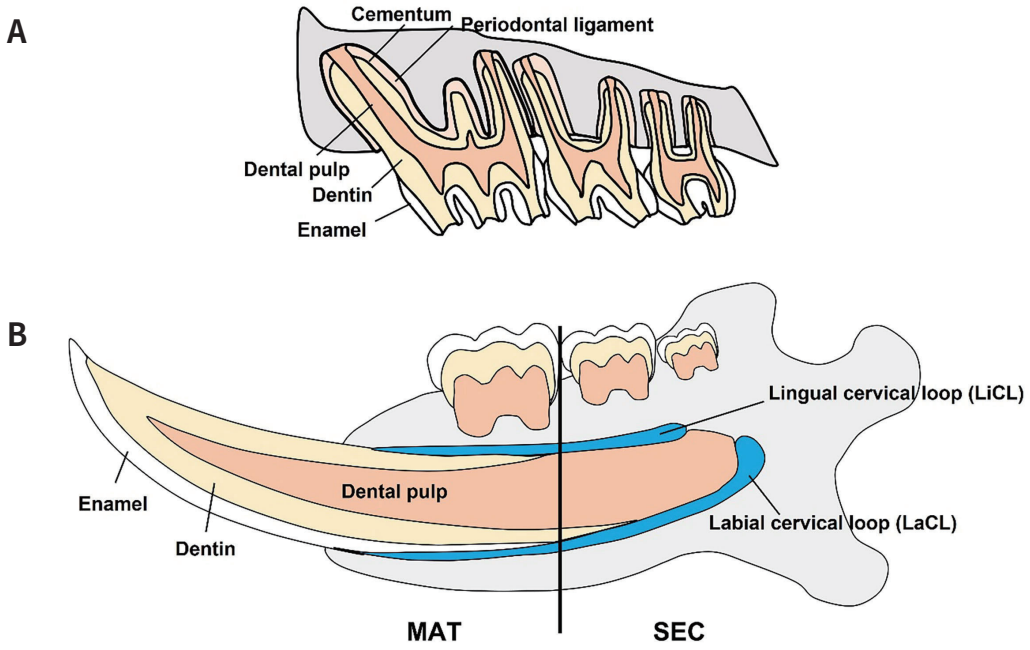

Fig. 3. Diagram showing sagittal views of the maxillary molar and mandibular incisor. (A) Schematic diagram of rat's hemi-maxillary molar. (B) Schematic diagram of rat's hemi-mandibular incisors. MAT: maturation; SEC: Secretion.

5. Immunohistochemical analysis

For all groups, primary antibodies against the receptor activator of NF-kappa B ligand (RANKL, Novus Biologicals, Centennial, CO, USA) and osteoprotegerin (OPG, Abcam, Cambridge, UK) were used. Following the manufacturer's recommendations, secondary antibodies were used for IHC. Visualization was performed using diaminobenzidine (DAB), and counterstaining was performed using hematoxylin. The expression levels of RANKL and OPG were determined in mandibular incisors and maxillary first molars. Three random sections were selected to calculate average IHC staining intensity. The same regions of interest observed during histological analysis were magnified 200 times, and measurements were performed using the IHC profiler plugin of ImageJ software (version 1.53, National Institutes of Health, Bethesda, MD, USA).

6. Statistical analysis

Statistical analysis was performed using SPSS (version 23.0; IBM Corp., Armonk, NY, USA) with a significance level of 95%. One-way ANOVA was used to compare tooth movement and the expression levels of RANKL and OPG among the three incisor groups, three molar groups on day 7, and three molar groups on day 14. Post-hoc analysis was conducted using Tukey's test. An independent t-test was performed to compare the MC, MF, and MNF group results on days 7 and 14.

Results

1. Clinical observation

In the InF group, the teeth erupted to a degree similar to that before coronectomy. In the InNF group, the teeth erupted to the same extent as in the InC group, with no notable postoperative complications observed. In the MNF group, no significant clinical differences were observed between day 7 and 14 marks, and no postoperative complications, such as gingival and mucosal swelling, redness, or abscesses, were noted. The MF group exhibited varied healing patterns among individuals. Among the three rats sacrificed on day 7, one had partially covered and partially exposed residual roots in the gingiva, the other had buccal gingival recession with some alveolar bone exposure, and the third had delayed healing with alveolar bone exposure at the mesial site of the first molar due to flap tearing. Among the three rats sacrificed on day 14, two had palatal root coverage but buccal gingival recession with root exposure and one had the gingiva completely covering the roots. No other signs of gingival or mucosal swelling, redness, or abscesses were observed in any of the subjects.

