Clinical Outcomes of Full-Mouth Scaling and Root Planing with Locally delivered Minocycline in Treatment of Chronic Periodontitis

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A Dissertation Thesis

Submitted to the Department of Dental Science

and the Graduate School of Yonsei University

in partial fulfillment of the

requirements for the degree of

Master of Dental Science

Se-Jin Park

June 2010

This certifies that the dissertation thesis

of Se-Jin Park is approved.

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June 2010

감사의 글

이 논문의 연구계획에서 완성에 이르기까지 부족한 저를 열정적으로 지도해 주시고 격려해 주신 김창성 교수님께 진심으로 깊은 감사를 드립니다. 그리고, 세심한 조언을 베풀어주시고 따뜻한 관심을 보여 주신 김종관 교수님, 채중규 교수님, 조규성 교수님, 최성호 교수님, 정의원 교수님께도 감사 드립니다.

연구를 진행하는 내내 많은 조언과 아낌없는 도움을 주신 김영택 선생님께도 감사 드리며, 부족한 점을 채워주고 도와준 윤재민, 정동열 선생님께도 감사의 마음을 전합니다.

그리고, 언제나 저에게 든든한 버팀목이 되어주시고 사랑과 관심을 아끼 않았던 아버지, 어머니와 동생에게 고마움과 사랑의 마음을 전합니다.

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2010년 6월
저자 씀

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ABSTRACT

Clinical Outcomes of Full-Mouth Scaling and Root Planing with Locally delivered Minocycline in Treatment of Chronic Periodontitis

The purpose of this study was to evaluate the clinical effect of locally delivered minocycline in combination with full-mouth scaling and root planing for the treatment of moderate or advanced periodontitis.

A total of 40 patients with moderate or severe chronic periodontitis were enrolled to participate in this trial. Plaque index (PI), probing depth (PPD), clinical attachment level (CAL) and bleeding on probing (BOP) were measured at baseline and 4 and 12 weeks after treatment protocol. The test groups had full-mouth scaling and root planing at baseline with the subgingival administration of minocycline ointment, whereas the control group had one-stage scaling and root planing only.

PI decreased from the baseline to weeks 4 and 12 after treatment in both groups, but there was no significant difference between the two groups. Both groups had clinical improvement, however, the test group showed greater statistically significant improvement in pocket reduction and attachment gain than the control group. Similarly,

both groups also showed significant decreases in BOP, and the BOP reductions at given healing period were statistically significant in the test group.

Minocycline used with full-mouth scaling and root planing resulted in statistically significant reduction of probing depth and BOP. Therefore, full-mouth scaling and root planing with locally delivered minocycline were able to achieve satisfactory results in treatment of moderate or advanced periodontitis in a short-term basis.

Key Words : Periodontal disease, Minocycline, Local anti-infective agents, Periodontal index

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I. Introduction

Periodontitis is an inflammation of the periodontal tissues featuring the loss of alveolar bone support and the attachment of periodontal ligament. The presence of periodontitis is correlated with the accumulation of a microbial biofilm of pathogenic micro-organisms such as A. actinomycetemcomitans, B. forsythus, P. gingivalis, and P. intermedia (Socransky 1994). The success of periodontal therapy depends on the reduction of

pathogenic micro-organisms present in the microbial biofilm (Haffajee 1997, Slots 1979; 1999). To eliminate the microbial biofilm, conventional scaling and root planing can be used (Cobb 1996; Petersilka et al. 2002). A number of studies demonstrated the effects of conventional scaling and root planing (Badersten et al. 1981; 1984; 1985; 1987; Loos et al. 1989; Hammerle et al. 1991). However, pathologic bacteria can move to areas that have already been treated from not yet treated sites (Hinrichs et al. 1985; Sbordone et al. 1990; Johnson et al. 2008). These pathogens can cause a re-infection of the periodontal pocket after treatment (Quirynen et al. 2001). Quirynen (1995) introduced the 'one-stage full-mouth disinfection' to minimize the risk of subgingival bacterial biofilm recolonization. In the 'one-stage full-mouth disinfection' protocol, scaling and root planing are performed within 24 hours, with the use of chlorhexidine. Several long-term studies were reported that 'one-stage full-mouth disinfection' had improved clinical results, with minimal systemic side-effects than conventional scaling and root planing in treatment of chronic peridontitis (Bollen et al. 1996; Vandekerckhove et al. 1996).

