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Evaluation of wound healing at inflamed socket: Experimental and clinical study

염증이환 발치와의 창상치유 평가

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- *Abstract* -

Evaluation of wound healing at inflamed socket: Experimental and clinical study

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(Directed by Professor Young Ku, D.D.S., Ph.D.)

Healing of extraction sockets is a very important biologic process that may affect the resulting edentulous sites both functionally and esthetically. Following the development of endosseous dental implants, understanding the dynamics and mechanics of extraction socket healing has become even more important. The timing for placement of a dental implant (immediate, early, delayed and late) depends on the quality and quantity of bone that are formed following the wound healing of the extraction socket. Additionally, horizontal and vertical atrophy of edentulous sites after extractions is a critical element for esthetic rehabilitation. Extensive researches including pre-clinical and clinical experiments have focused on the healing dynamics

and dimensional changes in healthy extraction sockets. The healing process in diseased extraction sockets that are encountered more frequently in our daily clinical practice is poorly understood because majority of the previous studies have only considered healing of healthy extraction sockets.

In the first part, healing events of diseased extraction sockets were compared to healthy extraction sockets as control in 5 beagle dogs using a split mouth design. The fourth premolars were selected and received either a mechanical plaque control regimen 3 times per week or a protocol to artificially induce an inflammatory lesion. The dogs were sacrificed at 1, 7, 30, 60 and 90 days after extraction. Specimens were prepared for scanning electron microscopy (SEM) to show surface of the socket on the day of extraction, for histological examination to evaluate the healing process, and for micro-computerized tomography (micro-CT) to analyze the 3-dimensional volumetric changes of the extraction socket during healing. The results exhibited different healing patterns between the healthy and diseased extraction sockets at different time intervals. During the inflammation induction period, sclerotic changes were observed near apical endodontic lesions and these gradually thickened over time in the periapical X-rays. Volkmann's canal of the bundle bone in diseased sockets appeared collapsed in the SEM images. In the histologic and histomorphometric evaluation of diseased sockets, infiltration of inflammatory cells was observed in the early phase of the extraction and active formation of trabeculae and the remodeling sequence were delayed during the bone formation phase. Additionally, micro-CT studies revealed that overall healing of diseased sockets was compensated with retardation bone marrow formation at days 60 and 90 compared to healthy sockets. Buccal bone plate resorption of diseased sockets was more pronounced from day 1 to day 90.

Healing of extraction sockets proceeds as follows: blood clot formation,

granulation tissue deposition, fibrous tissue change, active formation of trabeculae and bone marrow development. However, in the clinical setting, even following the strict guidelines for meticulous wound debridement and despite ample healing periods, the sockets are observed filled with fibrous tissue instead of newly formed bone inhibiting the placement of dental implants and forcing guided bone regeneration (GBR) procedures as an alternative. In the second part, the extraction sites with chronic inflammation characterized by connective tissue infiltration that led to the formation of fibrous scar tissue rather than bone formation were designated to as exhibiting 'erratic socket healing'. The prevalence and impeding factors for erratic healing were reported in this study. A total of 1226 subjects were evaluated. Seventy subjects (5.71%) and 97 sites (4.24%) exhibited erratic extraction socket healing. Maxillary incisor/canine sites showed the lowest occurrence of erratic healing (0.47%), whereas mandibular molar sites showed the highest (5.41%) occurrence. In multivariable analysis, erratic healing was more likely to occur in subjects <60 years old (OR = 2.37), in molar sites (OR= 4.91), and following single tooth extractions (OR = 2.98). It was concluded that erratic extraction socket occurred frequently and local factors appeared to be major contributors to its occurrence.

In conclusion, inflammation compromised the healing potential and delayed the remodeling of the extraction sockets. Additionally, erratic socket healing occurred frequently and local factors seem to be important for its occurrence.

Key words: chronic periodontitis, inflammation, tooth extraction, tooth socket, wound healing
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TABLE OF CONTENTS

PREFACE

The present thesis is based on the following papers, which will be referred to in the text by their Roman numerals.

I Kim, J. H., Koo, K. T., Kim, S. T., Kim, T. I., Seol, Y. J., Lee, Y. M., Ryu, I. C. & Ku, Y. (2014) Extraction sockets: healing of compromised teeth with inflammation. Submitted for publication.

II Kim, J. H., Susin, C., Min, J. H., Suh, H. Y., Sang, E. J., Ku, Y., Wikesjo, U. M. & Koo, K. T. (2014) Extraction sockets: erratic healing impeding factors. *Journal of Clinical Periodontology* **41,** 80-85.

INTRODUCTION

Numerous teeth are extracted annually, and the primary choice for rehabilitation of those edentulous sites has been endosseous dental implants. To successfully restore sockets with dental implants, it is necessary to understand the healing process that occurs at the extraction site. The surgical timing for the placement of dental implants depends on the quantity and quality of the healed soft and hard tissues at the extraction site (Hammerle et al. 2004). A decrease in the width and height of the alveolar crest results in functional and aesthetic problems when fabricating implant supported restorations (Iasella et al. 2003).

Healing of an extraction socket requires a series of steps, such as coagulum formation, maturation, fibrous collagen tissue deposition, and ultimately bone formation (Amler 1969, Kuboki et al. 1988, Lin et al. 1994, Cardaropoli et al. 2003). Previous studies of extraction socket healing suggest that two thirds of sockets fill after 4 weeks and completely fill after 10 weeks with bone minerals (Boyne 1966, Amler 1969, Evian et al. 1982). However, these studies focused on healing dynamics and dimensional changes of fresh extraction sockets without inflammation (Cardaropoli et al. 2003, Araujo et al. 2003). Regardless, the fact that most extractions are associated with periodontal and/or endodontic lesions seems to indicate that new data are needed. Diseased extraction sockets show delayed formation of new bone compared to healthy extraction sockets (Ahn & Shin 2008). Furthermore, in the clinical setting, healing of diseased extraction sockets is frequently complicated by infiltration of connective tissues that lead to the formation of fibrous scar tissue rather than bone, which is referred to an erratic socket healing. However, understanding the steps in the healing process of diseased extraction sockets has rarely been studied in the

literature.

In this study, we discussed the healing dynamics and 3-dimensional healing process of diseased sockets with histological and micro-computed tomography analysis in the animal study (part I). Additionally, we analyzed the prevalence of extraction sockets that underwent erratic healing, and elucidated factors that potentially impede the process of healing in the clinical study (part II).

MATERIALS AND METHODS

Animal study

Five adult male beagle dogs, approximate weight 10 kg, were used. The fourth premolars (PM_4) in the contralateral jaw quadrants were selected as the experimental sight to receive either a mechanical plaque control regimen 3 times per week or a protocol to artificially induce an inflammatory apical lesion. Only animal 1 was scheduled to be sacrificed on day x and received an additional intervention on the second premolar (PM_2) for scanning electron microscope (SEM) analysis. Using a split-mouth design, a #2 carbide round bur was used to expose the pulp tissue, followed by the injection of dental plaque suspension into the site and then by sealing the site using intermediate restorative materials. An indentation was formed slightly below the cementoenamel junction (CEJ) to facilitate the fixation of the ligature wires. Additional silk wires were soaked in *Porphyromonas gingivalis* to induce periodontitis lesions, as well. Oral hygiene measures were stopped and the silk and ligature wires were removed 4 weeks later. Plaque was allowed to accumulate for 8 additional weeks.

Histologic sections representing the diseased extraction socket and healthy extraction socket were attained for days 1, 7, 30, 60 and 90, respectively. Intra-oral radiographs were taken twice at baseline (before inducing inflammation), following ligature removal (1 month) and immediately prior to extraction (3 months) using Radiovisiograhs. Heparin was injected into the tissues at PM_2 of dog 1 to prevent blood clot formation which may have interfered with the SEM analysis of the inner wall of the extraction socket. Scanning electron microscopy was used to compare the bundle and Volkmann's canal, which were located in the inner-lining of the socket walls of the diseased and healthy extraction sockets. The animals were

euthanized and block necropsies, including the sockets of the mesial and distal roots, were prepared for computerized tomography (micro-CTs).

The image analyses were performed to calculate the bone morphometric parameters for each volume of interest (VOI). The VOI, in this study, was determined by two calibrated experienced, masked examiners (JHK and JEK) to correspond to the entire socket bone in schematic drawing (Figure 3). All dimensional units are given as parameters and are named according to Parfitt's system (Parfitt et al. 1987): bone volume (BV), total volume of the VOI (TV), bone volume density (BV/TV), bone surface (BS), bone surface density (BS/BV), trabecular bone pattern factor (TbPf) and structural model index (SMI). To compare the histological parameters, the proportion of bone area (BA) and tissue area (TA) were calculated from the mid-sagittal section (BA/TA). Two calibrated experienced masked examiners (JHK and YAC) performed the histometric evaluation (obj x 10, 200), using a light microscope, an image system and analysis software. The following parameters were evaluated for the mesial and distal surfaces of each section in reference to a previous study (Cardaropoli et al. 2003): blood clot (CLOT), inflamed granulation tissue (IGT), fibrous tissue (FT), bone trabeculae (BT) and bone marrow (BM).

Clinical study

Following anecdotal evidence of extraction sites that failed to heal properly, three periodontists (JHK, KTK, YK) initiated a strict protocol including minimally traumatic tooth extraction and meticulous extraction socket debridement. Healing was allowed to proceed for at least 12 weeks. At subsequent surgical implant placement, recordings describing the clinical findings including characteristics of the healed socket hard or soft tissue components were collected. Extraction sites requiring additional meticulous debridement to remove soft tissue infiltration and need for bone

augmentation were designated as erratic extraction socket healing. Records were reviewed (JHK) to identify cases featuring extraction sockets showing erratic healing defined as extraction sockets that were occupied by soft tissue infiltration and required repeated debridement followed by guided bone regeneration. The following demographics, medical and dental data were retrieved from the hospital database records: age, gender, history of diabetes mellitus or hypertension, smoking habit, position of extraction site, duration of healing following extraction.

Extraction sockets were classified into three categories according to the recorded rationale for extraction. In cases where the information regarding the rationale for extraction was missing, the radiologist performed the classification using pre-extraction tooth status (Low et al. 2008, Janner et al. 2011) as follows: Sites showing marginal bone loss encompassing more than 50% of the root length or included the furcation(s) in molars were classified as periodontal lesions. Sites presenting with a peri-apical radiolucency were categorized as endodontic lesions. Extraction sockets yielding evidence of both periodontal and endodontic pathology were considered as periodontal-endodontic lesions. Sites without written documentation or radiographically discernable pathology were classified as of unknown pathology. Computerized tomography scans were available for 69 of 97 subjects diagnosed as having erratic extraction socket healing. Defect characteristics, number of extraction socket walls, and Hounsfield unit (HU) scores were recorded. Regions of interest were measured on the parasagittal.

Subjects were dichotomized according to age into < 60 and ≥ 60 years old. Data regarding smoking exposure was inconsistent; subjects were classified as smokers and non-smokers. Subjects were classified as diabetic or hypertensive using data derived from their medical history. The distribution of subjects according to demographics and medical history was

assessed using χ^2-test. Prevalence and 95% confidence intervals are reported. Generalized estimating equations were used to assess the associations among predictors and erratic healing. Measurements at site level were used and estimates were adjusted for the clustering of observations into individuals using a robust variance estimator.

RESULTS

Animal study

Sclerotic changes were observed at 4 sites where apical lesions had developed and became more apparent as the healing progressed. SEM was used to analyze the inner surface of the extraction sockets immediately following extraction. In the lesion area of the diseased group where the inflammation resided, the bone surfaces appeared to be smoothed as minimal peaks and images of the collapse of Volkmann's canal were observed. However, in healthy extraction sockets, the surface seemed to be more rugged with a clear resolution of the Volkmann's canals.

The overall histomorphometric changes in both groups over time were similar for both groups, stemming from blood clot formation to fibrous tissue formation and, then followed by active trabecular formation. At day 30, remodeling of the tissues occurred, as they were slowly replaced by normal fatty bone marrow. At day 1, inflamed granulation tissue was observed both in the CEJ and apex area. Additionally, osteoclast-like cells and destroyed periodontal ligament were observed in the walls of the diseased socket. At day 7, a drastic decrease in blood clot content, as replaced by a fibrous network radiating from the socket walls towards the center of the socket, was observed for both sites. The fibrous tissue comprised 55.1% of the total content for the healthy extraction sockets but 58.8% for the diseased sockets, showing no difference between the sites. At day 30, active trabecular formation of the fibrous tissue was observed. Bone remodeling with bone marrow formation was observed on the periphery of the healthy socket walls. On the contrary, bone marrow formation was not observed in the diseased extraction sockets. At day 60, bone remodeling was apparent based on the cortical bone formation in the coronal part of the

sockets. In the healthy extraction sites, cancellous bone with a similar density to that of the surrounding bone comprised 78.6% of the content, although the remaining trabecular bone (21.4%) was partially observed in the center and coronal regions of the socket. In the diseased extraction sockets however, trabecular bone (53.5%) continued to occupy most of the space, and tissue remodeling into bone marrow (46.5%) was observed in the periphery of the socket walls with relatively slower healing compared to healthy extraction sockets. At day 90, the bone remodeling appeared to be almost complete at the healthy extraction sites, with bone marrow formation comprising 78.9% of de novo bone formation, excluding the cortical bone formed in the coronal part of the extraction sockets. The maturation of the bone in this cortical region made it difficult to distinguish among pristine bones with diminished borders interspersed. On the contrary, bone marrow comprised 65.9% and active trabecular bone, 34.1% of the diseased extraction socket sites with remodeling incomplete and ongoing. The borderline with the pristine bone was visible.

