UNIVERSITY OF MEDICINE AND PHARMACY CRAIOVA

THE DOCTORAL SCHOOL

CLINICAL AND EXPERIMENTAL STUDY REGARDING THE HEALING PROCESS OF CHRONIC APICAL PERIODONTITIS THROUGH ORTHOGRADE ENDODONTIC TREATMENT

PhD THESIS ABSTRACT

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SUMMARY :

INTRODUCTION……pg.3

THE CURRENT STATE OF KNOWLEDGE……...pg.3

PERSONAL CONTRIBUTION……..pg.4

Aim and objectives of the study……pg.4

Material and methods…….....pg.5

Results……pg.6

Discussions……pg.8

Conclusions……pg.9

SELECTIVE REFERENCES……pg.11

KEY TERMS: chronic apical periodontitis, orthograde endodontic treatment, healing process.

INTRODUCTION

The periapical lesions of endodontic origin play a very well-defined role among the pathological states of the pulp disease. The most frequent forms are the chronic ones, which are asymptomatic evolve on a long-term basis.

The orthograde treatment in the case of apical periodontitis provides very high advantages, both biological (removing most of the microorganisms before instrumenting the apical area) and mechanical (an increased efficiency and reliability in determining the apical constriction). These aspects of the preparation technique, as well as the choice of an efficient and adequate irrigants for endodontic lavage, lead to optimal solutions of the endodontic treatment.

Thus, all the progress made in the modern dentistry encourages us to continue pursuing the research in the field and to try to find the most adequate solutions in the conservatory treatment of the chronic apical periodontitis in order to achieve a very high healing rate.

I would like to present my thanks and admiration to Professor Dr. Med. Maria Iancău who wisely and patiently guided my research and my work in the field, providing me with important advice and suggestions every time I needed them.

THE CURRENT STATE OF KNOWLEDGE

CHAPTER 1 presents the morphofunctional features of the apical area, providing general notions regarding the components of the periapex, as well as morphological data regarding the endodontic system; this information has a great impact upon the endodntic therapy and its long-term effects. ***(Vertucci FJ., 2005)***

CHAPTER 2 deals with etiopathogenic and histopathological aspects of the chronic apical periodontitis. The bacteria are the most important microorganisms involved in the etiology of this affection. In a lower percentage, there are yeats (candida albicans), as well as archaea and certain types of viruses. **(*Vianna ME, 2006, Rocas I. N., Siqueira J. F. Jr, 2008)***

CHAPTER 3 provides notions regarding the reparatory process in the cases of chronic lesions of the apical periodontal tissue. According to Nair PNR, 2008, the removal of the irritation factors, as well as the irritations, through the root canal preparation and its adequate obturation, allows the regression of the inflamation area. Accordind to the

width of the affected tissue, the healing process varies from a mere reduction and resolution of the inflamation to a more complex regeneration involving the process of bone remodelling, as well as the remodelling of periodontal ligament and of the cement ***(Gusiyska A, Dyulgerova E., 2009)*.**

CHAPTER 4 presents modern concepts regarding the chemomechanical root canal treatment in the cases of chronic apical periodontitis. Obeying the principles of root canal preparation and irrigation, during the development of the endodontic treatment, leads to the removal of every organic residue and microorganisms present in the endocanalicular system, thus shaping eventually a "clean" endodontic area, ready to undergo the obturation process.

PERSONAL CONTRIBUTION

CHAPTERS 5 and 6 describe the **AIM** and the **OBJECTIVES OF THE RESEARCH**, as well as the **STUDY LOT** and the **WORKING METHODS**.

I decided to choose this topic in order to emphasize the effect held by a conservatory endodontic therapy performed by obeying all the working principles and techniques upon the healing process of the chronic apical lesions and, eventually, upon the preserving of the viability of these teeth on the dental arcade.

The aim of this study, deriving from the high level of variety of the etiopathogenic factors involved in the process of the emergence of the chronic apical periodontitis, is to underline the healing mechanisms of the chronic lesions of the apical periodontal tissue, through the means of the orthograde conservatory endodntic treatment.