In the 'one-stage full-mouth disinfection' protocol, chlorhexidine is used as the choice of antiseptic. However, its local side effects including ulceration, sores on mucosa, unpleasant taste, and discoloration were reported. In addition, full-mouth scaling and root planing without using chlorhexidine had same clinical benefits compared to the full-mouth disinfection (Quirynen et al. 2000)

For the elimination of pathogenic microbiota, the use of antibiotics was introduced and studied (Listgarten et al. 1978; Lindhe et al. 1983; Garrett et al. 1999; van Steenberghe et al. 1999; Ramberg et al. 2001; Wennstrom et al. 2001; Aimetti et al. 2004). Antibiotics can be administered systemically or locally, and help improve the effect of mechanical periodontal treatment (Haffajee et al. 2003). For example, amoxicillin and metronidazole in conjunction with full-mouth scaling and root planing served to improve the clinical status compared to full-mouth scaling and root planing only (Cionca et al. 2009). Gomi (2007) examined the effect of orally administered azithromycin with full mouth scaling and root planing. Improved clinical parameters were reported with the use of azithromycin than with conventional scaling and root planing.

Minocycline is a broad spectrum antibiotic, and is effective against a broad spectrum of Gram-negative and Gram-positive anaerobes including periodontal pathogenic bacteria (Drisko and Lewis 1996). Williams (2001) reported that the administration of minocycline microsphere in combination with scaling and root planing had a more advantageous clinical outcome than scaling and root planing alone. Hellström (2008) studied the effect of minocycline microspheres in the treatment of moderate to advanced periodontitis in combination with periodontal surgery. They found the use of locally delievered minocycline as an adjunct to surgery had more probing depth reduction. However, the effect of local administration of minocycline in combination with full-mouth scaling and root planing has not yet been evaluated.

The aim of the study was to evaluate the clinical effect of locally delievered minocycline in combination with full-mouth scaling and root planing for the treatment of moderate or advanced periodontitis.

II. Material and methods

1. Patient Selection

A total of 40 adult patients between the ages of 24 and 74 years with moderate or severe chronic periodontitis were selected in Department of Periodontology, College of Dentistry, Yonsei University, Seoul, Korea. The study was reviewed and approved by the The Medical Ethics Committee of the Yonsei University College of Dentistry. Written informed consent was obtained from all the subjects to be entered in the study.

The subjects were selected based on the following inclusion and exclusion criteria (Hellström et al. 2008). The patients who had at least 18 teeth and six of more teeth with a periodontal pocket depth of >4mm with bleeding on probing and radiologic evidence of alveolar bone loss were included in the study (Armitage 1999). The exclusion criteria were as follows: (1) pregnant or breast-feeding women, (2) systemic illness(i.e., diabetes mellitus, immunological disease), (3) periodontal treatment within 12 months of the baseline visit, (4) use of systemic antibiotics in the previous 6 months, (5) use of medicine that affect periodontal status within past 3 month, (6)allergies to tetracycline

2. Study Design & Treatment Protocol

The study's design is summarized in figure 1. At the first visit, clinical parameters were recorded in both groups. The control group received full-mouth scaling and root planing (SRP) within 24 h with an ultrasonic scaler and periodontal curette under local anesthesia. If needed, flap repositioning and suturing were performed. The study group received the same treatment with subgingival administration of minocycline (Periocline® ; Sunstar Inc., Osaka. Japan). Additional mechanical instrumentation was performed at 4 and 12 weeks after initial treatment and adjunctive minocycline were re-administered in the test group to maintain the effect of minocycline.

3. Clinical Assessment method

The clinical assessment was carries at baseline and 4 and 12 weeks after treatment, and the following clinical parameters were recorded. Plaque index (PI, Loe et al. 1964) was recorded from 0 to 3. The periodontal probing depth (PPD, Magnusson et al. 1980; Listgarten et al. 1980) was recorded to the nearest 1mm using Color-coded probes (CP-15UNC, Hu-Friedy). The amount of gingival recession (REC) was measured the distance from the cement-enamel junction to the gingival margin or margin of restoration. The bleeding on probing (BOP, Meitner et al 1979; Armitage et al. 1996) was evaluated 10 seconds after probing the pocket. The clinical attachment level (CAL) was calculated in

the sum of PPD and REC. The additional clinical data of periodontal sites with a PPD<4mm were recorded. The clinical attachment level (CAL) was calculated in the sum of PPD and REC. All parameters were measured at six sites per tooth (mesial, middle and distal; bucally and lingually)

4. Statistical analysis

The clinical parameters (PI, BOP, PPD, and CAL) were calculated to obtain a mean score and standard deviation (SD). Separately, clinical parameters of the baseline PPD>4 mm were measured and calculated. Differences between test and control group at given healing periods were measured using an unpaired t-test. To analyze the change of clinical parameters from the baseline to week 12, the data were analyzed using Analysis of covariance (ANCOVA) and post-hoct test. A p-value of less than 0.05 was considered statistically significant.