On days 30, 60 and 90, the values of BV/TV for the healthy extraction sockets were 56.0 ± 1.94, 26.2 ± 2.61 and 19.7 ± 1.51%. At the diseased sockets, these values were 69.3 ± 0.59, 70.5 ± 6.31 and 50.6 ± 5.85. The bone surface density values (BS/BV) were similar between healthy and diseased sockets. The BA/TA values in the mid-sagittal sections of the extraction sockets were very similar based on histomorphometric analysis values. On days 30, 60 and 90, the values of BA/TA for the healthy sockets were 48.8 ± 1.10, 17.5 ± 1.50 and 13.8 ± 2.57%. The values of the diseased sockets were 53.9 ± 4.33, 63.2 ± 8.33 and 31.4 ± 9.69%. The TbPf, which tests the level of bone interconnectivity, appeared to gradually increase for both sites. On days 30, 60 and 90, the values for healthy extraction sockets were -0.45 ± 0.01, 0.25 ± 0.13 and 0.52 ± 0.0, respectively, showing a tendency to gradually increase. n contrast, the

corresponding values were -0.65 ± 0.02, -0.16 ± 0.05 and 0.18 ± 0.1, respectively, for diseased extraction sockets with relatively low values. SMI, similar to TbPf, displayed increased values in both healthy and diseased extraction sockets. The values were relatively lower for the diseased sockets at all time-points. The difference in height between the buccal and lingual crests using the central parasagittal section is outlined in table 3. Figure 8 shows the linear line connecting the two points of interest. At day 1 in the healthy extraction sockets, the buccal crest was located 0.2 ± 0.12 mm apical to the lingual crest, whereas in the diseased extraction sockets, the corresponding value was 2.2 ± 0.03 mm. For days 30, 60 and 90, this distance was 0.9 ± 0.34, 1.6 ± 0.18 and 1.7 ± 0.09 mm for the healthy extraction sockets, whereas the values for the diseased sockets were 2.7 ± 0.14, 3.0 ± 0.7 and 3.8 ± 0.12 mm, respectively.

Clinical study

Complete dental records were available for 1,226 of 1,457 subjects. The sample comprised 552 females and 674 males, mean (± SD) age 55.9 ± 11.3 years, age range 18-87 years. Seventy (5.71%) subjects were diagnosed as exhibiting erratic extraction socket healing. Subjects < 60 years old showed a significantly higher prevalence of erratic extraction socket healing than older subjects. Data for 2,288 extraction sockets were retrieved for analysis. The average post-extraction healing period was 5.5 ± 2.6 months (range 3-24 months). Ninety-seven (4.24%) sites were classified as extraction sockets showing erratic healing. The mean healing interval for the erratic healing sites was 5.6 ± 3.4 months, corresponding values for the normal healing group was 5.5 ± 2.5 months.

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erratic healing. The mean healing interval for the erratic healing sites was 5.6 ± 3.4 months, corresponding values for the normal healing group was 5.5 ± 2.5 months. Of the 97 sites with erratic healing, 70 (72.16%) were due to periodontal pathology, 11 (11.34%) due to combined periodontal-endodontic lesions, and 2 (2.12%) due to endodontic pathology. The rationale for extraction was not documented/could not be classified in 14 cases. Computerized tomography scans from 69 of 97 extraction sockets showing erratic healing obtained at 3.8 ± 2.9 months were evaluated. Eleven four-wall (15.9%), 39 three-wall (56.52%) and 19 two-wall (27.53%) extraction sockets were recorded. Half of the extraction sockets had lost the buccal wall (n= 34, 49.3%), a quarter had lost both buccal and lingual walls (n = 19, 27.5%), and few had lost only the lingual wall (n = 5, 7.3%). Average (± SD) HU score for these sites was 110 ± 119.

After adjusting for other factors in the multivariable analysis, erratic extraction socket healing was more likely to occur in younger subjects (OR = 2.23), subjects with hypertension (OR = 2.37), in molar sites (OR = 4.91), and following single tooth extractions (OR = 2.98). Gender, diabetes or smoking were not significantly associated with erratic extraction socket healing.

DISCUSSION

Animal study

Diseased extraction sockets in general display delayed healing, especially in the central region of the socket during bone marrow formation. Additionally, buccal crest resorption in comparison with lingual crest resorption was more pronounced in diseased extraction sockets.

The animal model used represented an attempt to mimic the combined periodontal-endodontic lesions observed in clinical practice and could be divided into two areas of interest, the apical portion of the root and the area adjacent to the CEJ. Radiographic observations up to the extraction showed sclerotic changes in the apical lesion and increased density as the healing time progressed. These sclerotic changes may be regarded as an immune response of the bone to chronic pulpitis or infection by low virulence microorganisms and can be diagnosed as condensing osteitis when the symptoms become chronic and severe (Elfenbaum 1967, Morse et al. 1985, Monahan 1994). These changes in the bone are thought to reduce bone marrow and to induce atrophy (Abrahams & Berger 1998). The innermost surface of the diseased extraction socket containing the apical lesion showed a smooth topography of the surfaces, and no Volkmann's canals were observed. Reductions of the bone marrow and the Volkmann's canal may compromise the supply of growth factors and blood, interrupting the socket healing cascade from the initial blood clot formation and eventually to the erratic socket healing (Kim et al. 2014). Figure 1 shows schematic drawings of the theory with chronic inflammation and changes in the surrounding tissues.

The healthy sockets at days 60 and 90 showed almost complete maturation with bone marrow contents of 78.6% and 78.9% and complete

cortical bone formation in the coronal part of the socket. This result corroborates findings by Cardaropoli et al. (2003), who showed that the bone marrow comprised 63-85% after 60 days. In the diseased extraction sockets, the bone marrow comprised 46.5% at day 60 and 65.9% at day 90, indicating that remodeling remains ongoing. At day 90, remodeling in the healthy extraction sockets was almost complete, with no definitive borders between pristine bone and the newly formed cortical bone; however, in diseased extraction sockets, a clear demarcation line can be observed.

For 3-dimensional morphometric analysis, In the healthy extraction sockets, the radiographic parameters had a tendency to gradually decrease for days 30, 60 and 90 days. This finding may be due to the limitations of a radiographic analysis restricted to the binary formula, which thus only allowed for the measurement of the bone trabeculae and a limited analysis of the fibrous tissue and bone marrow. In contrast, the those values for the disease sockets showed a relatively high but similar trend as those of the histologic specimens.

In dogs, such data may suggest that the newly formed bone within the socket excluding the cortical bone portion may be less favorable for the primary stability of a dental implant as the healing time progresses. Additionally, this finding may be interpreted such that, in humans, if the healing time is prolonged and the cortical bone near the coronal cortical bone part is compensated, the primary stability during implant placement may be severely jeopardized. This instability in healing, especially in cases with inadequate cortical bone, may not support the paradigm that a longer healing interval results in an enhanced primary stability in such cases, additional research regarding the appropriate time of implant placement seems necessary in diseased sockets.

Following tooth extraction, a pronounced loss of the buccal plate has

been reported extensively by previous studies (Pietrokovski & Massler 1967, Schropp et al. 2003, Araujo & Lindhe 2005). Similar to the previous studies, a line parallel to the long axis of the root, subtracting the line connecting the line connecting the buccal and lingual intersection, was found. The values for the diseased sockets much higher tendency towards reduction. This finding showed that the diseased sockets displayed greater dimensional changes compared to the healthy sockets.

Clinical study

Extraction sockets, if meticulous debridement or curettage is executed, are expected to heal with bone. However, observations of radiolucencies and clinical observations of fibrous scar tissue occupying the extraction site rather than bone, prohibiting the placement of dental implants prompted the current exploratory study. Previous studies have focus on the occurrence of dry sockets mostly related to third molar extractions (Larsen 1992, Blum 2002), and more recent studies on healing dynamics of extraction sites using preclinical and clinical models (Cardaropoli et al. 2003, Araújo & Lindhe 2005, Schropp et al. 2003). Implant peri-apical lesions likely associated with unsuccessfully healing extractions sockets have also been identified but limited data exists (Quirynen et al. 2005, Romanos et al. 2011, Lefever et al. 2013). The prevalence of extraction sockets showing erratic healing and factors potentially impeding healing however remain elusive. The term erratic healing was defined as healing of extraction sockets resulting in soft tissue infiltration, likely fibrous scar tissue, rather than bone formation even following meticulous debridement and a healing interval exceeding 12 weeks. Approximately 5% of the extraction sites in this study thus featured erratic extraction socket healing.

Studies providing histologic documentation of tissue formation/maturation in extraction sockets conclude that extraction sockets will heal with

mineralized bone within 6 weeks (Amler 1969). Others suggest that 10 weeks are necessary for complete bone fill (Evian et al. 1982). Still others demonstrate inconsistent bone healing and high individual variability showing formation of 35% woven bone in a provisional matrix at 6-8 weeks and 41% at 12-24 weeks (Trombelli et al. 2008). These studies evaluated extraction sockets generally absent of inflammatory lesions in contrast to the focus on erratic extraction socket healing in the present study. Another difference between studies is constituted in the healing interval; in the present study averaging approximately 22 weeks, some cases showing erratic healing even after 24 months suggesting a chronic nature of erratic extraction socket healing.

Local factors including intra-oral location and multiple extractions were also significantly associated with erratic extraction socket healing. Molar sites showed the highest occurrence, followed by premolar sites (5.22% vs. 3.23%). Compared with incisor and canine sites, premolar and molar sites were three and five times as likely to experience erratic healing, respectively. At the present it is unclear which factors would explain the higher likelihood of erratic healing in posterior sites, however similarities shared with condensing osteitis relative to frequent occurrence in the premolar and molar region should not be overlooked. It must also not be overlooked that posterior extractions are likely more challenging to manage surgically and post-surgically, and healing would conceivably be more challenging due to relatively larger extraction sockets. Erratic extraction socket healing was three-fold greater for single tooth compared with multiple teeth extraction sites. It seems counterintuitive that single tooth extractions would have higher chances of erratic healing and reasons for this observation are currently unknown. It must be pointed out that in the multiple extraction cases interproximal bone loss may affect modeling and remodeling processes to eventually impose a decreased propensity of erratic

healing.

Our finding that approximate 5% of the subjects and extraction sockets show erratic healing impeding replacement of missing teeth with dental implants should be seen in light of the characteristics of the present study. A convenience sample derived from a teaching dental hospital might have a peculiar patient population including complex management cases and patient in need of more specialized treatment. Nevertheless, the fact that most extractions were associated with periodontal and/or endodontic lesion seems to indicate otherwise. Studies including subjects from different clinical settings should be conducted to confirm our findings. The case definition used herein was based on a combination of clinical findings and treatment outcomes constrained by the retrospective nature of the study. Future studies should use case definitions that can be used prospectively and are less reliant on the clinician judgment.

CONCULUSION

The primary indication for extraction is inflamed tooth with a periodontal, endodontal, or combined lesion. These inflammatory lesions compromise the healing potential, delay new bone formation and impede the remodeling of the extraction socket (part I). Additionally, erratic socket healing occurs frequently, and local factors seem to dictate the frequency of its occurrence (part II).

In the first part of this study, we used an animal model to compare the healing events in sockets between healthy and diseased teeth. We found that there were differences in the inflammatory lesion area following the time sequence between healthy and diseased socket. During the induction of inflammation, sclerotic changes were observed in the area of the apical lesions, and they became more apparent as the lesions progressed. After extraction, the inner surface of the diseased extraction socket where the apical lesion existed showed a smooth topography and the collapse of the Volkmann's canals when imaged by scanning electron microscopy. In the histological evaluation of diseased sockets, we found that inflammatory cells infiltrated the lesion, and bone remodeling was delayed.

We used micro-CT to evaluate 3-dimensional pattern of bone formation in the socket and the trabecular pattern of the bone. We found that healing of diseased sockets was delayed days 60 and 90 compared to healthy sockets. Additionally, vertical resorption of the buccal bone crest in diseased sockets was more pronounced in the mid-sagittal plane.