2. Amount of tooth movement

The amount of tooth movement in the InC group was 0.01±01 mm, and the amount of tooth movement in the InF and InNF groups was 4.80±0.60 mm and 2.31±0.11 mm, respectively, demonstrating statistically significant differences among the three groups (P<0.001). Post-hoc analysis revealed significant differences between InC, InF, and InN groups. For day 7 molar groups, the amount of tooth movement in the MC group was 0.01±0.01 mm, while that in the MF and MNF groups was 0.17±0.01 mm and 0.17±0.07 mm, respectively, also showing statistically significant differences among the groups (P=0.006). Post-hoc analysis indicated significant differences between the day 7 MC and both the MF and MNF groups. On day 14, the MC group showed tooth movement of 0.01±0.01 mm, whereas the MF and MNF groups showed movements of 0.21±0.01 mm and 0.21±0.06 mm, respectively, again demonstrating statistically significant differences among the three groups (P<0.001). Post-hoc analysis revealed significant differences between the day 14 MC and both the MF and MNF groups (Fig. 4).

3. Histological observation

In the InC group, the pulp displayed orderly arranged odontoblasts and normal periodontal tissue.

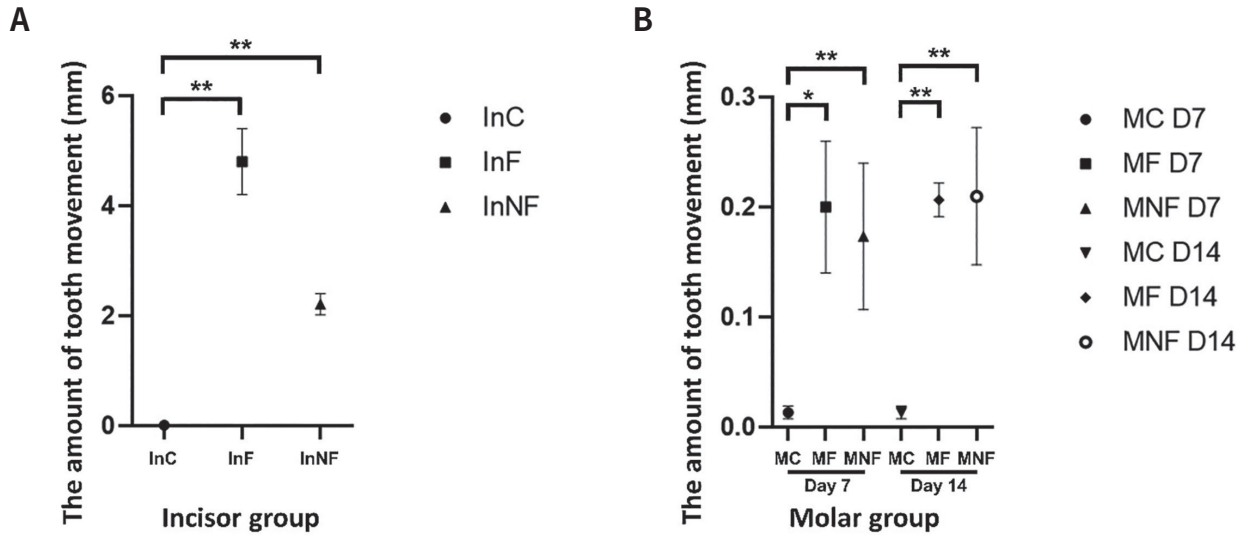

Fig. 4. The amount of tooth movement. (A) The tooth movement distance in the incisor groups. (B) The tooth movement distance in the molar groups. InC: incisor control; InF: incisor flap; InNF: incisor non-flap; MC: molar control; MF: molar Flap; MNF: molar non-flap. *: P<0.05; **: P<0.01.