III. Results

1. Baseline Assessment

A total of 40 patients were participated the study initially. The test group had three premature terminations due to lack of compliance. Consequently, 37 patients completed the final assessment. Table 1 shows the clinical data at baseline. No significant differences were found between the test and control group. Table 2 and Figure 2 show the changes in periodontal clinical parameters over time at baseline and at 4 and 12 weeks after treatment. Table 3 and Figure 3 show the clinical outcome (PPD, CAL) at baseline and at 4 and 12 weeks after treatment with deep pockets (>4mm).

2. Plaque index (PI)

At baseline, no stastically significant differences were detected. After treatment, the PI reduced significantly in both groups, indicating that patients had an improved oral hygiene state. There were no significant differences between the test and control group ($p>0.05$).

3. Bleeding on probing (BOP)

The BOP reduced significantly after treatment in both groups. In the control group, the BOP at first visit was 50.18±14.38 %. It changed to 37.83±18.38 % and 33.80±17.26 % at 4 and 12 weeks after full-mouth SRP, respectively. In the test group, the BOP at baseline was 53.87±22.96 %, and at 4 and 12 weeks after treatment, it was 28.02±19.66 % and 22.34±15.96 %, respectively. ANCOVA test revealed that the reduction of the test group showed stastically significant than the control group during the given healing intervention ($p<0.05$).

In the deep pockets (>4 mm), ANCOVA test showed stastically significant BOP reduction in the test group than the control group. At baseline the BOP was 63.07±18.81% in the test group and 65.16±18.45% in the control group, respectively. After treatment, the test group was 39.11±26.46% at the 4 weeks and 31.52±20.50% at 12 weeks. The control group was 47.15±23.68% at 4 weeks and 41.33±19.17% at 12 weeks. The difference between the test and the control group showed statistically significant differences compared to control group at 12 weeks.

4. Periodontal pocket depth (PPD)

Before treatment, there was no significant difference between the test and the control group. However, after initial treatment, the PPD was significantly decreased. In the test

group, the PPD at baseline was 3.86±0.83 mm. At 4 and 12 weeks of follow-up, the PPD was reduced to 3.22±0.64 mm and 3.04±0.55 mm, respectively. In the control group, these values were 3.80±0.48 mm at baseline, and 3.44±0.37 mm and 3.38±0.32 mm at 4 and 12 weeks, respectively. There was no statistically significant difference at 4 weeks. However at 12 weeks, statistically significant difference was found between two groups. During the given healing period, the test group had additional PPD reduction when compared to the control group ($p<0.05$).

In deep pockets (>4 mm), the PPD on the test group was 5.24±0.96 mm at baseline and reduced to 4.01±1.03 mm and 3.70±0.96 mm at 4 and 12 weeks. The control group showed 4.91±0.42 mm at baseline and 4.10±0.49 mm and 3.94±0.47 mm at 4 and 12 weeks. There was a statistically significant PPD reduction in the test group compared to the control group in ANCOVA test ($p<0.05$).

5. Clinical attachment level

Significant CAL gain was observed between baseline and 4 weeks after treatment ($p<0.05$), however there was no additional gain at 12 weeks. The CAL at baseline was 4.25±0.81 mm on the test group and 4.26±0.69 mm on the control group. The changes in CAL after the experiment were: 3.69±0.60 mm and 3.48±0.56 mm for 4 weeks and 12 weeks in the test group and 3.97±0.80 mm, and 3.92±0.76 mm for 4 weeks and 12 weeks

in the control group, respectively. When we drew comparison between the test and control group, there was statistically significant difference at 4 and 12 weeks. By ANCOVA test, the test group presented more CAL gains than the control group ($p<0.05$).

In pockets with probing depths of 4 mm or more, the difference between the two groups was apparent. The CAL on the test group was 5.66±0.93 mm at baseline, which reduced to 4.70±0.93 mm and 4.28±0.94 mm at 4 weeks and 12 weeks, respectively. In the control group, the CAL was 5.39±0.62 mm at baseline and 4.68±0.86 mm and 4.53±0.82 mm at 4 and 12 weeks. The results illustrated that more CAL gain was shown on the test group than the control group ($p<0.05$).

IV. Discussion

The purpose of this study was to examine the effects of locally delievered minocycline accompanied by one-stage full mouth SRP in 3 months of follow-up.

In the present study, the test group showed improved CAL gain and fewer sites with BOP than the control group after 12 weeks of treatment. On the other hand, the differences of PI between the experimental and the control groups were not found. This meant that the use of minocycline did not affect the oral hygiene of patients, whereas it played a significant role in the reduction of BOP. To determine the prognosis of periodontal treatment, the reduction of BOP was known to be a important factor (Lang et al. 1990). Therefore, this result suggested that the application of minocycline had the ability to enhance the clinical outcome of one-stage full mouth SRP.