In the second part of this study, we analyzed the prevalence of extraction sockets that showed erratic healing, and we evaluated the factors

potentially impeded the process of healing in the clinical setting. In the study, 5.71% of the subjects and 4.24% of the extraction sites exhibited erratic healing. Mandibular molar sites had the highest (5.41%) occurrence of this. Erratic healing was more likely to occur in subjects < 60 years old (OR = 2.23), in molar sites (OR= 4.91), and following single tooth extractions (OR = 2.98). Our findings suggest that erratic healing of sockets occurs frequently.

FIGURE

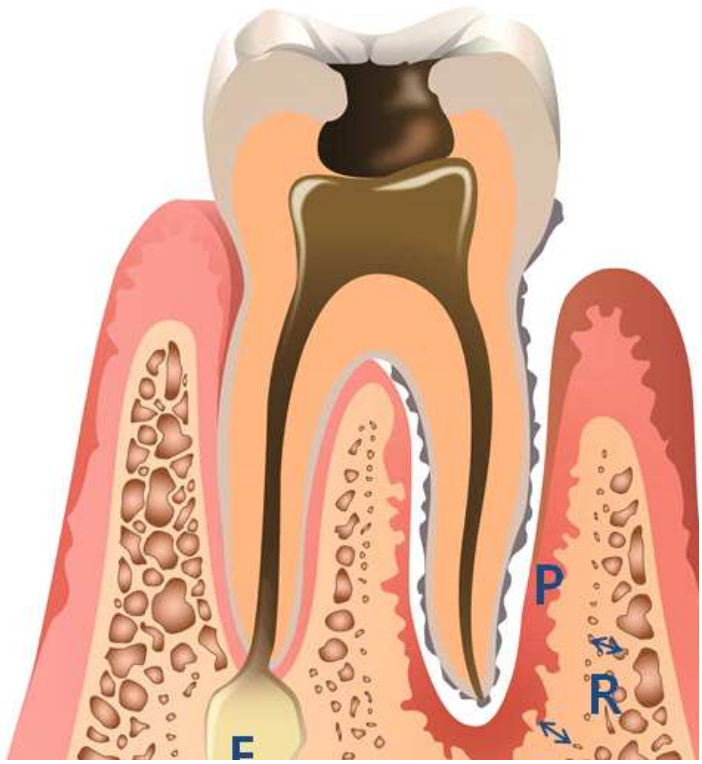

Fig. 1 Scheme of chronic inflammatory lesion. E = endondontic lesion, P = periodontal lesion, S = sclerotic change, R = reduced bone marrow

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Part I.

Extraction Sockets: Healing of Compromised Teeth with Inflammation

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ABSTRACT

Aim: The aim of this experiment was to analyze the healing events of extraction sockets after extracting the compromised tooth.

Materials and Methods: Five beagle dogs were used for the experiment. The fourth mandibular premolars were selected for study, and perio-endo combined lesions were induced using ligation and pulp exposure for 3 months. The contralateral premolars were remained without any intervention as controls. Three months later, the mesial and distal roots were removed atraumatically, followed by meticulous wound debridement. The dogs were sacrificed 1, 7, 30, 60 and 90 days after the extractions. A scanning electron microscope (SEM) was used to evaluate the socket surface. Specimens were prepared for micro computerized tomography (micro-CT) and histological examination. Radiographic parameters were calculated and morphometric measurements were performed.

Results: There were some differences of the diseased sockets following the time sequence when they were compared to the healthy sockets. In the peri-apical radiographic X-ray, sclerotic changes were shown near the apical endodontic lesion. The Volkmann's canals of bundle bone in the diseased sockets were collapsed in the SEM. In the morphometric analysis of the diseased sockets, an infiltration of inflammatory cells was observed in the early phase of the extraction, and the mineralized bone portion remodeling to bone marrow was delayed on days 30, 60 and 90. Evaluating the 3-D parameters of the micro-CT indicated that the healing of the diseased sockets was delayed on days 60 and 90 compared to that in the healthy sockets. Additionally, the vertical resorption of the buccal bone crest in diseased sockets was more pronounced on the mid-sagittal plane.

Conclusion: By comparing healthy and diseased extraction socket healing, we concluded that inflammation compromised the healing potential, affected the remodeling and collapsed the buccal ridge of the extraction socket.

INTRODUCTION

The healing of extraction socket has been studied extensively by many preclinical and clinical studies (Pietrokovski & Massler 1967, Amler 1969, Cardaropoli et al. 2003, Schropp et al. 2003, Araujo & Lindhe 2005). The results of these studies were attained by analyzing of histological samples, radiographic data and volumetric changes using cast models. The healing of human extraction sockets progresses according to the following sequence. The extraction socket is immediately filled with blood clot, which is soon replaced by granulation tissue, which in turn finally is remodeled into an osseous tissue (Amler 1969). A study on the healing of extraction sockets in beagles demonstrated a similar sequence and pattern, supporting this progression (Cardaropoli et al. 2003).

Most of the previous studies regarding extraction sockets have dealt with healthy extraction sockets and have yielded positive results. However, in real clinical settings, tooth extraction is more often caused by chronic periodontal or endodontic inflammatory lesions that are difficult to treat and carry a poor prognosis. It has been reported that the healing of such sockets with inflammatory lesions is associated with a severe delay in healing compared to healthy extraction sockets (Ahn & Shin 2008). In addition, it has been suggested that fibrous tissue, rather than newly formed bone, may be the end result of such processes, even if a strict protocol involving thorough debridement and a healing interval longer than 12 weeks are followed (Kim et al. 2014). Eventually, the clinical results are compensated, making it difficult to acquire the primary stability of dental implants in some cases and hindering the potential for other restorative possibilities. As serious as this matter seems, studies regarding the outcomes of extraction sockets with inflammatory lesions are scarce.

The purpose of this study is to induce in beagles a periodontal-endodontic

lesion and then, through histomorphometric and radiographic analysis, to compare the healing capacities and patterns to those demonstrated in dogs with healthy extraction sockets.

MATERIALS AND METHODS

Animals

All experimental protocols were approved by the Institutional Animal Care and Use Communities (IACUC no SNU-121204-5-1), Seoul National University, Korea. Five adult male beagle dogs, approximate weight 10 kg, were used. To avoid direct trauma to the extraction sites, the animals were fed a soft diet throughout the entire period of the study. The study outline is shown in figure 1.

Surgical protocol

The animals were anesthesized using a mixture of Zoletil, Rompun and atropine sulfate (0.1 mg/kg, 2.3 mg/kg, 0.05 mg/kg IV, respectively). The dogs additionally received lidocaine (1.8 ml/quadrant) to provide regional nerve block anesthesia.

The fourth premolars (PM_4) in the contralateral jaw quadrants were selected as the experimental sight to receive either a mechanical plaque control regimen 3 times per week or a protocol to artificially induce an inflammatory apical lesion (Buttke et al. 2005). Only animal 1 was scheduled to be sacrificed on day x and received an additional intervention on the second premolar (PM_2) for scanning electron microscope (SEM) analysis. In short, using a split-mouth design, a #2 carbide round bur was used to expose the pulp tissue, followed by the injection of dental plaque suspension into the site and then by sealing the site using intermediate restorative materials (IRM). Next, an indentation was formed slightly below the cementoenamel junction (CEJ) to facilitate the fixation of the ligature wires. Additional silk wires were soaked in *Porphyromonas gingivalis* to

induce periodontitis lesions, as well (Figures 2a and 2b). Oral hygiene measures were stopped and the silk and ligature wires were removed 4 weeks later (Figure 2c). Plaque was allowed to accumulate for 8 additional weeks (Figure 2d).

Postsurgery procedures

Following the described intervention, the animals were prohibited from receiving any form of antibiotics or non-steroidal anti-inflammatory drug (NSAID) to induce the lesions. Tooth cleanings were performed 3 times a week after extraction (Cardaropoli et al. 2003). Histologic sections representing the diseased extraction socket and healthy extraction socket were attained for days 1, 7, 30, 60 and 90, respectively.

Radiographic examination

Intra-oral radiographs were taken twice at baseline (before inducing inflammation), following ligature removal (1 month) and immediately prior to extraction (3 months) using Radiovisiograhs (Kodak RVG 6100 Digital X-ray Sensor, Eastman Kodak, Rochester, NY, USA). A computer assisted image analysis system (PiView STAR™ 5.0, Informer Technologies, Seoul, Korea) was used for radiographic analysis.

Electron micrographs

Heparin was injected into the tissues at PM_2 of dog 1 to prevent blood clot formation which may have interfered with the SEM analysis of the inner wall of the extraction socket. The specimens were fixed with 2.5% (vol/vol)

glutaraldehyde and phosphate buffered saline (PBS, pH 7.4) for 20 min and rinsed with PBS twice at 4 °C for 20min. Each sample was postfixed with 1% osmium tetroxide at 4 °C for 1 h and immersed in saturated thiocarbohydrazide at room temperature for 20 min before dehydration in graded ethyl alcohol (70%-80%-90%-95%-100% each for 15 min and 100% for 15 min). The samples were dried with hexamehtyldisilazane in air overnight before being coated with ion-beam sputtering. The split extraction sockets were then mounted on aluminum stubs and, sputter coated with a 30 nm lay of gold. Scanning electron microscopy (SEM S4700, Hitachi, Tokyo, Japan) was used to compare the bundle and Volkmann's canal, which were located in the inner-lining of the socket walls of the diseased and healthy extraction sockets. The voltage was set at 15 kV; the type of signal used was secondary electrons; the working distance was 13 mm; and the scan speed was 16 frames per 20 s.

Micro computerized tomography (micro-CT) sampling method

The animals were euthanized and block necropsies, including the sockets of the mesial and distal roots, were prepared for computerized tomography (micro-CTs).

Histologic processing

The specimens were fixed in 10% neutral buffered formalin, dehydrated with ethylenediaminetetraacetic acid and embedded in paraffin blocks for histologic analysis. The specimens were sectioned on the mesio-distal plane, processed to approximately 4 μm of thickness, and stained using hematoxylin and eosin (H&E). The most central section was used for the histologic analysis.

Micro computerized tomography (micro-CT) analysis

The micro-CT examination of each extraction socket specimen was taken using appropriate equipment (SkyScan-1173, Kontich, Belgium) after the fixation of the tissue blocks with a positioner and parallel to the long axis. Additionally, two dimensional images of 2240X2240 pixels were saved as BMP files. The exposure conditions were 240° rotation, 1.0 aluminum filter, 90 kV, 88 μA, and 15.98 μm pixel size. The projection image data were reconstructed to create 3D images and analyzed using a computer program, CT-An software (CT Analyser, Skyscan, Kontich, Belgium).

The image analyses were performed to calculate the bone morphometric parameters for each volume of interest (VOI). The VOI, in this study, was determined by two calibrated experienced, masked examiners (JHK and JEK) to correspond to the entire socket bone in schematic drawing (Figure 3). All dimensional units are given as parameters and are named according to Parfitt's system (Parfitt et al. 1987): bone volume (BV), total volume of the VOI (TV), bone volume density (BV/TV), bone surface (BS), bone surface density (BS/BV), trabecular bone pattern factor (TbPf) and structural model index (SMI). To compare the histological parameters, the proportion of bone area (BA) and tissue area (TA) were calculated from the mid-sagittal section (BA/TA).

Histological examination

Two calibrated experienced masked examiners (JHK and YAC) performed the histometric evaluation (obj x 10, 200), using a light microscope (DP72; Olympus, Tokyo, Japan), an image system (DPController; Olympus, Tokyo,

Japan) and analysis software (TOMORO ScopeEye, JNOpTIC, Seoul, Korea). The following parameters were evaluated for the mesial and distal surfaces of each section in reference to a previous study (Cardaropoli et al. 2003): blood clot (CLOT), inflamed granulation tissue (IGT), fibrous tissue (FT), bone trabeculae (BT) and bone marrow (BM).

Data analysis

This experimental study presents mean values and standard deviations (SD) of the mesial and distal roots to compare disease extraction sockets to healthy extraction sockets. Due to the aims of the study and our limited number of dogs, statistical analysis may not necessary.

RESULTS

Intraoral x-ray observations

Sclerotic changes were observed at 4 sites where apical lesions had developed (Figure 2c) and became more apparent as the healing progressed (Figure 2d). However, the periodontal lesions in the coronal region failed to show any sclerotic changes despite the severe bone loss.

SEM

SEM was used to analyze the inner surface of the extraction sockets immediately following extraction. In the lesion area of the diseased group where the inflammation resided, the bone surfaces appeared to be smoothed as minimal peaks and images of the collapse of Volkmann's canal were observed (Figure 4b). However, in healthy extraction sockets (Figure 4a), the surface seemed to be more rugged with a clear resolution of the Volkmann's canals.