In InF and InNF groups, some parts of the pulp in the maturation zone were mineralized and infected with bacteria, and the odontoblasts were irregularly arranged. The InF group showed more extensive mineralization in the maturation zone pulp than in the InNF group. The secretory zone maintained its vitality, and no signs of periodontal ligament elongation or new bone formation were observed at the root apex (Fig. 5). After coronectomy, the MC group displayed viable pulp tissue with uniformly arranged odontoblasts in the pulp chamber and root canal, and normal periodontal tissue was observed at the root apex. In contrast, on day 7, MF and MNF groups showed bacterial infection and inflammatory infiltration in the coronal pulp, with signs of pulp degeneration and fibrosis starting to appear (Fig. 6). Fibroblasts began to appear, and odontoblasts were irregularly arranged or difficult to identify, although no mineralized areas were observed. On day 14, both the MF and MNF groups exhibited mineralization and necrosis in the coronal pulp, with a similar bacterial presence in both groups. Vitality of the apical pulp was maintained in all groups. In the MNF group, the periodontal ligament at the root apex was wider than that observed in the MC group. Osteoclasts were also observed in both MF and MNF groups.

4. Expression of RANKL and OPG

In Fig. 7, positive expression of RANKL and OPG is indicated by a brownish-yellow color. Comparing the expression levels among the InC, InF, and InNF groups, OPG showed statistically significant differences (P<0.001). Post-hoc analysis revealed that the InF group had significant differences compared to both the InC and InNF groups. For the day 7 molar groups, the expression levels of RANKL in the MC, MF, and MNF groups showed statistically significant differences (P=0.003). Post-hoc analysis indicated that the day 7 MC group showed significant differences compared to both the day 7 MF and day 7 MNF groups. A comparison of the OPG values of day 7 MF and day 14 MF groups revealed statistically significant differences (P=0.034).