Fujise and co-workers studied the influence the treatment outcome of pathogenic bacteria. SRP reduced the levels of P. gingivalis and B. forsythus. However, poorly healed sites with BOP and suppuration had high level of P. gingivalis (Fujise et al. 2002). It might be concluded that the reduction of BOP refered to the reduction of bacterial infection. Therefore, re-infection might be reduced by the local use of minocycline. These improvements seemed to appear after 1 month of treatment and additional improvements were shown at 3 months after treatment. In particular, the experimental group had additional BOP reduction between 1 and 3 months after treatment. The effects of minocycline in periodic check-up showed similar results compared to our study. Our

study was based on a relatively short follow-up period, however it was known that healing after treatment of period is complete after 3 month following therapy (Badersten et al. 1987)

In the treatment of deep pockets, incomplete treatment outcome might have occurred because of difficult accessibility. The use of the antibiotics combined with full-mouth scaling and root planing were studied as a means to compensate for incomplete mechanical debridement. Amoxicillin and metronidazole in conjunction with full-mouth SRP were examined (Cionca et al. 2009). The subjects treated with amoxicillin and metronidazole had more BOP reduction compared to the control group. Gomi (2007) studied the effect of systemically administarated azithromycin for patients receiving full mouth scaling and root planing. Before full-mouth scaling and root planing, instead of chlorhexidine, azithromycin was systemically administered to patients. The test group demonstrated more reduction of pocket depth and gain of clinical attachment. They concluded that the systemically administered azithromycin with full-mouth disinfection was an effective treatment for severe chronic periodontitis.

In the present study, minocycline was selected as the antimicrobial agent because it was effective against many organisms associated with chronic and aggressive periodontitis (Drisko et al. 1996). Also, it had stronger antibiotic effects on Gram-negative microorganisms and a broader spectrum of activity compared to other members of the

tetracycline group. It was maintained for a long period of time in the gingival sulcus, because it showed no chelation activity and inhibits the formation of plaque. Minocycline had a less chance of emergence of resistant strains compared to tetracycline. However, the amount needed to maintain the effective level in the gingival sulcus via systemic administration could develop resistance of certain bacterias. Local delivery system could minimize these side effects and at the same time maintain an adequate level in the gingival sulcus. Van Steenberghe (1993) studied the effects of local application of minocycline in treatment of chronic periodontitis. Subgingival minocycline application had more reduction of pathogenic bacteria, such as P. gingivalis, P. intermedia, and A. actinomycetemcomitans. Probing depth reduction was more prominent in the minocycline group, but gingival index and attachment gain were not statistically significant. Split-mouth clinical trial was performed to ensure the clinical effect of locally administered minocycline (Lu and Chei 2005). The experimental group showed significantly greater probing depth reduction and attachment gain, but bleeding on probing showed no difference between either groups. In our study, the subgingival administration of minocycline ointment led to a significant improvement in probing depth and bleeding on probing.

Hellström (2008) evaluated the effects of minocycline when used in combination with periodontal surgery in moderate to advanced periodontitis. The patients who received the periodontal surgery and minocycline showed more reduction in pocket depth at 13 weeks

after treatment. No significant differences in the mean percent of BOP reduction were observed at week 13, however greater mean BOP reduction was observed (66%) in the minocycline group than the control group (54%) at week 25. The number of sites with probing depth reduction was greater in the test group than the control group.

In addition, our study defined the periodontal pockets of 4mm or more as a deep pocket and compared the effect of minocycline. The deep pockets exhibited a better clinical outcome at the end of the study. In the treatment of deep periodontal pockets, full-mouth scaling and root planing seemed to have limited effect because of its poor accessability. The local delivery of antibiotics could overcome the poor accessability and achieve additional treatment effects.

V. CONCLUSION

In this study, minocycline used in conjunction with full-mouth scaling and root planing, resulted in a more statistically significant reduction of probing depth and BOP. Therefore, a one-stage full-mouth scaling and root planing featuring locally delivered minocycline was able to achieve satisfactory results on a short-term basis.

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Tables

Table 1. Baseline sample groups by treatment strategy

	Control group (n=20)	Test Group (n=17)	p value
Male/Female	8 / 12	3 / 14	
Age	48.4±8.14 (37 ~ 63)	45.9±14.6 (24 ~ 74)	0.52
PI	1.53±0.34	1.52±0.25	0.92
BOP (%)	50.18±14.38	53.87±22.96	0.56
PPD (mm)	3.80±0.48	3.86±0.83	0.77
REC (mm)	0.46±0.39	0.39±0.41	0.61
CAL (mm)	4.26±0.69	4.25±0.81	0.99