Histomorphometric analysis

The histomorphometric changes in both groups over time are outlined in table 1. The overall changes were similar for both groups, stemming from blood clot formation to fibrous tissue formation and, then followed by active trabecular formation. At day 30, remodeling of the tissues occurred, as they were slowly replaced by normal fatty bone marrow.

1 day (Figures 5a and 5f)

In the healthy extraction sockets, blood clot constituted 37.5% of the overall

contents whereas artifact hollow filled the rest (62.5%). The corresponding values for the diseased extraction sockets were 26.0% blood clot and 38.4% artifact hollow. Inflamed granulation tissue was observed both in the CEJ and apex area, consuming 35.6% of the space. Additionally, osteoclast-like cells and destroyed periodontal ligament were observed in the walls of the socket.

7 days (Figures 5b and 5g)

A drastic decrease in blood clot content, as replaced by a fibrous network radiating from the socket walls towards the center of the socket, was observed for both sites. The fibrous tissue comprised 55.1% of the total content for the healthy extraction sockets but 58.8% for the diseased sockets, showing no difference between the sites.

30 days (Figures 5c and 5h)

In the healthy extraction sites, active trabecular formation of the fibrous tissue was observed. In some specimens, the remodeling and transition of these tissues into fatty bone marrow was observed. Soft tissue healing seemed complete in the coronal part of the sockets, but cortical bone was not observed. The bone trabeculae comprised 43.3% of the overall content, whereas the 27.4% fibrous tissue was partially observed in the central region of the socket. Bone remodeling with bone marrow formation (29.4%) was observed on the periphery of the socket walls. On the contrary, bone marrow formation was not observed in the diseased extraction sockets, with collagen and bone trabeculae comprising 51.5% and 48.5% of total content, respectively.

60 days (Figures 5d and 5i)

Bone remodeling was apparent based on the cortical bone formation in the

coronal part of the sockets. In the healthy extraction sites, cancellous bone with a similar density to that of the surrounding bone comprised 78.6% of the content, although the remaining trabecular bone (21.4%) was partially observed in the center and coronal regions of the socket. In the diseased extraction sockets however, trabecular bone (53.5%) continued to occupy most of the space, and tissue remodeling into bone marrow (46.5%) was observed in the periphery of the socket walls with relatively slower healing compared to healthy extraction sockets.

90 days (Figures 5e and 5j)

The bone remodeling appeared to be almost complete at the healthy extraction sites, with bone marrow formation comprising 78.9% of de novo bone formation, excluding the cortical bone formed in the coronal part of the extraction sockets. The maturation of the bone in this cortical region made it difficult to distinguish among pristine bones with diminished borders interspersed. On the contrary, bone marrow comprised 65.9% and active trabecular bone, 34.1% of the diseased extraction socket sites with remodeling incomplete and ongoing. The borderline with the pristine bone was visible.

Micro-CT 3D morphometric analysis

The morphometric parameters according to the healing time interval are present in table 2. Only the specimens from days 30, 60 and 90 were analyzed, because days 1 and 7 showed minimal hard tissue formation in the sockets. The images were reconstructed in to 3-dimensional images to manifest the complex patterns of healing occurring within the socket (Figures 6 and 7).

On days 30, 60 and 90, the values of BV/TV for the healthy extraction

sockets were 56.0 ± 1.94, 26.2 ± 2.61 and 19.7 ± 1.51%. At the diseased sockets, these values were 69.3 ± 0.59, 70.5 ± 6.31 and 50.6 ± 5.85. The bone surface density values (BS/BV) were similar between healthy and diseased sockets. The BA/TA values in the mid-sagittal sections of the extraction sockets were very similar based on histomorphometric analysis values. On days 30, 60 and 90, the values of BA/TA for the healthy sockets were 48.8 ± 1.10, 17.5 ± 1.50 and 13.8 ± 2.57%. The values of the diseased sockets were 53.9 ± 4.33, 63.2 ± 8.33 and 31.4 ± 9.69%. The TbPf, which tests the level of bone interconnectivity, appeared to gradually increase for both sites. On days 30, 60 and 90, the values for healthy extraction sockets were -0.45 ± 0.01, 0.25 ± 0.13 and 0.52 ± 0.0, respectively, showing a tendency to gradually increase. In contrast, the corresponding values were -0.65 ± 0.02, -0.16 ± 0.05 and 0.18 ± 0.1, respectively, for diseased extraction sockets with relatively low values. SMI, similar to TbPf, displayed increased values in both healthy and diseased extraction sockets. The values were relatively lower for the diseased sockets at all time-points.

Bone crest level change in microCT bucco-lingual section

The difference in height between the buccal and lingual crests using the central parasagittal section is outlined in table 3. Figure 8 shows the linear line connecting the two points of interest. At day 1 in the healthy extraction sockets, the buccal crest was located 0.2 ± 0.12 mm apical to the lingual crest, whereas in the diseased extraction sockets, the corresponding value was 2.2 ± 0.03 mm. For days 30, 60 and 90, this distance was 0.9 ± 0.34, 1.6 ± 0.18 and 1.7 ± 0.09 mm for the healthy extraction sockets, whereas the values for the diseased sockets were 2.7 ± 0.14, 3.0 ± 0.7 and 3.8 ± 0.12 mm, respectively.

DISCUSSION

The healing dynamics and tissue changes found in the present study on the healthy extraction sockets concurs with the results of a previous study (Cardaropoli et al. 2003). However, diseased extraction sockets in general display delayed healing, especially in the central region of the socket during bone marrow formation. Additionally, buccal crest resorption in comparison with lingual crest resorption was more pronounced in diseased extraction sockets.

The animal model used represented an attempt to mimic the combined periodontal-endodontic lesions observed in clinical practice and could be divided into two areas of interest, the apical portion of the root and the area adjacent to the CEJ. Radiographic observations up to the extraction showed sclerotic changes in the apical lesion and increased density as the healing time progressed (Figure 2).

These sclerotic changes may be regarded as an immune response of the bone to chronic pulpitis or infection by low virulence microorganisms and can be diagnosed as condensing osteitis when the symptoms become chronic and severe (Elfenbaum 1967, Morse et al. 1985, Monahan 1994). These changes in the bone are thought to reduce bone marrow and to induce atrophy (Abrahams & Berger 1998). The innermost surface of the diseased extraction socket containing the apical lesion showed a smooth topography of the surfaces, and no Volkmann's canals were observed (Figure 4). Reductions of the bone marrow and the Volkmann's canal may compromise the supply of growth factors and blood, interrupting the socket healing cascade from the initial blood clot formation and eventually to the erratic socket healing (Kim et al. 2014). Throughout this ligation process, a substantial amount of horizontal bone loss was observed, but intrabony defects do occur frequently as chronic lesion in clinical practice.

Additionally, it has been reported that condensing osteitis can occur if periodontitis patients are exposed to low virulence factors long term (Abrahams & Berger 1998).

The histomorphometric results of healing the fresh extraction sockets correspond well to those of a previous study (Cardaropoli et al. 2003) and are outlined in table 1. However, on day 1, a hollow space resembling an artifact composed of 62.5% in the healthy socket and 38.4% in the diseased socket of the socket space was observed in the socket space (Figures 5a and 5f). This artifact is thought to be a result of a soft tissue collapse during micro-CT, which was not performed in the previous study. At day 1, 99.5% blood clot formation was reported, however, this process could have been easily disrupted by the preparation of the micro-CT specimens. On day 1, inflamed granulation tissue, appearing to be distinct from normal tissue in the healthy extraction sockets, was observed in the coronal and apical aspects of the diseased extraction sockets (35.6%), along with the infiltration of the inflammatory cells (Figure 5f).

Notable differences of both sites were not found on day 7 (Figures 5b and 5g), but an accelerated remodeling was observed in the healthy extraction sockets as early as day 30. On day 30, bone remodeling with bone marrow formation starting at the periphery of the socket wall was observed with a fibrous tissue content of 27.4% filling the middle space of the healthy sockets (Figure 5c). This finding is in agreement with the 12% provisional matrix (PCT) in the previous study (Cardaropoli et al. 2003), even though bone marrow formation seems to be slightly accelerated in the present study. Contradicting results are shown for the diseased sockets with fibrous tissue contents of 51.5% filling up the space from the coronal to apical side and bone trabeculae of 48.5%, far lower than the 88% from a previous study (Figure 5h).

The healthy sockets at days 60 and 90 showed almost complete maturation with bone marrow contents of 78.6% and 78.9% and complete cortical bone formation in the coronal part of the socket (Figures 5d and 5e). This result corroborates findings by Cardaropoli et al. (2003), who showed that the bone marrow comprised 63-85% after 60 days. In the diseased extraction sockets, the bone marrow comprised 46.5% at day 60 (Figure 5i) and 65.9% at day 90 (Figure 5j), indicating that remodeling remains ongoing. At day 90, remodeling in the healthy extraction sockets was almost complete, with no definitive borders between pristine bone and the newly formed cortical bone; however, in diseased extraction sockets, a clear demarcation line can be observed.

For 3-dimensional morphometric analysis, the bone volume fraction (trabecular BV per TV expressed as percentage) has been applied (Parfitt et al. 1987). Bone volume density (BV/TV) is a ratio of the trabecular bone volume to the total VOI (Fanuscu & Chang 2004). In the healthy extraction sockets, the BV/TV values had a tendency to gradually decrease for days 30, 60 and 90 days. This finding may be due to the limitations of a radiographic analysis restricted to the binary formula, which thus only allowed for the measurement of the bone trabeculae and a limited analysis of the fibrous tissue and bone marrow. The bone trabeculae comprised 43.3, 21.4 and 21.1% at days 30, 60 and 90, resepectively. In contrast, the BV/TV values for the disease sockets were 69.3, 70.5 and 50.6%, showing a relatively high but similar trend as that of the histologic specimens, at 48.5, 53.5 and 34.1%, respectively.

Bone surface density (BS/BV) is a ratio of the bone surface area to the total bone volume of the VOI (Moon et al. 2004). Denser bone corresponds to a high bone volume density and low bone surface density. This finding implies that the trabeculae are a decreasing bone quality as the healing

interval becomes prolonged from 30, 60 and 90 days.

The BA/TA values in the mid-sagittal area were 68.0, 77.4 and 47.6% and are thought to be caused by the inconsistent remodeling of the active trabeculae (Figure 8). The BA/TA for the diseased socket at day 90 was 50.6%, when compared to the corresponding values in the healthy sockets, this value fall between days 30 and 60. This finding may suggest that delays in socket healing of the central area are possible in the diseased sockets by 30-60 days.

TbPf is an indicator of the connectivity of the trabeculae and is inversely proportional to the interconnectivity (Sugisaki et al. 2009, Roze et al. 2009). In the healthy extraction sockets, TbPf values increased to -0.45, 0.25 and 0.52, indicating the remodeling of the trabeculae into fatty bone marrow. In the diseased sockets, TbPf increased to -0.65, -0.16 and 0.18 in a similar fashion, reaching a value of 0.18 at day 90, which is 0.25 less than day 60 of the healthy extraction sockets. TbPf is a parameter capable of showing the complexity of this structure and may hold some correlation with the SMI. The SMI indicates the relative prevalence of rods and plates.

In dogs, such data may suggest that the newly formed bone within the socket excluding the cortical bone portion may be less favorable for the primary stability of a dental implant as the healing time progresses. Additionally, this finding may be interpreted such that, in humans, if the healing time is prolonged and the cortical bone near the coronal cortical bone part is compensated, the primary stability during implant placement may be severely jeopardized. This instability in healing, especially in cases with inadequate cortical bone, may not support the paradigm that a longer healing interval results in an enhanced primary stability in such cases, additional research regarding the appropriate time of implant placement seems necessary in diseased sockets.

Following tooth extraction, a pronounced loss of the buccal plate has been reported extensively by previous studies (Pietrokovski & Massler 1967, Schropp et al. 2003, Araujo & Lindhe 2005). Similar to the previous studies, a line parallel to the long axis of the root, subtracting the line connecting the line connecting the buccal and lingual intersection, was found in healthy sockets -0.3, -0.9, 1.6 mm at days 7, 30 and 60, respectively, corresponding well with the results of Araujo & Lindhe (2005). However, in the diseased sockets, vertical bone loss was observed on day 1 with a value of -2.2 mm. The values at days 60 and 90 for the healthy extraction sockets were -1.6 and -1.7 mm, reflecting some degree of saturation. However, the corresponding values for the diseased sockets at days 60 and 90 were -3.0 and -3.8 mm, showing a higher tendency towards reduction (Table 3). These sagittal sections were traced using micro-CT images (Figure 8). These findings may suggest that the buccal plate is comprised of thinner bone, which seems more vulnerable to infection in the coronal region at which the periodontal lesions were induced using ligatures. Further, the diseased sockets displayed greater dimensional changes compared to the healthy sockets.