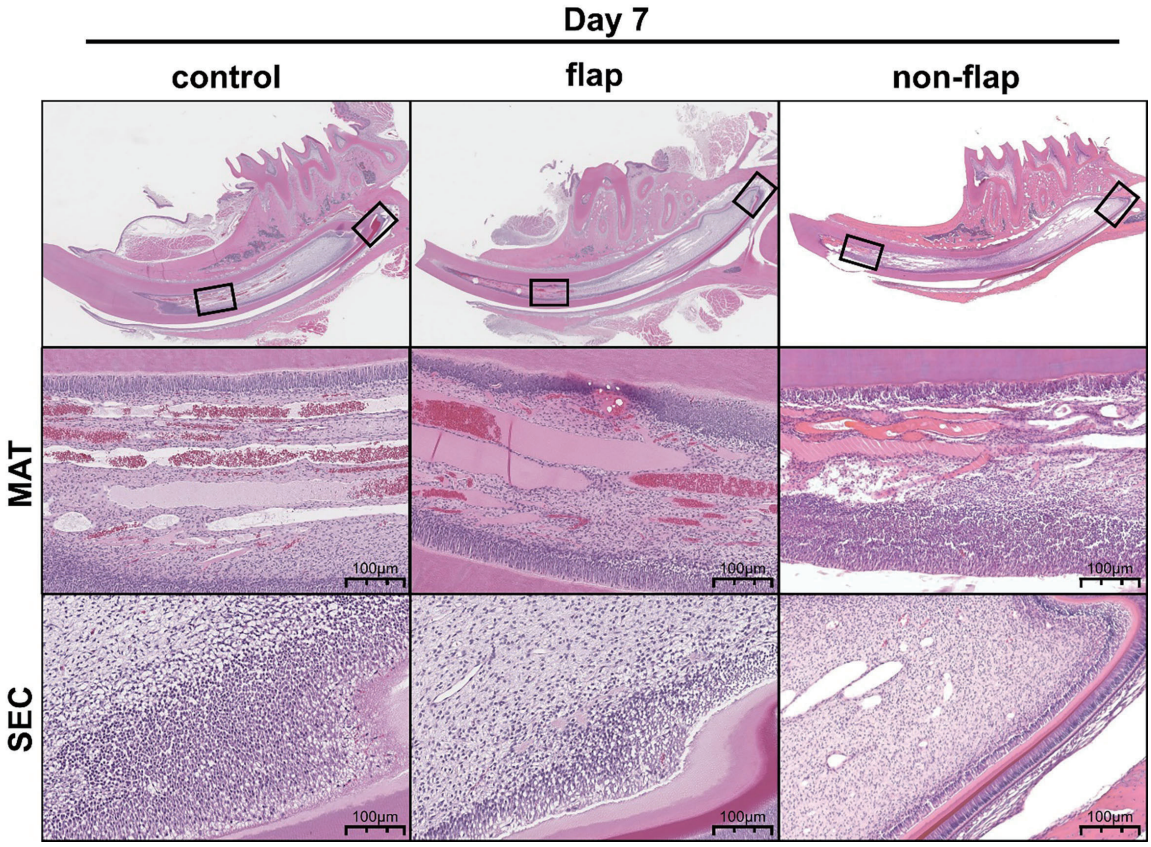

Fig. 5. Longitudinal section of rat mandibular incisor in the incisor groups. Enamel and dentin in purple and pink, respectively. MAT: maturation; SEC: Secretion.

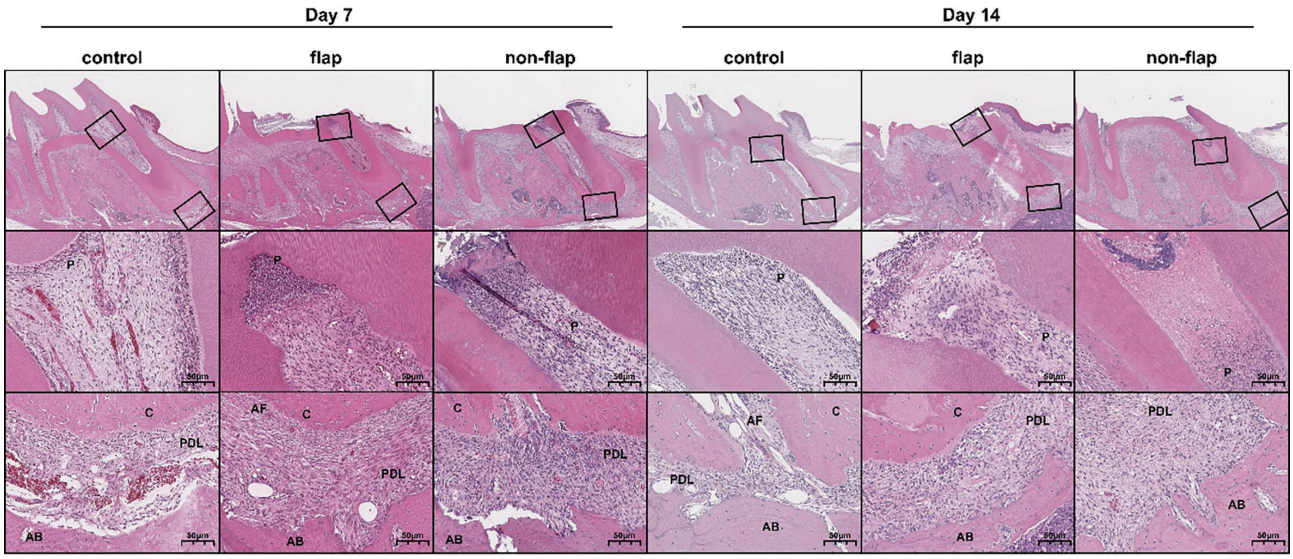

Fig. 6. Sagittal section of rat maxillary first molar in the molar groups. AF: apical foramen; P: pulp; C: cementum; PDL: periodontal ligament; AB: alveolar bone.