Table 2. Clinical Data (mean ± SD) at Different Time Points

		baseline	4W	12W
PI	Test	1.52±0.25	1.28±0.32*	1.11±0.41*
	Control	1.53±0.34	1.26±0.53*	1.08±0.49*
BOP	Test	53.87±22.96	28.02±19.66*†	22.34±15.96*†
	Control	50.18±14.38	37.83±18.38*	33.80±17.26*
PPD	Test	3.86±0.83	3.22±0.64*	3.04±0.55*†
	Control	3.80±0.48	3.44±0.37*	3.38±0.32*
CAL	Test	4.25±0.81	3.69±0.60*†	3.48±0.56*†
	Control	4.26±0.69	3.97±0.80*	3.92±0.76*

* Statistically significant difference compared to baseline (P <0.05)

† Statistically significant difference compared to Control group (P <0.05)

Table 3. Clinical Data (mean ± SD) of the deep pockets (≥4mm)

		baseline	4W	12W
PI	Test	1.71±0.14	1.43±0.25*	1.26±0.31*
	Control	1.80±0.43	1.39±0.55*	1.16±0.50*
BOP	Test	63.07±18.81	39.11±26.46*†	31.52±20.50*†
	Control	65.16±18.45	47.15±23.68*	41.33±19.17*
PPD	Test	5.24±0.96	4.01±1.03*	3.70±0.96*†
	Control	4.91±0.42	4.10±0.49*	3.94±0.47*
CAL	Test	5.66±0.93	4.70±0.93*†	4.28±0.94*†
	Control	5.39±0.62	4.68±0.86*	4.53±0.82*

* Statistically significant difference compared to baseline (P <0.05)

†Statistically significant difference compared to Control group (P <0.05)