The present study was designed to show healing only up to day 90, because healing after 60 days to 90 days of a previous study only involves or confirms the remodeling process (Cardaropoli et al. 2003). However, the diseased extraction sockets in the present study were associated with moderate to severe delays in healing, prolonging the remodeling process to a point beyond 90 days and making it impossible to observe the time point of saturation. Further, in the micro-CT analysis, 3-dimensional healing was delayed in the diseased socket due to the continuing remodeling and vertical bone resorption, even at day 90, making it difficult to estimate the further changes that are to occur.

Within the limitations, the healing of the diseased extraction sockets were compromised, as evidenced by the delayed healing dynamics and more pronounced vertical resorption compared to healthy extraction sockets. Therefore, it may be suggested that the treatment of diseased extraction sockets should involve paying special attention to the time of implant placement, as well as other methods to minimize the vertical bone loss in the buccal aspects.

TABLES

Table 1. Proportions (%) of the tissues between healthy and diseased sockets during the different time intervals, means (SD)

	IGT	CLOT	FT	BT	BM
1 day					
Healthy sockets		37.5(8.86)			
Diseased sockets	35.6(4.95)	26.0(3.57)			
7 days					
Healthy sockets		44.9(3.03)	55.1(3.03)		
Diseased sockets		41.2(19.66)	58.8(19.66)		
30 days					
Healthy sockets			27.4(24.12)	43.3(2.42)	29.4(26.53)
Diseased sockets			51.5(1.51)	48.5(1.51)	
60 days					
Healthy sockets				21.4(5.21)	78.6(5.21)
Diseased sockets				53.5(2.29	46.5(2.29)
90 days					
Healthy sockets				21.1(3.84)	78.9(3.84)
Diseased sockets				34.1(13.25)	65.9(13.25)

IGT: inflamed granulation tissue, CLOT: blood clot, FT: fibrous tissue, BT: bone trabeculae, BM: bone marrow

Table 2. Micro-CT 3- or 2-D values in the healing sockets during the different time intervals, means (SD)

	BV/TV(%)	BS/BV	BA/TA(%)	TbPf	SMI
30 days					
Healthy sockets	56(1.94)	0.26(0.01)	48.8(1.10)	-0.45(0.01)	-1.13(0.06)
Diseased sockets	69.3(0.59)	0.26(0.01)	53.9(4.33)	-0.65(0.02)	-3.30(0.11)
60 days					
Healthy sockets	26.2(2.61)	0.08(0)	17.5(1.50)	0.25(0.13)	5.16(1.34)
Diseased sockets	70.5(6.31)	0.15(0.02)	63.2(8.33)	-0.16(0.05)	1.17(1.02)
90 days					
Healthy sockets	19.7(1.51)	0.14(0.02)	13.8(2.57)	0.52(0.01)	7.96(1.26)
Diseased sockets	50.6(5.85)	0.07(0.01)	31.4(9.69)	0.18(0.10)	6.38(1.68)

BV: bone volume, TV: tissue volume, BS: bone surface, BA: bone area, TA: tissue area, TbPf: trabecular pattern, SMI: structural model index

Table 3. Vertical distance (mm) between the buccal and lingual intersection, mean (SD)

	1 day	7 days	30 days	60 days	90 days
Healthy sockets	-0.2(0.12)	-0.3(0.02)	-0.9(0.34)	-1.6(0.18)	-1.7(0.09)
Diseased sockets	-2.2(0.03)	-2.4(0.14)	-2.7(0.14)	-3.0(0.70)	-3.8(0.12)

Figures & Legends

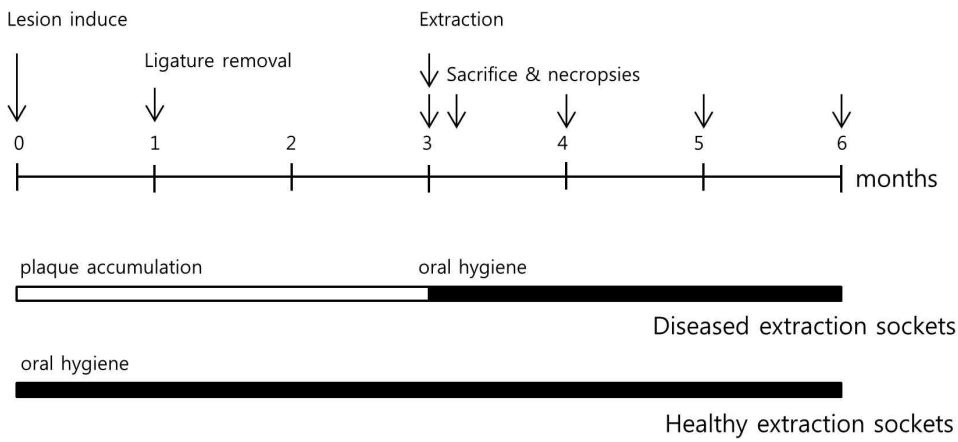

Fig. 1 Outline of the study design. A 4th mandibular premolar was induced to develop a periodontal and endodontic lesion with pulp exposure and ligature enhanced plaque accumulation. One month later, the ligature was removed. The contralateral site of the 4th premolar was maintained with plaque control. Three months after the intervention, both sites were extracted. Block necropsies were obtained after 1, 7, 30, 60 and 90days.

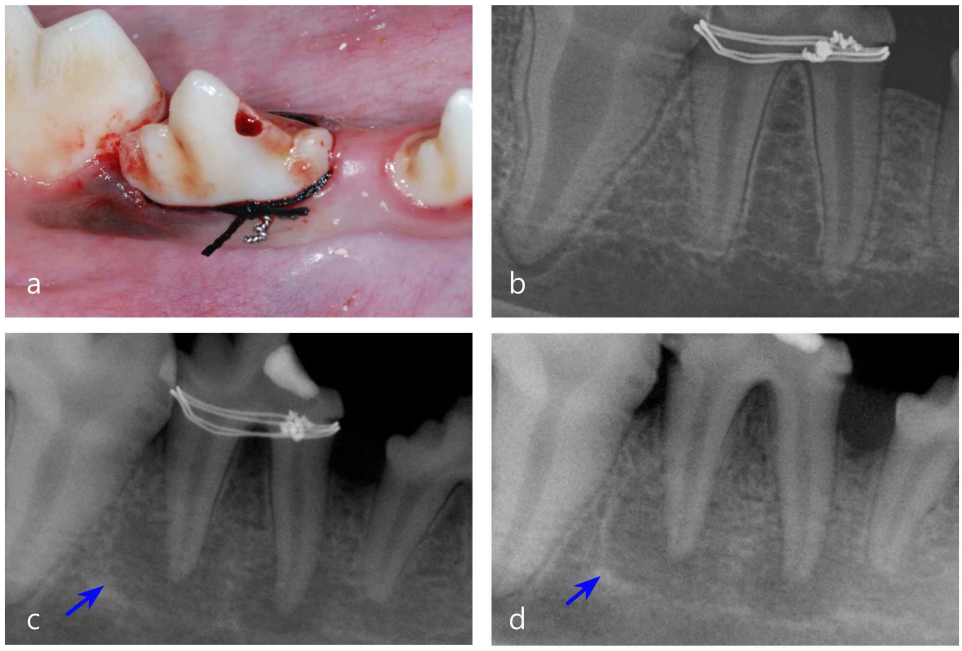

Fig. 2 (a),(b) Clinical view and intra oral x-rays of the inflammation-induced tooth after intervention (c) 1 month (d) 3months later after intervention. Note the sclerotic change near to the margin of lesion (blue arrows)

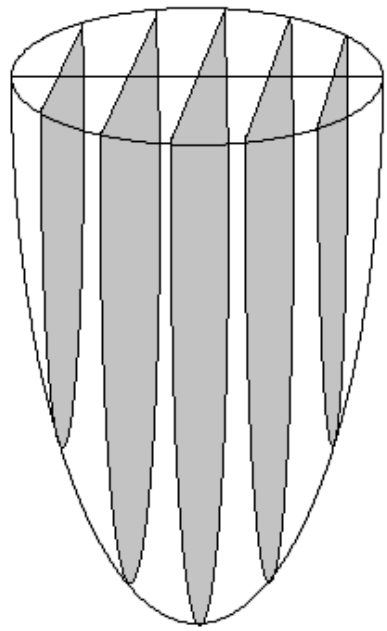

Fig. 3 Schematic drawing of 3D socket reconstruction volume of interest (VOI) for micro-CT analysis.

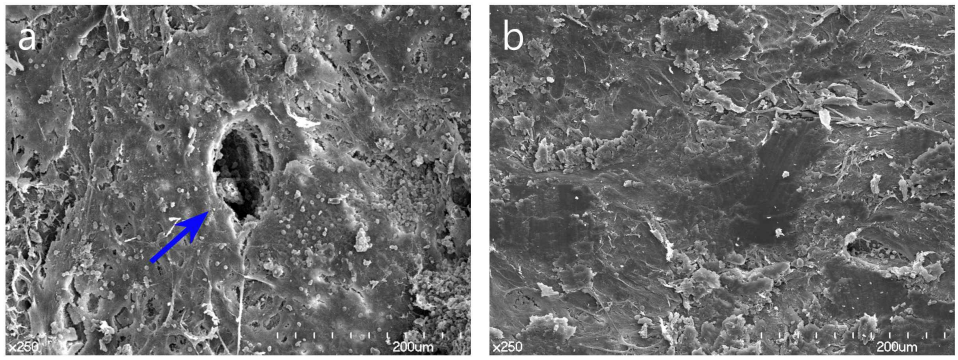

Fig. 4 (a) SEM shows apical side surface of healthy extraction sockets which had Volkmann's canal (blue arrow). Notice that erythrocyte cluster inside the canal (b) SEM shows apical side surface of diseased extraction sockets which collapsed surface of Volkmann's canal

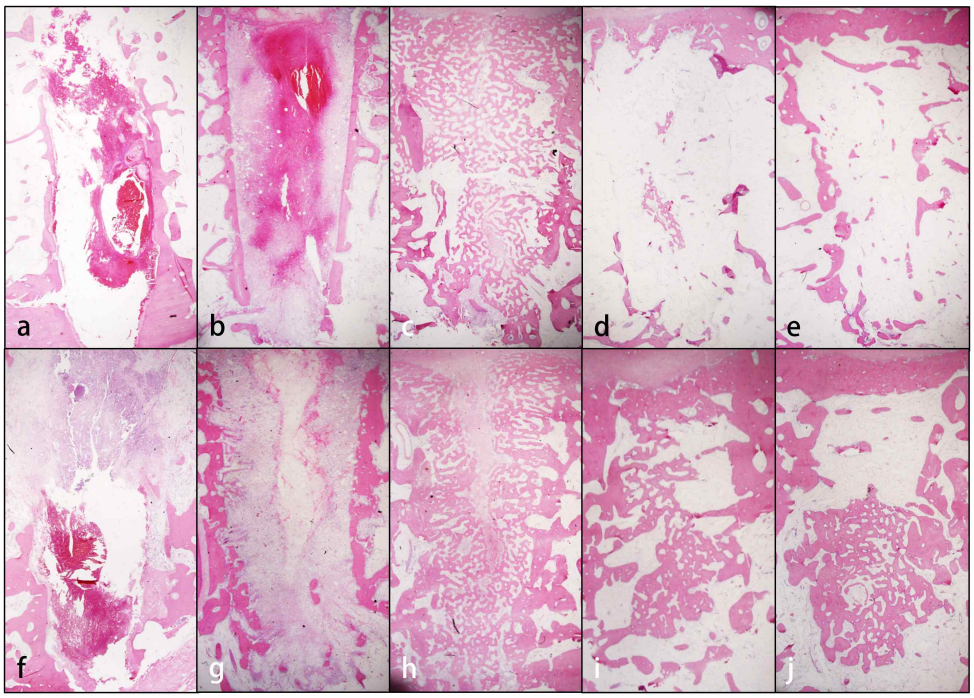

Fig. 5 Overview of the extraction site of extraction sockets: healthy sockets; (a) day 1, (b) day 7, (c) day 30, (d) day 60, (e) day 90, diseased sockets; (f) day 1, (g) day 7, (h) day 30, (i) day 60, (j) day 90. Notice that remodeling of diseased sockets was delayed in the central part of the sockets at days 60 and 90. H&E staining; original magnification x 16

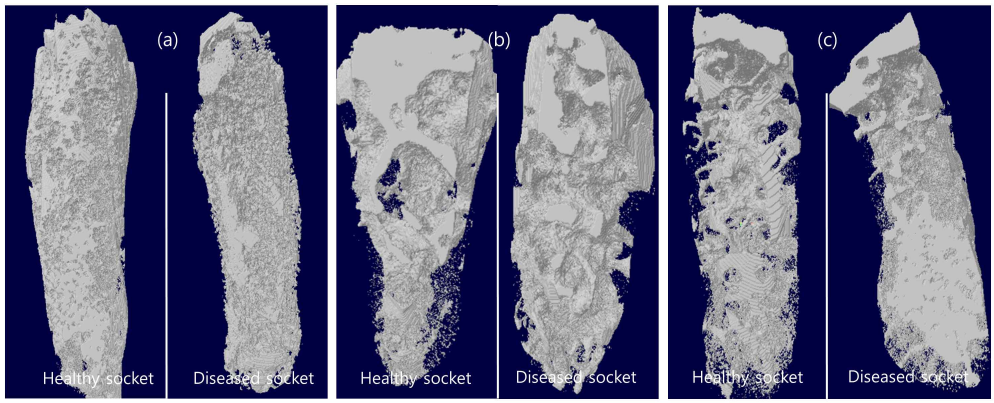

Fig. 6 3D images of extraction socket (a) day 30 (b) day 60 (c) day. Notice that remodeling was delayed in diseased sockets especially at day 60 and 90.