During the pursue of the aim of this study, the following **objectives** will be achieved:

1. performing the orthograde conservatory endodontic treatment;

2. setting a precise therapeutical protocol for performing the conservatory treatment which should determine the healing of the periapical lesions;

3. the clinical monitoring of the patients who underwent the endodontic treatment;

4. the radiological monitoring of the patients who underwent the endodontic treatment;

5. completing radiologic interpretations and comparisons during the conservatory treatment, in order to establish up to which degree the apical periodontal tissue was affected and then healed;

6. taking biologic material (apical granulomas) in order to perform the histological and immunohistochemical examinations for the corelation of the clinical symptoms and radiological signs with the periradicular tissue changes generated by the pulp infections or by the endodontic therapeutical work.

7. emphasizing through the means of imunohistochemical studies the matriceal metalloproteinases 2 and 8 which are involved in the bone resorption and remodelling (their presence being responsible for the healing of the periapical lesions), as well as the profibrilogenetic factors TIMP 1,TIMP 2 and TGFβ1; their level cand be considered a factor of prognosis for the healing of the granulomatose lesion.

The accomplishment of the aforementioned objectives is based on employing the following **studies**:

1. The study regarding the clinical and radiologic evaluation of the selected cases will pursue the healing condition of the periapical lesions, considering the principles of the mechanical root treatment.

2. The study regarding the clinical-statistical evaluation of the selected cases will follow processing of the data from the clinic monitoring files and through the patients' direct anamnesis. The aim of this study is a descriptive analysis of the patients included in the research, from the perspective of certain pre, intra and post operative factors, which can influence at some moment the healing of the apical lesions, as well as a corelation of the new data with that from the literature, and to determine the existence of some differences statistically meaningful, regarding the rate of periapical healing processes.

3. The study regarding the morphological evaluation of the selected cases will analyze various macro- and microscopic aspects of the granulomas.

4. The study regarding the histopathological and immunohistochemical evaluation of the chronic apical lesions; its main aim is to evaluate the inter-relations between the cells and the cellular matrix, as well as between the cells with epithelial origin, mezenchimal cells and pro-inflammatory cells identified in the structure of the chronic periapical inflammations, as related to particular histological aspects. It should be mentioned here that we developed the research and the aforementioned studies obeying the priciples of the research ethics.

The study lot included in the research consists of 128 patients with 153 chronic apical lesions. The patients were recruited from the Endodontics Clinic of the Dentistry Faculty of the U.M.F. Craiova, as well as from the medical practice center in Craiova.

We performed an analysis of the 128 patients with chronic apical periodontitis lesions taking into consideration many prognosis factors, pre-, intra- and post-operatory.

Working methods

The patients underwent a **clinical examination** doubled by classical determinations by classical investigations (**radiological examination**) and with modern determinations (**tomograph computer with conical fascicle**), followed by **the treatment** and **the clinico-radiological monitoring** of the temporal evolution of the target parameters. All the data obtained was processed using Microsoft Excel tables and worksheets and underwent a study of **statistical analysis.**

In the cases of failure, ended with extraction or apical resection, biological material was prelevated, namely apical granulomas, which underwent a **morphological analysis** and then were included in paraphine for the **histological and immunohistochemical exam**.

CHAPTER 7 presents **THE RESULTS** of the studies performed.

Following the ***statistical analysis*** of the data taken from the observation forms, we noticed that the results of the study performed prove the efficiency of the endodontic conservatory treatments in the cases of chronic periapical lesions, both the periapical granuloma type and the diffuse periapical osteitis.

Therefore, the periapical index score (PAI) decreased during the monitoring intervals, from an intitial average of 4.07 to 3.43 after three months, 3.14 after six months, 2.72 after twelve months and 2.19 after 24 months. There is a very significant difference regarding the PAI index score distribution, between its initial value and the one after 3 months (p Chi square 7.98×10^{-8}); and for the following months this difference turns out to be even more significant. (Table 1)

Using the Kruskall-Wallis test to draw a comparison between the initial values of the PAI index scores and the ones found during the evolution, after 3, 6, 12 and 24 months, we found that, therefore there is a very significant difference between the initial values and those obtained during the evolution (table 1).

Table 1: The significance level of the statistic tests for PAI Index Score

PAI score	Average	Dev.std.	C.V. (%)
Initial	4,07	0,78	19,28%
3 months	3,43	1,17	34,22%
6 months	3,14	1,17	37,11%
12 months	2,72	1,22	44,94%
24 months	2,19	1,14	52,06%
p K-W	7.33×10^{-46}		HS

The results regarding the influence of the dental group (frontal, premolar, molar) upon the periapical healing rate showed a higher percent of lesion healing in the case of molars (40.54%) than in the cases of other dental groups, and more at the level of the maxillar arcade (58.56%) than the mandibular one (41.44%).