Figures

Figure 1. The study design

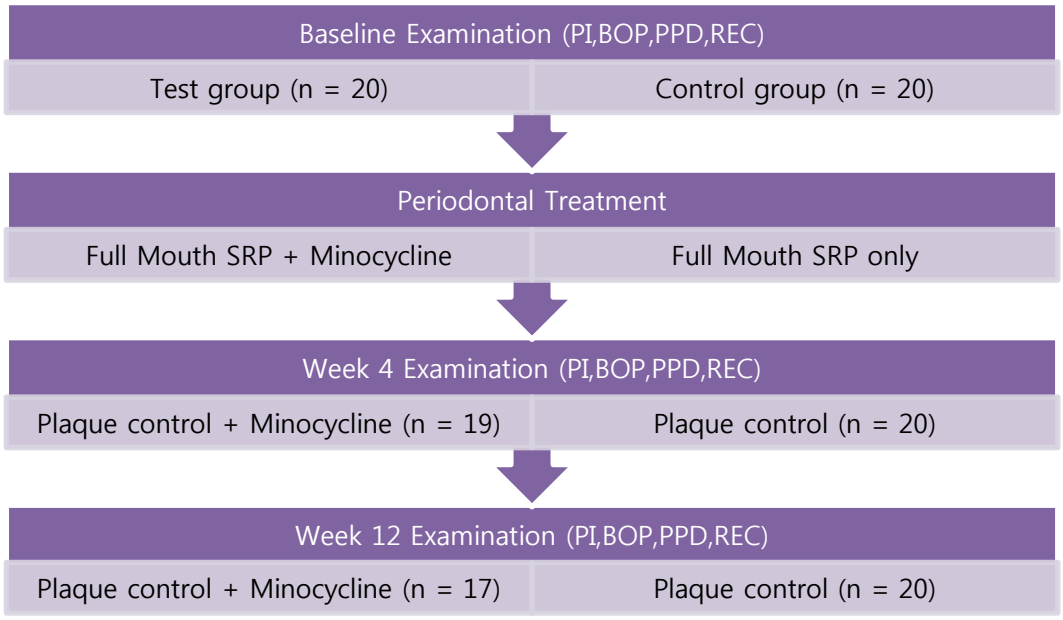
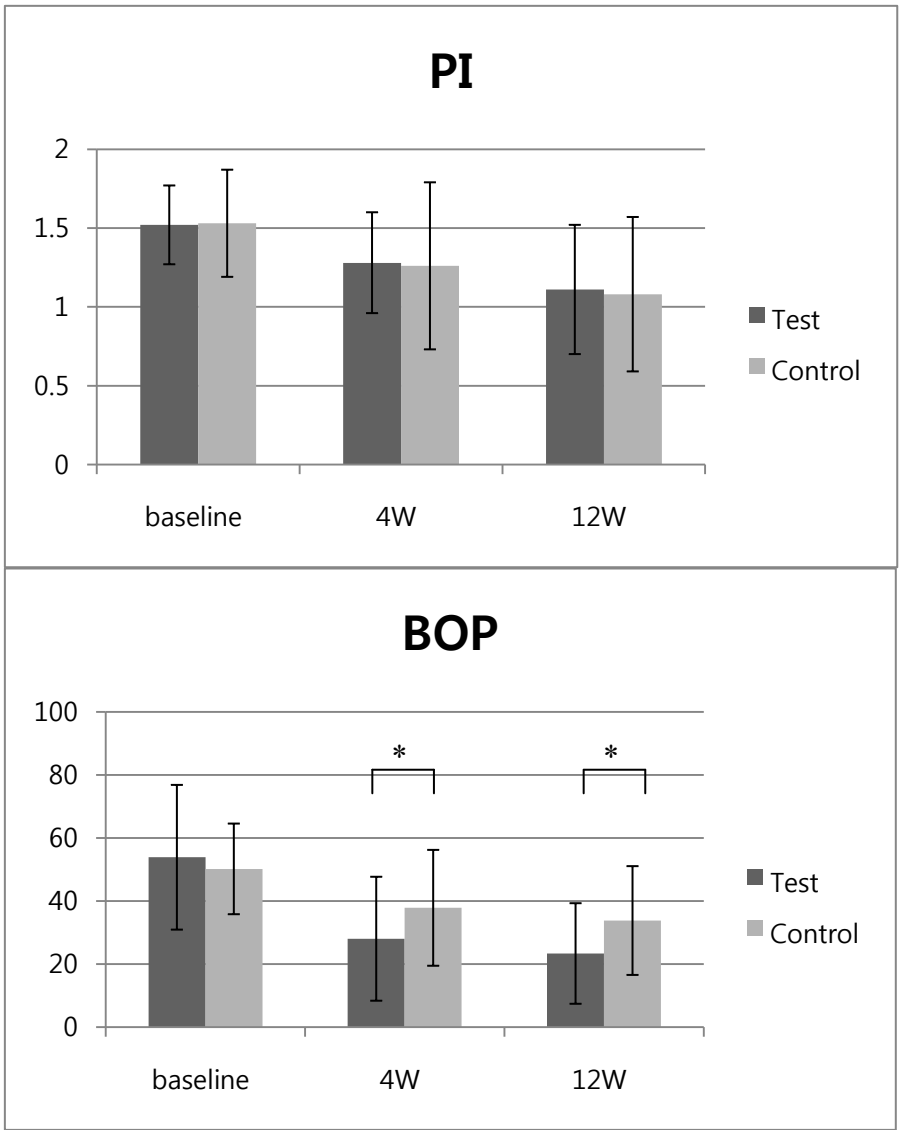
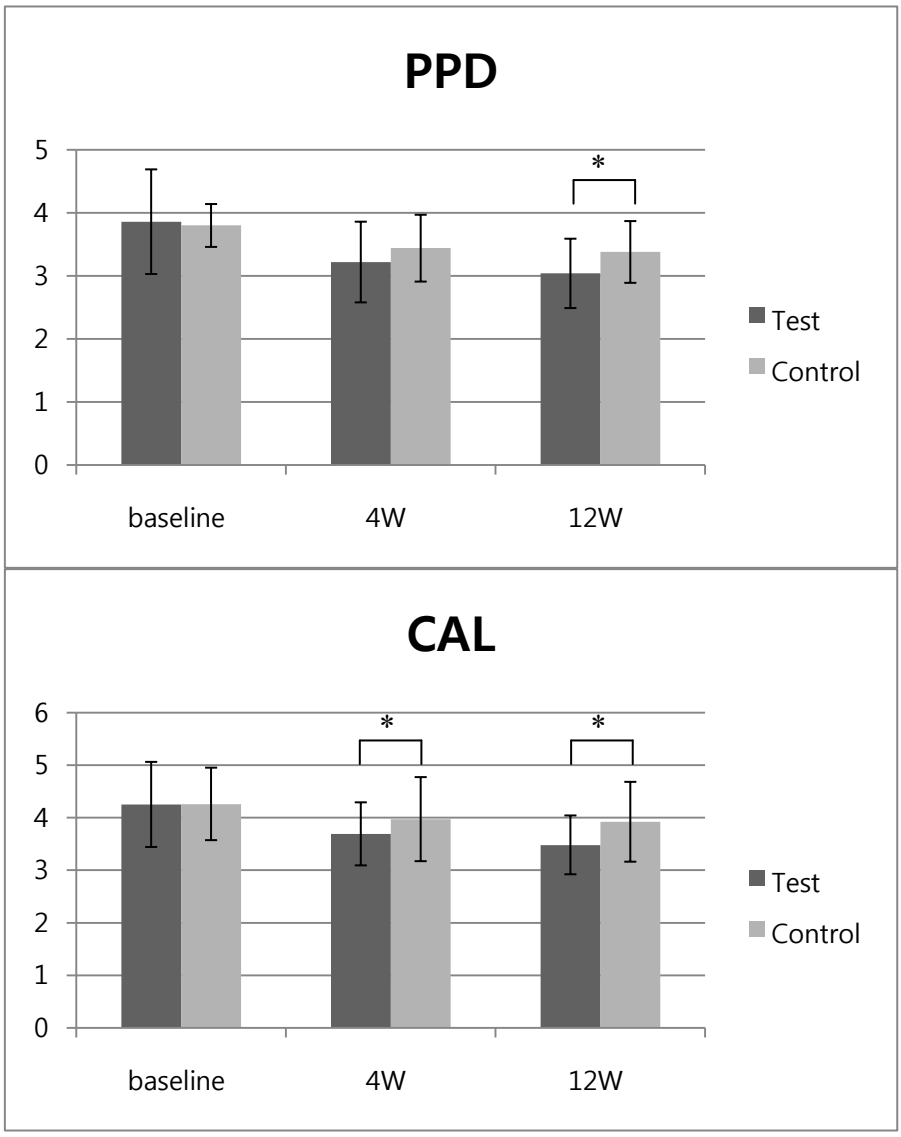