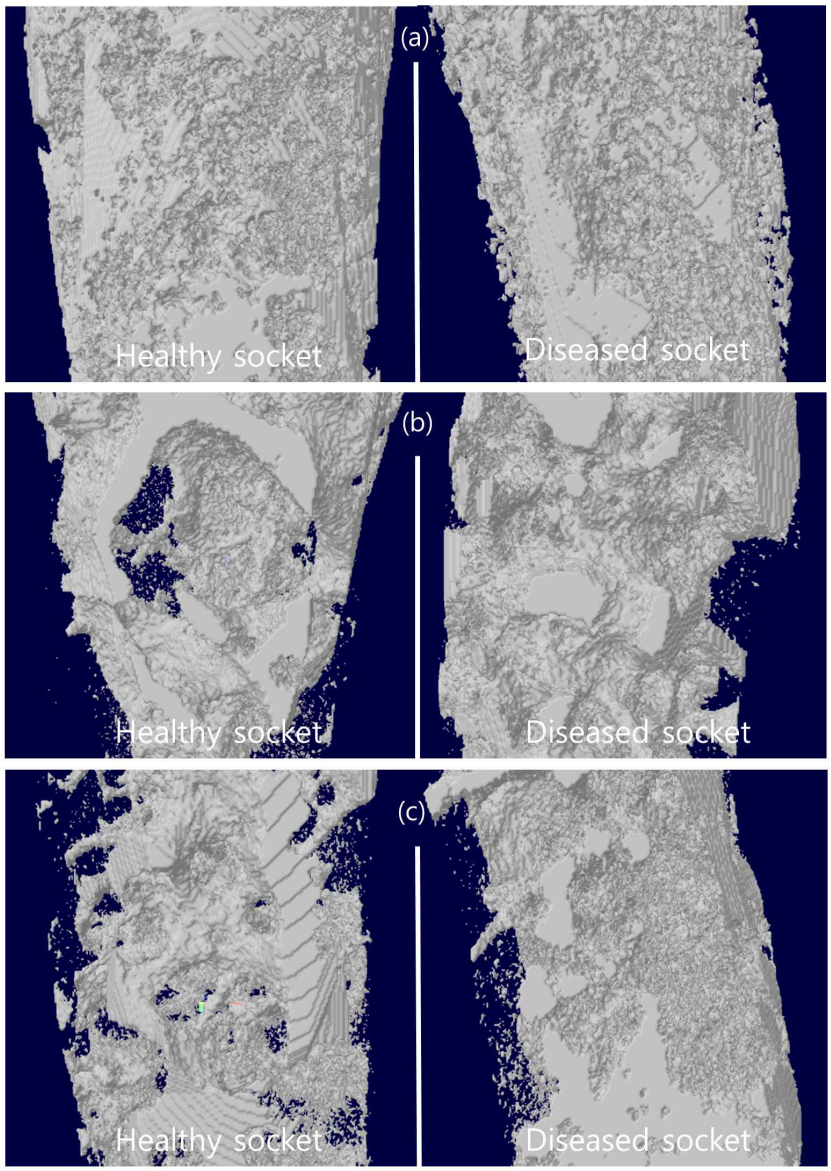

Fig. 7 Central third magnification 3D images of extraction socket (a) day 30 (b) day 60 (c) day 90. Note that remodeling was delayed in diseased sockets especially at day 60 and 90.

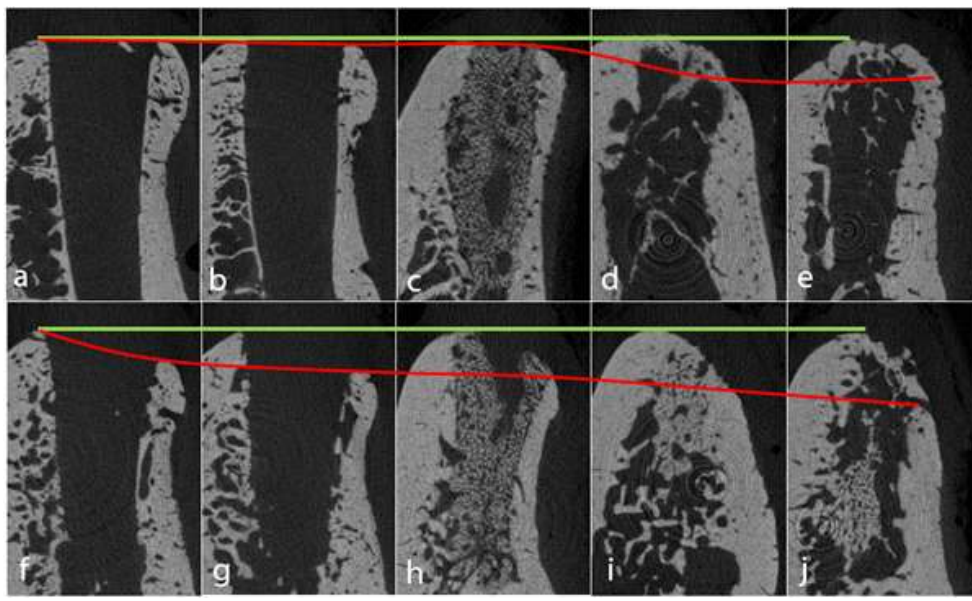

Fig. 8 Mid-sagittal section images of extraction sockets: healthy sockets; (a) day 1, (b) day 7, (c) day 30, (d) day 60, (e) day 90, diseased socket; (f) day 1, (g) day 7, (h) day 30, (i) day 60, (j) day 90. Notice that vertical resorption of the buccal bone crest in diseased sockets was more pronounced in the mid-sagittal plane.

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Extraction Sockets: Erratic Healing and Impeding Factors

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CONFLICT OF INTEREST AND SOURCE OF FUNDING STATEMENT

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ABSTRACT

Aim: The aim of this exploratory study was to analyze prevalence of extraction sockets showing erratic healing and evaluate factors potentially impeding healing.

Methods: Erratic healing was defined as extraction sites showing clinical observations of fibrous scar tissue occupying the extraction site rather than bone, following 12 or more weeks of healing. Computerized tomography was used to evaluate characteristics and calculate Hounsfield unit scores for sites showing erratic healing.

Results: A total of 1,226 dental records from Seoul National University Dental Hospital archives including patients subject to extractions prior to implant placement were evaluated. Seventy subjects (5.71%) and 97 sites (4.24%) exhibited erratic extraction socket healing. Maxillary incisor/canine sites showed the lowest (0.47%), whereas mandibular molar sites the highest (5.41%) occurrence. In the multivariable analysis, erratic healing was more likely to occur in subjects < 60 years old (OR= 2.23, 95%CI= 1.26-3.94), subjects with hypertension (OR= 2.37, 95%CI= 1.24-4.55), in molar sites (OR= 4.91, 95%CI= 1.41-17.07), and following single tooth extractions (OR= 2.98, 95%CI= 1.36-6.53). Computerized tomography showed the highest incidence of bone loss for the buccal wall (49.3%).

Conclusion: Erratic extraction socket healing appears a not uncommon sequel and local factors seem to be major contributors to its occurrence.

CLINICAL RELEVANCE

Scientific rationale for the study: Reports regarding extraction socket healing have focus on dimensional changes of the alveolar ridge; data on the distribution of extraction sockets with erratic healing and associated factors are limited or non-existing.

Principal findings: Erratic extraction socket healing appears more frequent than anticipated and local factors seem to be major contributors to its occurrence.

Practical implications: Our findings suggest that an important proportion of extraction sockets do not heal adequately in spite of careful clinical protocol and sufficient healing time compromising implant surgery.

INTRODUCTION

Healing of extraction sockets has been studied extensively, animal and human clinical studies contributing to current understanding of the underlying biology (Pietrokovski & Massler 1967, Amler 1969, Cardaropoli et al. 2003, Schropp et al. 2003, Araújo & Lindhe 2005). These studies include evaluation of dimensional and radiographic changes derived from histologic sections, radiographs or diagnostic casts obtained immediately following tooth extraction and at various intervals thereafter. Extraction socket healing in humans follows a sequence of cellular and tissue changes; a blood clot is rapidly established within the extraction socket to be replaced by granulation tissue and subsequently osteoid (Amler 1969). Similarly, in dogs, the establishment of a blood clot is followed by an array of events that transitions formation of a provisional matrix, woven bone, lamellar bone and bone marrow over a 180-day interval (Cardaropoli et al. 2003). Nevertheless, previous work largely comprises evaluation of fresh extraction sockets following removal of teeth absent pathologic processes projecting a favorable healing potential. In clinical settings, extraction sockets commonly result from removal of teeth affected by periodontal and/or endodontic pathology often in medically compromised patients. Even following strict guidelines of meticulous wound debridement and healing periods exceeding 12 weeks (Hämmerle et al. 2004), healing appears frequently complexed by connective tissue infiltration leading to fibrous scar tissue rather than bone formation. Recent reports concerning implant periapical lesions have emphasized that optimal extraction socket healing might not always occur (Quirynen et al. 2005, Romanos et al. 2011, Lefever et al. 2013) The aim of the present exploratory study was to analyze prevalence of extraction sockets showing erratic healing and elucidate factors potentially impeding healing.

MATERIALS AND METHODS

Study design

This retrospective study comprised an analysis of dental records from the archives of the Seoul National University Dental Hospital, Seoul, Korea. The study protocol was approved by the Institutional Review Board, Seoul National University Dental Hospital (IRB no CRI12035).

Sampling and data collection

Following anecdotal evidence of extraction sites that failed to heal properly, three periodontists (JHK, KTK, YK) initiated a strict protocol including minimally traumatic tooth extraction and meticulous extraction socket debridement. Flaps were not raised; neither were ostectomies or osteoplasties performed. The tooth was carefully removed with using elevators and limited use of forceps to minimize trauma. Bone biomaterials, grafts, membrane devices or hemostatic collagen sponges were not used. The patients were directed to use an antimicrobial mouth rinse post-extraction (0.1% chlorhexidine; 10 mL 60s bid 7 days). Healing was allowed to proceed for at least 12 weeks. At subsequent surgical implant placement, recordings describing the clinical findings including characteristics of the healed socket hard or soft tissue components were collected. Extraction sites requiring additional meticulous debridement to remove soft tissue infiltration and need for bone augmentation were designated as erratic extraction socket healing.

A convenience sample of all dental records pertaining to subjects who had extractions performed by the three periodontists January 2005 through

November 2011 were searched using a customized computer-based data mining software (Fig. 1). Dental records of subjects meeting the following inclusion criteria were selected: (1) patients 18 years and older; and (2) patients who consented to implant treatment. Exclusion criteria were: (1) patients who received guided bone regeneration and/or maxillary sinus augmentation at tooth extraction or within 12 weeks after tooth extraction; (2) patients with history of systemic disease and/or medication that may affect extraction socket healing; i.e., osteosarcoma, osteomyelitis and Paget's disease; (3) patients who underwent radiation therapy prior to or within 6 months post-extraction; and (4) patients with osteoporotic disease. Records were reviewed (JHK) to identify cases featuring extraction sockets showing erratic healing defined as extraction sockets that were occupied by soft tissue infiltration and required repeated debridement followed by guided bone regeneration. The following demographics, medical and dental data were retrieved from the hospital database records: age, gender, history of diabetes mellitus or hypertension, smoking habit, position of extraction site, duration of healing following extraction.

Sample size calculation

Since no reliable estimate of the prevalence of extraction sockets with erratic healing was available for sample size calculation, a worst-case scenario strategy (prevalence of 50%) was used and a sample size of approximately 1,400 subjects was estimated to be necessary to estimate the prevalence of erratic healing with a precision of ± 3% for the 95% confidence interval. Our sample size calculation accounted for an item-nonresponse of approximately 30%.