The results focusing on the influence of the patients' age upon the periapical healing rate (18-34 years, 35-54 years, 55-70 years) showed a higher percent of lesion healing in the lowest age group, 18-34 years (45.95%); there is a statistically significant difference in the results of the treatment, regarding the patients' age group (p Chi square 0.00165).

As the academic paper proceeds, it presents several ***clinical cases*** which are significant for the chosen topic.

Following the radiological diagnosis and the ***routine histological examination*** (morphological examination), twelve cases received the diagnosis of chronic apical periodontitis (apical granulomas) and six cases received the diagnosis of radicular cysts.

Most of the lesions which received the clinical and radiological diagnosis of apical granulomas displayed, during the routine histological examination, the aspect of round-oval lesions, well defined. When these were extracted, together with the root of the tooth, they seemed to be attached to the root.

In the area adjacent to the granuloma we frequently remarked the resorption of the tooth radicular tissue and the apparition of certain resorptive defects at the cement level.

The genuine histological aspects of the lesions which received the diagnosis of apical granulomas were characterized by the simultaneous and constant presence of two tissue types: fiber conective tissue and granulation tissue. The structure of the inflammatory tissue varied according to the age of the lesion; the most acute ones, in

the exudative state, displayed an intense inflammatory infiltration, placed in a central position, surrounded by a peripheral fiber area.

The immunohistochemical reactions showed different markings for fibroblasts, according to the state of the evolution of the granulomatous lesion and to the lesion area which underwent the study.

CHAPTER 8 presents the **DISCUSSIONS** regarding the results of the research by analyzing and comparing the data achieved with the data from the literature. The studies regarding the periapical status and the quality of the endodontic treatments reveal that the chronic apical periodontitis is the most wide-spread dental affection among the grown-up population ***(Kabak and Abbot 2005, Scudutyte-Rysstad and Eriksen 2006, Sunay et al . 2007, Ng YL et al . 2011, Pak J et al . 2012)***. The patients included in the study do not represent a randomized batch of the Romanian population, but the supply information needed regarding the dento-periodontal health status, the quality of the endodontic treatments, as well as the need to complete certain endodontic treatments.

The chronic apical periodontitis lesions had a prevalence of 68%. We consider this level to be high, although it is included in the margin which resulted from the studies performed in various other countries ***(Kabak and Abbot, 2005, Sunay et al . 2007, Ozbas et al . 2011, Al Omari et al , 2011)***.

In this study, most of the chronic apical periodontitis lesions healed in less than two years. It was only 2% of the lesions that needed an amount of time of three up to four years of clinical and radiological surveillance.

The therapeutic protocol employed in this study is based on multiple strategies directed towards removing from the root canals as many bacterial populations as possible. We employed strategies which have already been used in well-known clinical studies ***(Siqueira JF Jr. et al., 2008)***, in order to be able to compare the data obtained with that from the specialized literature. These are: wide apical preparations (widening considerably the apical constriction) ***(Card SJ et al . 2002)***, sodium hypochlorite 2.5% irrigations ***(Siqueira JF Jr, Rôças IN, 2000)*** and using, between the treatment sessions, a medicamentous treatment with calcium hydroxide for at least 10 days ***(Siqueira JF Jr. et al . 2007)***.

The studies prove that, when an apical lesion is radiologically detected, it corresponds histologcally to a medium or severe inflammation, and when the periapical

area receives a radiologic intact diagnosis, there are only 55% cases when there are no histologic inflammations ***(Ricucci and Bergenholtz, 2004, Ricucci et al., 2006)***.

The pathogenesis of the apical lesions and their histological aspects represented the main focus of plenty of specialized studies ***(Nair, 2004, 2006, 2008***, ***Garcia et al., 2007***, ***Graunaite et al., 2011***). The histological study is a protocol following the clinical diagnosis and the radiological exam, which is very useful for both evaluating the degree and nature of the periradicular alterations and distinguishing between periodontitis and certain non-endodontic origin lesions ***(Garcia et al.,2007)***.

Most of the authors agree with the fact that the chronic periapical lesions cannot auto-heal naturally ***(Nair, 2004, Kiss, 2004, Graunaite et al., 2011)***. Therefore, the only treatment option is either to remove the infection through draining the germs from the root canal, or to clean the lesion through surgically removing the granuloma, in the case of the failure of the endodontic treatment.