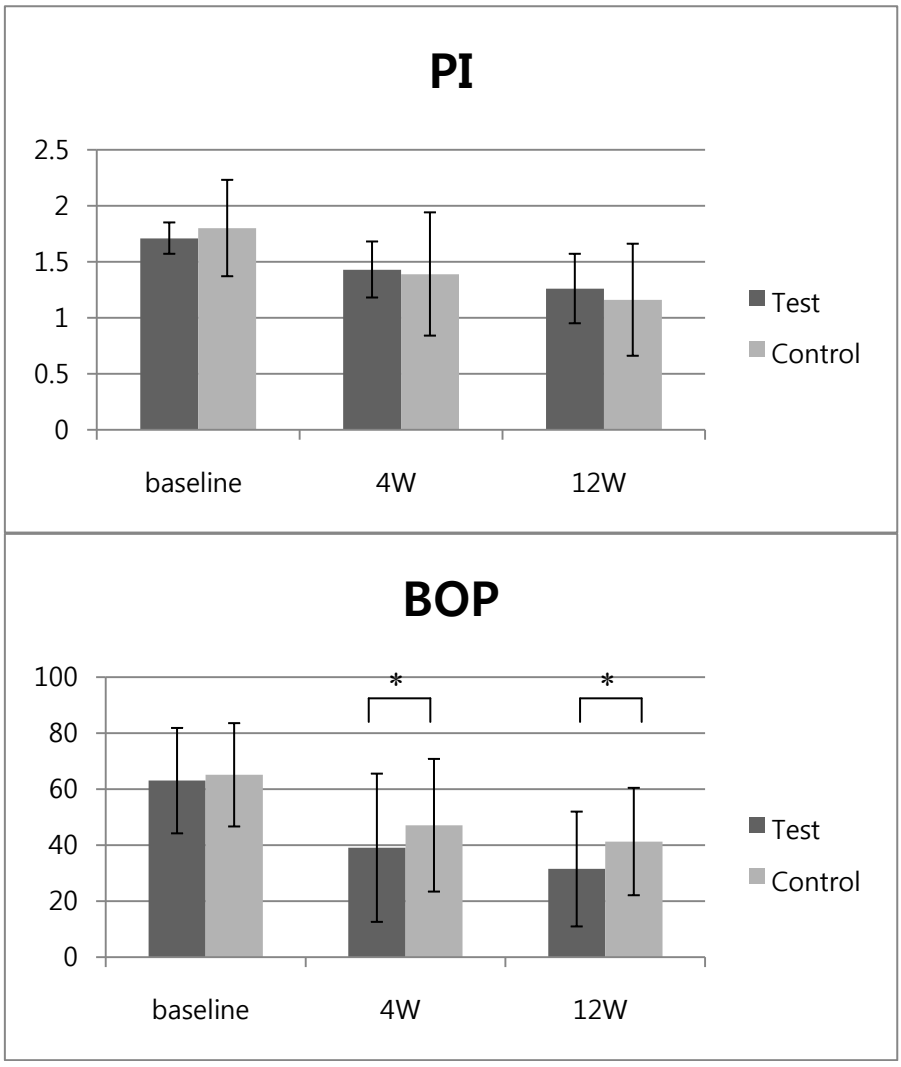
Figure 2. Changes in periodontal clinical parameters (PI, GI, PPD, CAL) over time at baseline and at 4 and 12 weeks after treatment sorted by treatment modality (control versus test).