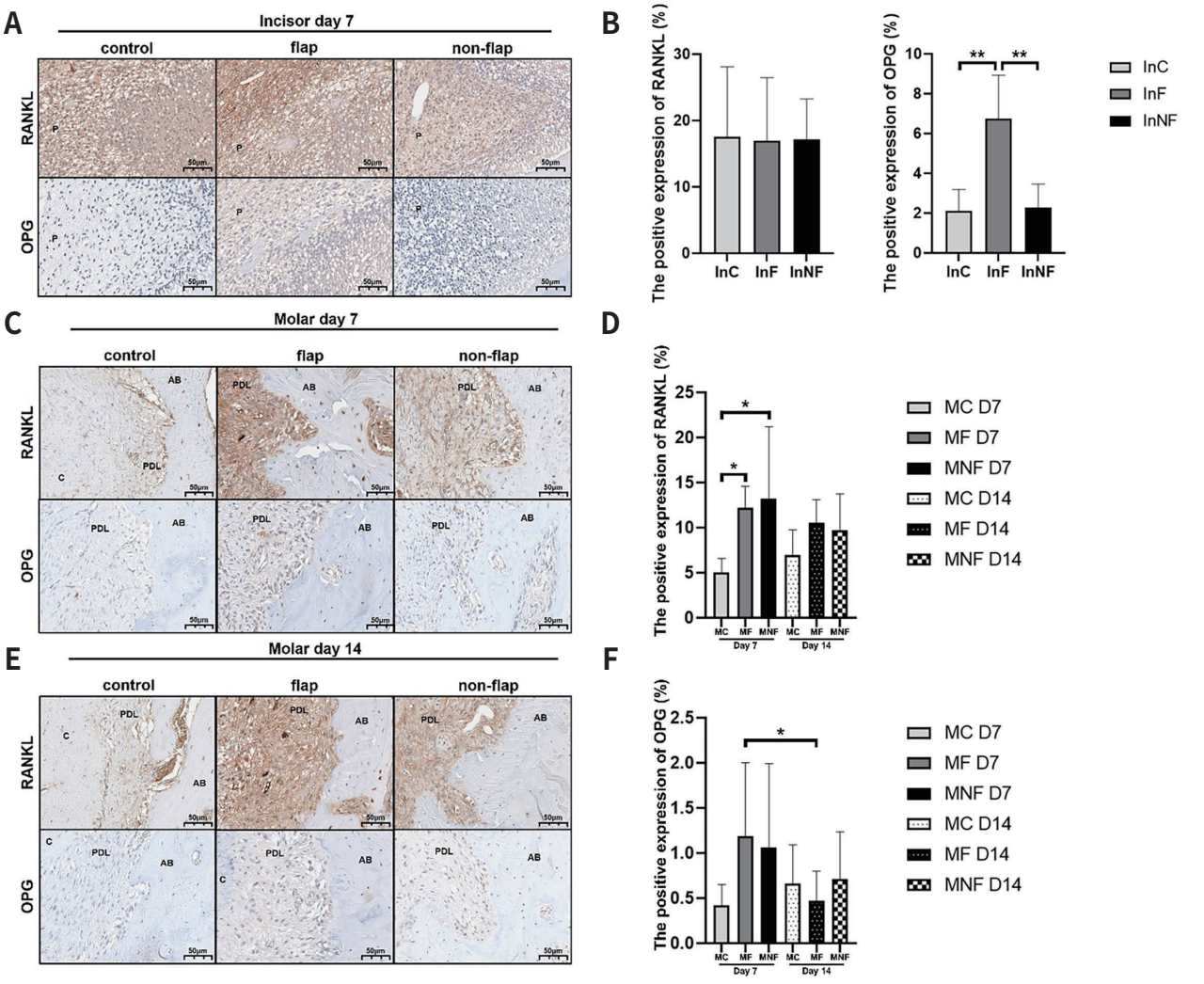

Fig. 7. Immunohistochemistry (IHC) staining of RANKL and OPG in the incisor and molar groups. (A) IHC staining of the mandibular incisor in the incisor groups. (B) The positive expression of RANKL and OPG on the apex in incisor groups. (C) IHC staining of maxillary first molar at day 7 in the molar groups. (D) The positive expression of RANKL on the apex in the molar groups. (E) IHC staining of maxillary first molar at day 14 in the molar groups. (F) The positive expression of OPG on the apex in the incisor and molar groups. P: pulp; AB: alveolar bone; C: cementum; PDL: periodontal ligament; InC: incisor control; InF: incisor flap; InNF: incisor non-flap; MC: molar control; MF: molar Flap; MNF: molar non-flap. *: P<0.05; **: P<0.01.