Radiographic analysis

An experienced radiologist (JHM) performed the radiographic evaluation. Pre-extraction panoramic radiographs were available for all subjects with extraction sites designated as erratic extraction socket healing. Radiographs were obtained using an orthopantomograph (op100, Instrumentarium Corp, Tuusula, Finland) and automated file processing using an x-ray film digitizer (DiagnosticPro plus x-ray film digitizer, Vidar, Herndon, VA, USA). Panoramic radiographs were evaluated using a computer-assisted system (PiView STAR™ 5.0, Informer Technologies, Seoul, Korea).

Extraction sockets were classified into three categories according to the recorded rationale for extraction. In cases where the information regarding the rationale for extraction was missing, the radiologist performed the classification using pre-extraction tooth status (Low et al. 2008, Janner et al. 2011) as follows: Sites showing marginal bone loss encompassing more than 50% of the root length or included the furcation(s) in molars were classified as periodontal lesions. Sites presenting with a peri-apical radiolucency were categorized as endodontic lesions. Extraction sockets yielding evidence of both periodontal and endodontic pathology were considered as periodontal-endodontic lesions. Sites without written documentation or radiographically discernable pathology were classified as of unknown pathology.

Computerized tomography scans (Somatom Sensation 10, Siemens, Erlangen, Germany) were available for 69 of 97 subjects diagnosed as having erratic extraction socket healing. Scans were obtained at 175X175 FOV, 120 kV, 100 mA, and 0.75 mm slices. Defect characteristics, number of extraction

socket walls, and Hounsfield unit (HU) scores were recorded. Regions of interest were measured on the parasagittal. For each measurement, the largest possible elliptical region of interest was drawn, excluding the cortical and sclerotic margins to prevent volume averaging. Using the digital software, mean HU scores for each point was calculated. The average of these readings represented the density for the site. The oral radiologist recorded each site three times. Each recording was made independently and the mean HU scores for each group were calculated.

Statistical analysis

Data analysis was performed using a statistical software (Stata 11.2 for Mac, Stata Corporation, College Station, TX, USA). Subjects were dichotomized according to age into < 60 and ≥ 60 years old. Data regarding smoking exposure was inconsistent; subjects were classified as smokers and non-smokers. Subjects were classified as diabetic or hypertensive using data derived from their medical history. The distribution of subjects according to demographics and medical history was assessed using χ^2-test. Prevalence and 95% confidence intervals are reported. Generalized estimating equations (binomial family, logit link, exchangeable correlation) were used to assess the associations among predictors and erratic healing. Measurements at site level were used and estimates were adjusted for the clustering of observations into individuals using a robust variance estimator. Wald tests were used for comparisons, and the level of significance was set at 5%. Confounding and effect modification were assessed.

RESULTS

Complete dental records were available for 1,226 of 1,457 subjects. The sample comprised 552 females and 674 males, mean (± SD) age 55.9 ± 11.3 years, age range 18-87 years. Seventy (5.71%) subjects were diagnosed as exhibiting erratic extraction socket healing. Table 1 shows the prevalence of cases categorized by age, gender, smoking habit, diabetes and hypertension. Subjects < 60 years old showed a significantly higher prevalence of erratic extraction socket healing than older subjects. No other significant differences were observed.

Data for 2,288 extraction sockets were retrieved for analysis. The average post-extraction healing period was 5.5 ± 2.6 months (range 3-24 months). Ninety-seven (4.24%) sites were classified as extraction sockets showing erratic healing. The mean healing interval for the erratic healing sites was 5.6 ± 3.4 months, corresponding values for the normal healing group was 5.5 ± 2.5 months.

Table 2 shows the occurrence and intra-oral distribution of erratic extraction socket healing. Maxillary incisors/canines showed the lowest occurrence (0.47%) of erratic extraction socket healing, whereas mandibular molars showed the highest (5.41%). Approximately 3% of mandibular incisors/canines and premolars were affected. Table 3 shows characteristics of extraction sockets with erratic healing. Of the 97 sites with erratic healing, 70 (72.16%) were due to periodontal pathology, 11 (11.34%) due to combined periodontal-endodontic lesions, and 2 (2.12%) due to endodontic pathology. The rationale for extraction was not documented/could not be

classified in 14 cases. Computerized tomography scans from 69 of 97 extraction sockets showing erratic healing obtained at 3.8 ± 2.9 months were evaluated. Eleven four-wall (15.9%), 39 three-wall (56.52%) and 19 two-wall (27.53%) extraction sockets were recorded (Fig. 2, 3). Half of the extraction sockets had lost the buccal wall (n= 34, 49.3%), a quarter had lost both buccal and lingual walls (n = 19, 27.5%), and few had lost only the lingual wall (n = 5, 7.3%). Average (± SD) HU score for these sites was 110 ± 119.

After adjusting for other factors in the multivariable analysis (Table 4), erratic extraction socket healing was more likely to occur in younger subjects (OR = 2.23), subjects with hypertension (OR = 2.37), in molar sites (OR = 4.91), and following single tooth extractions (OR = 2.98). Gender, diabetes or smoking were not significantly associated with erratic extraction socket healing.

DISCUSSION

Extraction sockets, if meticulous debridement or curettage is executed, are expected to heal with bone. However, observations of radiolucencies and clinical observations of fibrous scar tissue occupying the extraction site rather than bone, prohibiting the placement of dental implants prompted the current exploratory study. Previous studies have focus on the occurrence of dry sockets mostly related to third molar extractions (Larsen 1992, Blum 2002), and more recent studies on healing dynamics of extraction sites using preclinical and clinical models (Cardaropoli et al. 2003, Araújo & Lindhe 2005, Schropp et al. 2003). Implant peri-apical lesions likely associated with unsuccessfully healing extractions sockets have also been identified but limited data exists (Quirynen et al. 2005, Romanos et al. 2011, Lefever et al. 2013). The prevalence of extraction sockets showing erratic healing and factors potentially impeding healing however remain elusive. In the present study, the term erratic healing was defined as healing of extraction sockets resulting in soft tissue infiltration, likely fibrous scar tissue, rather than bone formation even following meticulous debridement and a healing interval exceeding 12 weeks. Approximately 5% of the extraction sites in this study thus featured erratic extraction socket healing.

Studies providing histologic documentation of tissue formation/maturation in extraction sockets conclude that extraction sockets will heal with mineralized bone within 6 weeks (Amler 1969). Others suggest that 10 weeks are necessary for complete bone fill (Evian et al. 1982). Still others demonstrate inconsistent bone healing and high individual variability showing formation of 35% woven bone in a provisional matrix at 6-8 weeks and 41% at 12-24 weeks (Trombelli et al. 2008). These studies evaluated extraction sockets generally absent of inflammatory lesions in contrast to the focus on

erratic extraction socket healing in the present study. Another difference between studies is constituted in the healing interval; in the present study averaging approximately 22 weeks, some cases showing erratic healing even after 24 months suggesting a chronic nature of erratic extraction socket healing.

In the multivariable analysis, erratic extraction socket healing was more likely to occur in subjects < 60 years old (OR= 2.23), subjects with hypertension (OR= 2.37), molar sites (OR= 4.91) and single tooth extraction sites (OR= 2.98). A weak association between erratic extraction socket healing and smoking and diabetes needs to be clarified since both factors consistently have been implicated in compromised wound healing (Haire-Joshu et al. 1999, Eliasson 2003). Advanced age frequently has been associated with reduced immune response, bone metabolism and regenerative potential (Delmas et al. 1983, Castle 2000); however, in the present study younger subjects appeared more likely to show erratic extraction socket healing than older subjects. Reasons for this observation can only be speculated upon.

In the present study, a positive association between erratic extraction socket healing and hypertension should be interpreted with caution since hypertension in this context is probably a generic proxy for general health rather than a true factor associated with the outcome. Local factors including intra-oral location and multiple extractions were also significantly associated with erratic extraction socket healing. Molar sites showed the highest occurrence, followed by premolar sites (5.22% vs. 3.23%). Compared with incisor and canine sites, premolar and molar sites were three and five times

as likely to experience erratic healing, respectively. At the present it is unclear which factors would explain the higher likelihood of erratic healing in posterior sites, however similarities shared with condensing osteitis relative to frequent occurrence in the premolar and molar region should not be overlooked. It must also not be overlooked that posterior extractions are likely more challenging to manage surgically and post-surgically, and healing would conceivably be more challenging due to relatively larger extraction sockets.

Erratic extraction socket healing was three-fold greater for single tooth compared with multiple teeth extraction sites. It seems counterintuitive that single tooth extractions would have higher chances of erratic healing and reasons for this observation are currently unknown. It must be pointed out that in the multiple extraction cases interproximal bone loss may affect modeling and remodeling processes to eventually impose a decreased propensity of erratic healing. Nevertheless, additional study is needed to verify the effect of the loss of interproximal alveolar bone on erratic extraction socket healing.

Computerized tomography showed the highest incidence of bone loss for the buccal crestal wall (49.3%) for sites exhibiting erratic extraction socket healing in the present study. Loss of the buccal, lingual or palatal crestal wall can compromise the healing potential of an extraction socket. The loss of a wall may mean reduction of healing vectors and a transformation of the defect morphology into a non-contained defect that is known to have a lesser healing potential. However, erratic healing may occur even in cases where all the walls are preserved resulting in fibrous scar tissue formation.

The computerized tomography evaluation encompassing 69 cases showed the highest prevalence of erratic healing (56.3%) for three-wall extraction sites. Consistent with previous studies the buccal wall appeared the most vulnerable (49.3%) (Pietrokovski & Massler 1967, Schropp *et al.* 2003, Araújo & Lindhe 2005). However, it was not possible to distinguish whether the buccal wall was missing/affected as a consequence of periodontal disease, extraction trauma, post-extraction remodeling or combinations of these factors. Also, the observation that 11 four-wall or circumferential defect sites in spite of their anticipated ample potential to heal satisfactory for dental implant placement were implicated as erratic healing sites may suggest additional factors complexing the healing process.

In the present study, HU scores for sites exhibiting erratic extraction socket healing averaged 110 ± 119. This value is consistent with HU scores for soft tissues and also implies that erratic healing may be diagnosed using the HU scores. In perspective, HU scores for sites exhibiting erratic extraction socket healing appear significantly lower than that reported using the Lekholm & Zarb (1985) classification for Type I (951 ± 210), Type II (706 ± 276), Type III (676 ± 282), and Type IV (464 ± 290) bone (Norton & Gamble 2001); as well as HU scores for the anterior and posterior maxilla (517 ± 177 and 333 ± 199), and the anterior and posterior mandible (559 ± 208 and 321 ± 132) showing a tendency decreasing HU scores for the posterior regions (Shapurian *et al.* 2006).

Our finding that approximate 5% of the subjects and extraction sockets show erratic healing impeding replacement of missing teeth with dental implants should be seen in light of the characteristics of the present study.

A convenience sample derived from a teaching dental hospital might have a peculiar patient population including complex management cases and patient in need of more specialized treatment. Nevertheless, the fact that most extractions were associated with periodontal and/or endodontic lesion seems to indicate otherwise. Studies including subjects from different clinical settings should be conducted to confirm our findings. The case definition used herein was based on a combination of clinical findings and treatment outcomes constrained by the retrospective nature of the study. Future studies should use case definitions that can be used prospectively and are less reliant on the clinician judgment.

CONCLUSION

Within the limitation of this study, observations herein suggest that erratic extraction socket healing appears a not uncommon sequel. In particular, sufficient healing time may not always support proper healing of the extraction sockets owing to the disruption in healing by connective tissue infiltration instead of bone formation. Erratic healing was associated with systemic and local factors.

TABLES

Table 1. Prevalence of subjects showing erratic extraction socket healing.

	n	Erratic healing	%	95%CI	*p* value
Age					
< 60 years	755	53	7.02	5.19-8.85	
≥60 years	471	17	3.61	1.92-5.30	0.01*
Gender					
Male	674	42	6.23	4.40-8.06	
Female	552	28	5.07	3.24-6.91	0.38
Smoking habit					
No	1127	64	5.68	4.33-7.03	
Yes	99	6	6.06	1.33-10.79	0.88
Diabetes					
No	1042	63	5.52	4.19-6.84	
Yes	84	7	8.33	2.38-14.29	0.28
Hypertension					
No	1084	57	5.26	3.93-6.59	
Yes	142	13	9.15	4.39-13.92	0.06
Total	1,226	70	5.71	4.41-7.01	

*Statistically significant ($p< 0.05$).

CI, confidence interval

Table 2. Distribution of erratic extraction socket healing according to tooth site.