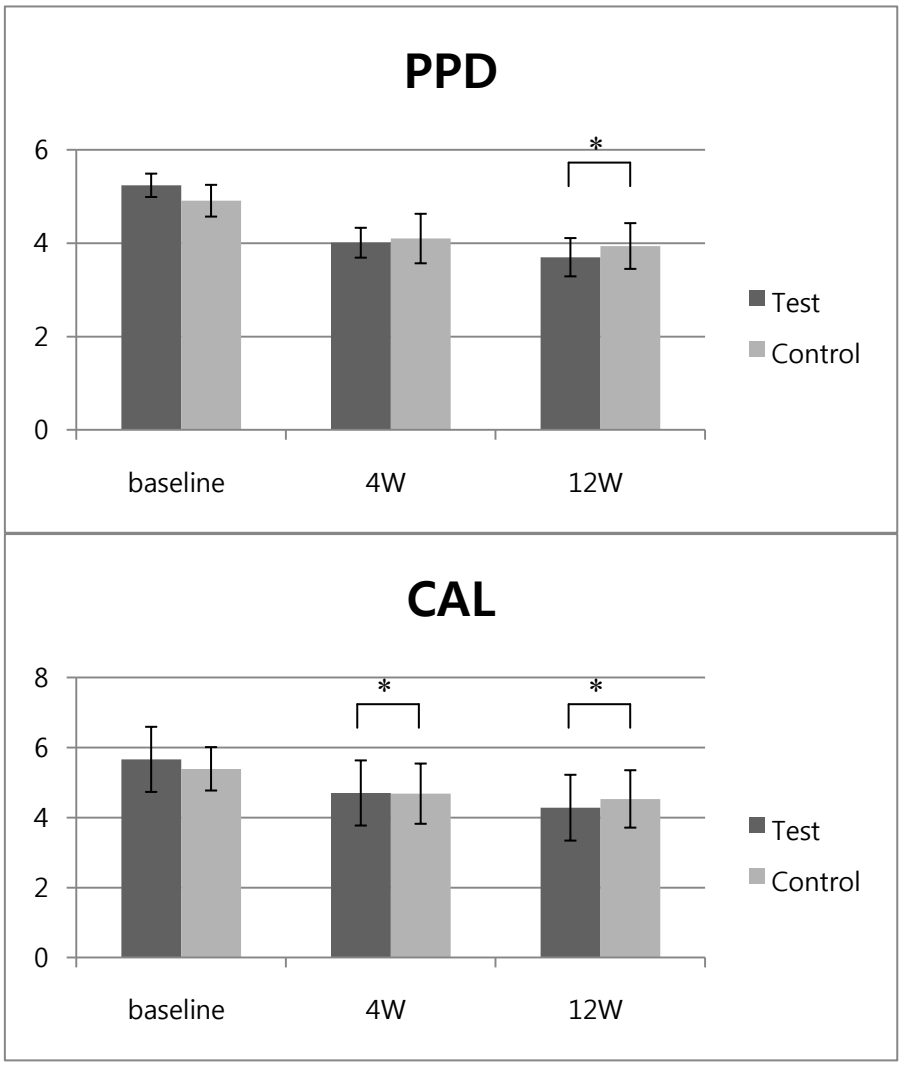




***** Statistically significant difference compared to Control group (P <0.05)

Figure 3. Changes in periodontal clinical parameters over time at baseline and at 4 and 12 weeks after the treatment sorted by treatment modality (PD ≥4mm)





***** Statistically significant difference compared to Control group (P <0.05)

국문요약

만성 치주염 환자에서 Full-Mouth Scaling and Root Planing 시 Minocycline 사용의 임상적 효과 연구

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본 연구에서는 중증도 이상의 치주염의 치료에서 Full-mouth scaling and root planing 과 동반되어 국소적으로 사용한 minocycline 의 효능을 평가하고자 한다. 40 명의 중증도 이상의 만성 치주염 환자를 대상으로 하였으며, plaque index, 치주낭 깊이, 부착 수준, 탐침시 출혈 정도를 실험 전, 4 주, 12 주에 측정하였다. 실험군은 full-mouth scaling and root planing 을 시행하고 minocycline 을 적용하였고, 대조군은 full-mouth scaling and root planing 만을 시행하였다. 실험 결과 plaque index 는 실험 전에 비해 4 주, 12 주째 많은 감소를 보였으나, 군간의 차이는 발견되지 않았다. 반면에 치주낭

깊이의 감소와 부착획득 수준은 두 군 모두 임상 개선이 있었지만 실험군에서 통계적으로 유의차 있는 개선을 보였다. 주어진 회복 기간동안의 탐침시 출혈 정도의 감소는 실험군에서 더 확연하게 나타났다. 이러한 차이는 4mm 이상의 깊은 치주낭에서 더 크게 나타났다.

full-mouth scaling and root planing 과 minocycline 을 병용할 경우 더 큰 probing depth 의 감소와 부착 획득을 보였다. 따라서 full-mouth scaling and root planing 과 minocycline 을 사용하면 단기적으로 만족할만한 결과를 얻을 수 있을 것이다.

Key Words : Periodontal disease, Minocycline, Local anti-infective agents, Periodontal index