In time, but not in space, the peri-radicular tissues undergo necrotic, exudative, granulomatous and fibrous aspects. It is under these forms that they can be found in the bone tissue around the root of the affected tooth. At the level of the bone tissue surrounding the root, these tissues advance centrifugally from the apical foramen, thus the average histological aspect of a granulomatous lesion is similar to an onion bulb (***Kiss, 2004)***.

In our study, we aimed to focus on a different component of the granulomas, the one represented by the autochthonous cells of the periapical tissues, namely the cells of a mesenchymal origin which constitute various fibroblast population residents in the periodontal ligament, but which are functionally involved in the turnover of the cement or of the alveolar bone.

At the same time, through mentioning the antibodies used, we also touched upon the problematic related to intercellular interactions between the resident cells of a mesenchymal and epithelial origin, and the pro-inflammatory mobile cells.

Lesion healing can occur through repairing or regeneration. The final aim of healing the lesion is to re-establish both the initial architecture and the biological function of the affected tissue. Irreversible pulpitis or apical periodontitis always heal through repairing of through a combination between repairing and regeneration ***(Lin LM, Rosenberg PA, 2011)***.

CHAPTER 9 displays the **CONCLUSIONS** of the present work, and we consider that the most important are:

1. The longitudinal study was developed on a batch of 128 patients with chronic apical periodontitis lesions. The patients underwent conservatory orthograde treatment which led to a tooth survival rate of 72.5% on the arcade.
2. It was noticed that the PAI index score decreased during the monitoring intervals, from an initial average of 4.07 to values of 3.43 after three months, 3.14 at six months, 2.72 at 12 months and 2.19 at 24 months. There is a highly significant difference regarding the distribution of the values of the PAI index score, between the initial value and the one measured after 3 months (p Chi square 7.98×10^{-8}), and then, for the following months, this difference becomes even more substantial.
3. It was emphasized that there is a highly significant difference between the initial values of the PAI index score and the values determined during the evolution, after 3, 6, 12 and 24 months, through the means of the Kruskall-Wallis test ($p=7.33 \times 10^{-46}$< 0,001).
4. The results regarding the influence of the dental group (frontal, premolar, molar) upon the periapical healing rate revealed a higher percent of the healed lesions at the level of the molars (40.54%), than of the other dental groups, and more frequent at the level of the maxillar arcade (58.56%), than of the mandibular one (41.44%).
5. The results regarding the influence of the age group upon the periapical healing rate (18-34 years, 35-54 years, 55-70 years) revealed a higher percent of healed lesions in the lowest age group, 18-34 years (45.95%). There is a statistically significant difference regarding the efficiency of the treatment, based upon the age group of the patients (p Chi square 0.00165).
6. The results of the histological study showed that the conective periradicular tissue of the periodontal ligament undergoes both in time and in space histological aspects which are exudative, necrotic, granulomatous and fibrous, and which are constantly accompanied by resorption of the radicular mineralized tissues (cement and alveolar bone).
7. We noticed that in the process of developing of the granulomatous lesions, there is a permanent dialogue between the migrated pro-inflammatory cells and the autochthonous cells, in the sense that the changes of the pro-inflammatory cytokines leads to changes in the phenotype and therefore in the activity of the fibroblasts, which further leads to changes at the level of the extracellular matrix.
8. Our results proved that the miofibroblasts are the main fibrilo-secretant cells which reside in the periodontal ligament of the granulomatous lesions, which also play a

part in the degrading of the extracellular matrix, through the synthesis and release of the matrix proteolytic enzyme, metalloproteinase (MMP), as well as inhibitors of these (TIMP).

9. The pro-fibrilogenetic factors TIMP 2 and TGFβ1 can become a possible therapeutic target in the conservatory treatment of the apical granulomas.
10. Our study underlines mainly the advantages of the orthograde endodontic treatment, as compared to the surgical one (retrograde). The advantages are determined by the removal, as complete as possible, of the endodontic bacterial biofilm, followed by the airtight obturation of the root canal. These aspects are confirmed by the evolutive histopathological and radiological monitorization, and they are also signaled by the differences regarding the age and location of the healing process. All the aspect mentioned build the original character of the present research work, as well as its importance for the medical praxis.

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