	Incisors/canines	Premolars	Molars	Total
Maxilla	0.47% (1/211)	3.17% (11/347)	5.01% (35/699)	3.74% (47/1,257)
Mandible	3.17% (2/63)	3.33% (7/210)	5.41% (41/758)	4.85% (50/1,031)
Total	1.10% (3/274)	3.23% (18/557)	5.22% (76/1,457)	4.24% (97/2,288)

Table 3. Distribution of erratic extraction socket healing characteristics

	n	Percent (%)
Lesion		
Periodontal	70	72.2
Periodontal-endodontic	11	11.3
Endodontic	2	2.1
Unknown pathology	14	14.4
Number of socket walls		
4	11	15.94
3	39	56.52
2	19	27.54
Region of lost wall		
Buccal	34	49.28
Lingual (or palatal)	5	7.25
Bucco-lingual	19	27.54
No lost wall	11	15.94

Table 4. Univariable and multivariable analysis of risk indicators for erratic extraction socket healing.

	Univariable			Multivariable		
	OR	95%CI	*p* value	OR	95%CI	*p* value
Gender						
Male	1.0					
Female	0.76	0.47-1.21	0.25	-		
Age						
≥ 60 years	1.0			1.0		
< 60 years	2.29	1.29-4.07	0.005*	2.23	1.26-3.94	0.006*
Diabetes						
No	1.0					
Yes	1.44	0.67-3.09	0.36			
Hypertension						
No	1.0			1.0		
Yes	1.75	0.95-3.22	0.07	2.37	1.24-4.55	0.009*
Smoking						
No	1.0					
Yes	1.27	0.59-2.76	0.54	-		
Arch						
Maxilla	1.0					
Mandible	1.35	0.90-2.04	0.15	-		
Site						
Incisors-canines	1.0			1.0		
Premolars	2.57	0.88-7.52	0.09	3.26	0.89-11.88	0.07
Molars	4.01	1.41-11.39	0.009*	4.91	1.41-17.07	0.01*
Number of extractions						
≥ 3 teeth	1.0			1.0		
2 teeth	2.19	0.94-5.10	0.07	2.04	0.89-4.68	0.08
1 tooth	3.41	1.53-7.58	0.001*	2.98	1.36-6.53	0.007*

*Statisticallysignificant($p < 0.05$).

OR, odds ratio; CI, confidence interval

FIGURES AND LEGENDS

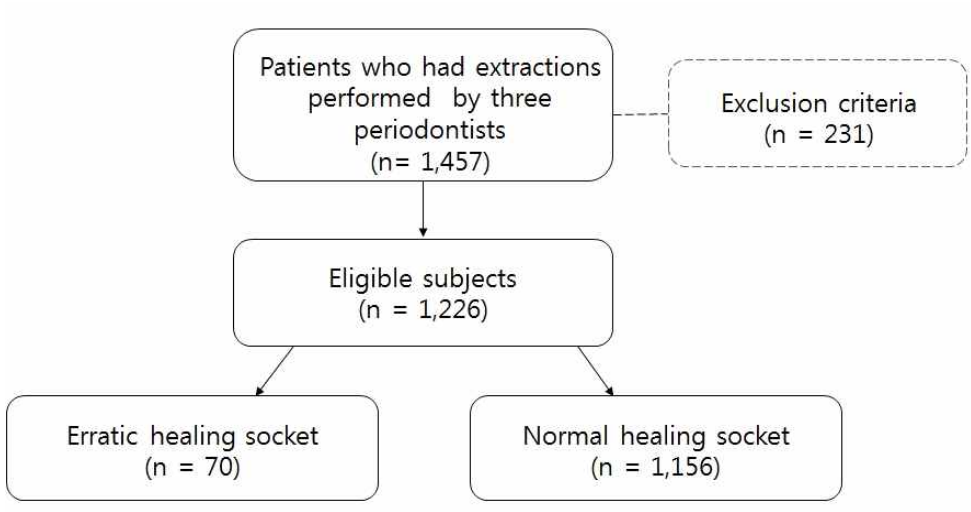

Fig. 1. Flow-chart showing the selection of the patients

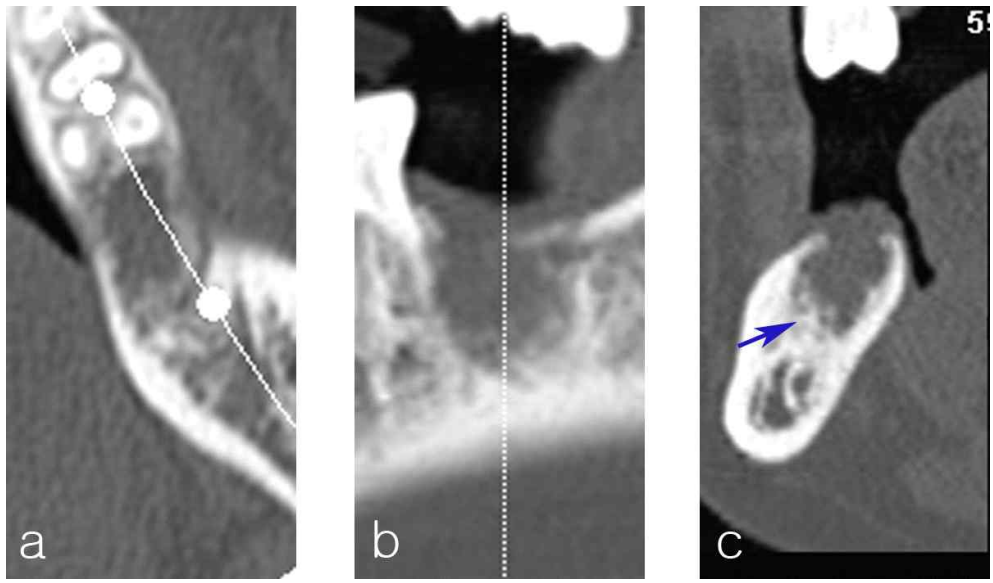

Fig 2. Computerized tomography of four-wall extraction socket following a healing interval in excess of 9 months; (a) axial view (b) coronal view (c) sagittal view. Note the sclerotic changes and reduced bone marrow (blue arrow).

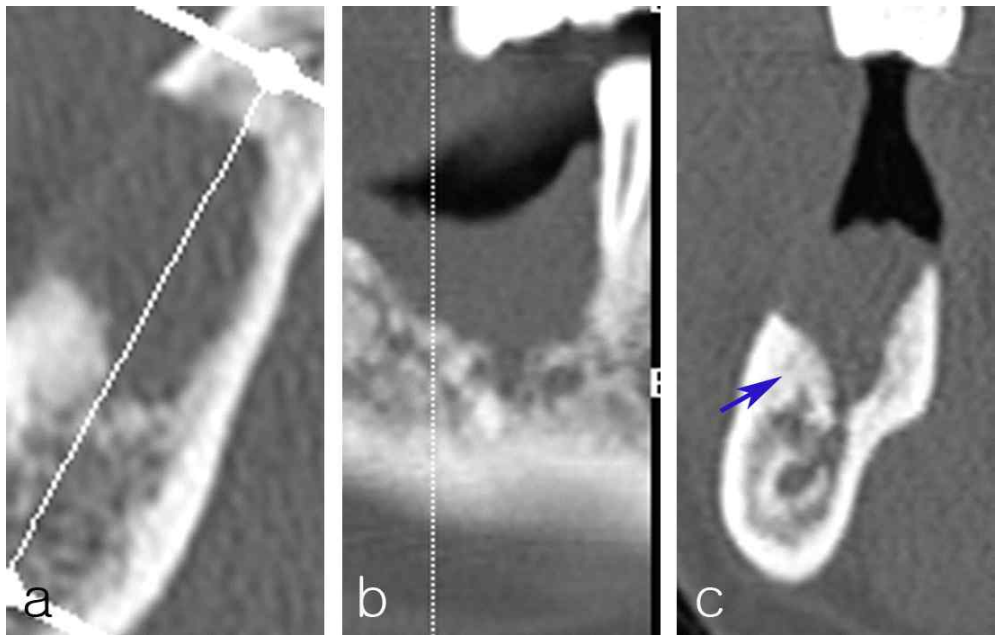

Fig 3. Computerized tomography of three-wall extraction socket following a healing interval in excess of 12 months; (a) axial view (b) coronal view (c) sagittal view. Note severe buccal bone loss, sclerotic changes and reduced bone marrow (blue arrow).

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- 국문초록 -

염증이환 발치와의 창상치유 평가

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발치와의 치유는 상실된 구강 기능과 심미적 재건에 있어서 매우 중요한 과정이다. 골에 식립하는 치근형 치과 임플란트의 개발 이후 발치와 치유 과정의 이해는 더 중요해 졌다. 발치와 골형성의 양과 질에 따라, 즉시, 조기, 지연, 만기의 치과 임플란트 식립시기를 결정할 수 있다. 또한 발치 후 일어나는 수직, 수평적 조직 수축은 심미적 재건에 매우 중요한 요소이다. 동물실험, 임상실험을 포함한 많은 연구들이 발치와 치유에 대한 조직학적, 공간적 부피 변화에 대해 연구해 왔다. 하지만 대부분의 연구가 염증이 없는 발치와의 치유에만 초점이 맞추어져, 우리가 실제 임상적 환경에서 발치의 적응증이 되는 병소가 있던 발치와에 대한 이해는 매우 부족하다.

파트1에서는, 5마리 비글견에서 분할 악궁 디자인으로 병소 유발 발치와의 치유과정을 병소가 없는 발치와와 비교 분석하였다. 제 4소구치를 한쪽은 인공적으로 염증의 유발하고, 반대편은 일주일에 3번 치태제거를 하여 염증이 없도록 유지하였다. 발치 후 동물을 1, 7, 30, 60, 90일에 단계적으로 희생하였다. 발치당일의 발치와 표면을 주사전자현미경 분석을 위한 시편과 발치 후 치유 기간의 조직학적 치유 과정을 평가,

마이크로-CT를 이용한 발치와의 3차원적 치유와 공간적 부피 변화 분석을 위해 시편들을 준비하였다. 결과는 병소가 없는 발치와와 병소 유발 발치와가 각기 다른 치유 기간 동안 다른 치유 패턴을 보였다. 염증 유발 기간 동안, 방사선 사진 상에 치근단 병소 주변으로 경화성 변화가 관찰되었고, 이 변화가 시간이 지남에 따라 짙어지는 경향을 보였다. 주사전자현미경으로 발치 당일의 발치와 관찰 시, 병소 유발 발치와에서 Volkmann 세관이 무너져 있었다. 병소 유발 발치와의 조직학적, 조직분석학적 평가결과, 발치 초기에는 염증 세포 침윤이 관찰되었고, 골형성 기간에는 활성 골소주의 골수로 골개조 과정이 상대적으로 지연되는 것이 관찰되었다. 또한 병소 유발 발치와의 마이크로-CT 분석에서도 염증이 없는 발치와보다, 60, 90일에 골수형성 지연이 관찰되었고, 1일에서 90일로 가는 동안 협측 골흡수가 상대적으로 훨씬 크게 나타났다.

발치와는 발치부터 시간의 흐름에 따라 혈병 형성, 육아조직 침착, 섬유성조직 변화, 활성 골소주 형성과 골수로 전환의 과정을 거친다. 그러나 임상적으로 오래된 염증을 가지고 있던 치아 중에는 발치와 소파술을 철저하게 하는 지침을 따르고, 적절한 치유 기간을 기다려도, 발치와 치유가 적절하지 않아서 치과 임플란트 식립을 못하고 골유도 재생술만 하는 경우가 있다. 파트2에서는, 발치와 처치를 적절하게 하고, 12주 이상의 치유 기간을 거쳐도, 발치와에 골형성 보다는 결체조직이 어지럽게 얽혀있는 섬유성 상처 조직으로 치유되는 것을 '비전형적 발치와 치유'라고 명명하고 유병률과 저해 인자들에 대해 조사하였다. 1226명의 환자를 조사하여, 70명(5.71%)의 환자, 97곳(4.24%)의 발치와에서 발병하였다. 상악 전치/견치에서 가장 낮은 값(0.47%)을 보였고, 하악 구치부(5.41%)에서 가장 높은 발병률을 보였다. 다변수 분석 결과, 60세 미만의 환자가 2.37배 더 많이 발병하고, 구치부에서 4.91배, 단일 치아 발치 시 2.98배 더 높게 나타났다. 비전형적 발치와 치유는 많이 발병하고, 국소적 인자들이 발생에 주요한 원인으로 생각된다.

결론적으로, 염증은 발치와 치유 능력을 불리하게 만들고, 새로운 골 형성을 지연시키며 골개조에 영향을 미친다. 또한, 비전형적 발치와 치유는 자주 발생하며, 국소인자들이 발생에 중요한 원인들이다.

주요어 : 만성 치주질환, 발치와, 비전형적 치유, 염증, 창상 치유
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