Discussion

This study aimed to develop an animal model for coronectomy by performing various procedures in rats. Small-animal models are more cost-effective than large-animal models and are suitable for high throughput testing[11]. Although the bacterial flora in rat root canals is slightly different from that in humans, the ratios of aerobic to anaerobic bacteria are similar[12]. The periodontal structure of rat molars is anatomically similar to that of humans; therefore, rat molars have been used as a pathological animal model[13]. Since third

molar extraction or coronectomy is mainly performed in adults, this study applied coronectomy to fully developed teeth in 12-week-old mature rats to investigate its effects.

After coronectomy, different movement patterns were observed in the incisors and molars of the rats. In this study, the mandibular incisors continued root formation, erupting significantly within 7 days to a level similar to or the same as preoperatively. Therefore, the experiment was conducted up to day 7. This continuous tooth formation results from an ongoing supply of mesenchymal and epithelial stem cells in the cervical loop of the incisors[14,15]. Although there was a difference in the movement of incisors in the InF and InNF groups, this was likely due to the difference in the surgical sites. This is because the teeth in the InNF group stopped growing once they erupted to a level similar to that of the InC group due to occlusal interference. In rare cases, coronectomy is performed on immature human teeth. Immature teeth develop continuously, have good regenerative capacity, and feature an open apex similar to rodent incisors[16,17]. This characteristic makes tooth movement easier in immature teeth than mature ones. Existing literature reports that immature teeth move more and exhibit less root resorption than mature teeth when subjected to orthodontic tooth movement[18].

Unlike rat incisors, which erupt continuously after root formation, most teeth, including rat molars, gradually close their root canals and seal their pulp chambers as they mature and erupt into the oral cavity[19]. In the present study, we observed that the remaining roots of the molars moved slowly. Additionally, tissue reactions such as partial pulp necrosis and inflammation at the exposed pulp sites were noted. Rats, with 30 days of life approximating 2.5 years in humans, exhibit faster biological processes[20]. In interpreting the results of day 7 and day 14, we considered the significantly faster metabolic rate and accelerated growth of rats compared to humans as critical factors. Similar to previous clinical studies that reported that most root migrations occurred within 6 - 12 months post-coronectomy[21], this study also observed tooth movement within the experimental period. These findings suggested that experimental coronectomy is feasible in animal models.

To compare the MF and the MNF groups, which are most clinically similar to third molar extraction, as animal models for coronectomy. The MF group displayed healing patterns similar to those of actual clinical coronectomy. However, despite extending the buccal flap sufficiently to cover the remaining roots, most subjects exhibited exposure of the roots or alveolar bone post-surgery. The high variability in healing among individuals suggests that the MF group may not be an ideal animal model. Additionally, in the MF group, the coronectomy was performed closer to the root apex than in the MNF group, resulting in a narrow root canal diameter at the cut surface, making pulp treatment difficult and creating unfavorable conditions for additional experiments, such as the placement of physical barriers. In contrast, although the MNF group differed in clinical presentation, the experimental results, including tooth movement and histological observations, were similar to those of the MF group. The MNF group showed consistent healing patterns across all individuals, making it more suitable for application in various additional experimental conditions, such as pulp treatment or installation of physical barriers.

This study observed the histological symptoms that may accompany coronectomy. After coronectomy, the remaining roots may migrate or become exposed, potentially leading to postoperative complications, such as wounds, infections, and pulpitis[22]. In this study, although some inflammation and mineralization were observed at the maturation zone of the incisors and in the pulp of the molars, the vitality of the root apex was maintained. Liu and Peng[23] reported similar results, showing that when the pulp of rat molars was exposed, numerous inflammatory cells appeared in the apical tissues from day 7 and alveolar bone resorption became more prominent. In the MF group and MNF group, despite the apex pulp maintaining vitality, bacterial

infection and inflammation were observed in the coronal pulp as early as day 7, with the severity increasing by day 14. This finding suggests that the coronal pulp is vulnerable to bacterial invasion and inflammatory processes post-coronectomy. The progression of these issues could potentially compromise long-term healing outcomes and lead to pulp necrosis. Additionally, in this study, the InNF group showed relatively lower levels of inflammation and mineralization at the maturation zone than those of the InF group. This suggests that the pulp may have normalized as the remnant roots in the InNF group began to erupt and wear down before being sacrificed after coronectomy.

To study the cytokines involved in controlling tooth eruption, research is being conducted on the signal transduction pathways RANKL and OPG[24,25]. Tooth eruption involves the activity of osteoblasts and osteoclasts, with repeated bone formation and resorption to form roots, leading to bone remodeling. These factors are known to influence root migration[24,26-29]. RANKL, a member of the tumor necrosis factor (TNF) superfamily, is primarily expressed in osteoblasts and affects bone remodeling. RANKL interacts with its receptor RANK to activate and differentiate into osteoclast lineage cells, leading to resorption induced by mature osteoclasts[30-32]. RANKL activity is inhibited by the decoy receptor OPG; thus, the balance between RANKL and OPG regulates osteoclast differentiation and determines the rate of bone resorption[33,34]. When bacteria invade the root canal, the immune response is activated, leading to RANKL production, which can result in differences in RANKL expression between the control and experimental groups at the root apex[34,35]. Higher RANKL expression is observed in inflamed tissues with cellular infiltration, such as in periapical periodontitis, than in healthy periapical tissue[22]. IHC staining in this study showed that coronectomy partially induced RANKL, with higher expression observed in the MF and MNF groups than in the MC. Although new bone formation was anticipated in the alveolar bone as tooth migration progressed coronally, no distinct new bone formation was observed.

In this study, we established an animal model for coronectomy by applying the procedure to the incisors and molars of rats, followed by clinical observation and histological analysis to confirm the usefulness of the model for up to 7 or 14 days. When comparing tooth movement, histological results of the alveolar bone and periodontal tissue, and markers involved in bone remodeling, it appears that coronectomy of the maxillary first molar is the most suitable method for animal models. Among the groups, the MNF group showed patterns similar to those of the MF group, with consistent healing patterns across all individuals. Despite some differences from the actual clinical situation, the MNF group is more suitable for experimental coronectomy as it allows for various experimental conditions, such as pulp treatment and installation of physical barriers.

Rat incisors and immature human teeth exhibit both similarities and differences. In immature human teeth, root formation occurs after crown formation, whereas in rat incisors, the eruption occurs from the root to the crown. During the pre-eruption and eruption phases in immature human teeth, odontoblasts are active in the roots and ameloblasts are active in the crown. In contrast, rat incisors contain both odontoblasts and ameloblasts during the secretory and maturation zones. There are some limitations in using rat incisors as experimental models to reproduce immature human teeth. However, because of fundamental similarities in tooth development mechanisms, rat incisors can still be meaningfully used as a model for studying immature teeth, provided the advantages and limitations are carefully considered when interpreting the experimental results. Considering the results of this study, the InF group appears to be the most appropriate coronectomy model among the incisor groups. This is due to its high clinical similarity, clear reference point for the alveolar crest through gingival incision, ease of tracking tooth eruption over a longer period than in the InNF group, and histological similarities in the

secretory zone between the InC and InNF groups.

Coronectomy may involve factors other than continuous eruption and bone remodeling markers in the incisors. Therefore, it is necessary to compare the mechanisms of coronectomy between rat incisors and molars in future studies. This study is limited by the difficulty in replicating clinical conditions, such as horizontally impacted molars and ankylosis, in the animal model. Another limitation of this study is the small number of experimental subjects and the lack of additional treatments following coronectomy. Overall, while the MNF group appears to be a suitable experimental coronectomy model, there is insufficient evidence for its clinical usefulness, safety, and efficacy. Consequently, further studies on pulp treatment and physical barriers are required. Although the animal model used in this study does not fully replicate all clinical conditions, it serves as an important preliminary step for future coronectomy research. We anticipate that follow-up studies will further evaluate the model's long-term stability and efficacy, paving the way for more accurate clinical applications.

Conclusion

Both incisors and molars are meaningful models for coronectomy; however, to conduct experimental coronectomy under consistent conditions, it seems most appropriate to proceed without opening a flap on the maxillary first molar. Since coronectomy is influenced by various cells and cytokines, modifying conditions such as treating the exposed pulp or introducing physical barriers will likely alter tissue responses and marker expression. Therefore, the animal model proposed in this study would be useful in establishing a biological basis for ensuring the safety and efficacy of coronectomy.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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