Anti-infective effect of metronidazole combined with minocycline as local adjunct to nonsurgical therapy of peri-implantitis: A multi-center randomized controlled trial

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Anti-infective effect of metronidazole combined with minocycline as local adjunct to nonsurgical therapy of peri-implantitis: A multi-center randomized controlled trial

Directed by Professor Chang-Sung Kim

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감사의 글

치주과에 입사하여 처음으로 만났었던 임상연구가 긴 시간 끝에 어느덧 논문으로 탄생하게 되어 감회가 새롭습니다. 국가고시를 통해 어엿한 치과의사가 되었음에도 치주에 대해 아는 것이 전무하였던 제게 4 년간의 대학원 과정은 단순히 치주과학에 대해 배우는 시간이 아닌 하나의 치과의사로서 가져야 할 기본적인 소양과 탐구정신을 일깨워준 뜻깊은 시간이었습니다.

이 논문이 있기까지 많은 도움과 조언을 주신 이중석 교수님, 논문 지식이 턱없이 부족하여 생겼던 수많은 질문들에 대해 막힘없이 답해주셨던 차재국 교수님과 송영우 교수님께 깊은 감사를 드립니다. 또한 임상에 있어 항상 모범적인 모습을 보여주시고 연세대 치주과 전공의로 성장하게끔 도와주신 조규성 교수님, 정의원 교수님, 백정원 교수님께도 감사드립니다. 그리고 저를 많이 아껴주시고 지도해주시며 4 년간의 긴 시간동안 때로는 엄한 스승, 때로는 친근한 학부형이 되어 저를 이끌어주신 김창성 교수님께 항상 마음 속 깊이 감사드립니다. 교수님이 있어 치주학에 대해 이해할 수 있었고, 보람차고 행복한 수련생활이었습니다.

2021 년 12 월 16 일

박승현

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Abstract

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Purpose: The objective of the study was to assess the clinical and microbiological outcomes of administering metronidazole in combination with minocycline as a local adjunct to the non-surgical treatment of peri-implantitis.

Materials and methods: One hundred and eighteen subjects with peri-implantitis were recruited in a four-centre, three-arm, 12-week randomized controlled trial. Subjects were randomly assigned to receive one of the following treatments: a) MM - mechanical debridement + metronidazole-minocycline ointment, b) MC - mechanical debridement + minocycline ointment, c) NST - mechanical debridement only.

Results: The treatment success rates (absence of bleeding or suppuration on probing, and sites showing pocket probing depth [PPD] ≥5 mm) on at 12 weeks were higher

in MM group (31.6%) and MC group (20.5%) compared to NST group (2.7%) (p = 0.011 and 0.040, respectively). Subjects with deepest PPD ≥8 mm showed a significant difference in the PPD reduction between MM and MC groups at week 4 (p = 0.025) and week 12 (p = 0.047). Detection ratio of T. forsythia was significantly lower for MM group than MC group (p = 0.038).

Conclusions: Additive use of either MM or MC results in significantly higher treatment success rates compared to sole mechanical debridement in non-surgical treatment of peri-implantitis. Moreover, MM contributes to a significantly greater reduction in the PPD compared to MC in deep pockets.

Keywords: Peri-implantitis, non-surgical therapy, metronidazole, minocycline, multicentre randomized controlled trial

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I. INTRODUCTION

Peri-implantitis is a plaque-associated inflammatory process causing peri-implant alveolar bone loss in conjunction with a deep pocket probing depth (PPD), bleeding on probing (BoP) and suppuration on probing (SoP) [1, 2]. For the purpose of eliminating bacterial biofilms, implant surface decontamination is considered to be the main objective when treating peri-implantitis. Non-surgical debridement usually precedes surgical treatment, but the treatment result has been considered to be rather unpredictable [2]. A previous systemic review found that mechanical submucosal debridement alone could be insufficient for resolving inflammation due to the topology of the implant fixture threads [3], which has prompted clinicians to look into applying several adjunctive options for implant

decontamination.

Among various additional methods, the local administration of antimicrobials combined with non-surgical treatment was found to exert positive effects on clinical parameters related to peri-implantitis [4]. Recent studies have found the local delivery of minocycline microspheres combined with non-surgical mechanical debridement to be effective in peri-implantitis [5, 6]. Nonetheless, these previous studies involved incipient peri-implantitis lesions and showed incomplete treatment results, and so the treatment modality of combining local medication with mechanical debridement for more effective decontamination is yet to be fully assessed.

The combined systemic administration of metronidazole—which is known to be effective for eliminating obligate anaerobes—and amoxicillin has shown promising results in the treatment of aggressive periodontitis [7, 8]. Obligate anaerobes can be present in a peri-implant deep pocket [9, 10], and some previous studies have confirmed the efficacy of metronidazole in peri-implantitis patients. Liñares et al. (2019) reported that systemic metronidazole was effective in reducing PPD and the radiographic defect size [11]. Another prospective clinical study found that combining amoxicillin and metronidazole systemically along with mechanical treatment significantly reduced PPD, BoP and SoP [12]. However, these studies were based on the systemic administration of the drugs, and so studies of the effect of locally applied metronidazole combined with other types of antibiotics in the non-surgical treatment of peri-implantitis are still needed. A recent study reported beneficial outcomes with the treatment modality, and therefore the study was designed to find out the additive effect of metronidazole as local adjunct [13].

The aim of this randomized controlled trial (RCT) was to determine the clinical efficacy of the local administration of metronidazole combined with minocycline in non-surgical debridement for treating peri-implantitis, compared to performing non-surgical treatment or the local application of minocycline alone.

II. MATERIALS AND METHODS

1. Study design and population

This study was designed as a multicentre RCT (competitive enrollment in 4 centers) with an observational period of 12 weeks. The enrolled patients were recruited and treated at one of the following centres from October 2017 to October 2018: Department of Periodontology, Yonsei University Dental Hospital (Seoul, Republic of Korea); Department of Periodontology, Gangnam Severance Dental Hospital (Seoul, Republic of Korea); Department of Periodontology, National Health Insurance Service Ilsan Hospital (Goyang, Republic of Korea); and Department of Periodontology, Dankook University Dental Hospital (Cheonan, Republic of Korea).

All of the investigators in the study participated in a calibration meeting in order to standardize the measurements prior to the experiment. The study protocol was approved by the institutional review board of each participating centre: Yonsei University Dental Hospital (2-2017-0037), Gangnam Severance Dental Hospital (3-2017-0220), National Health Insurance Corporation Ilsan Hospital (NHIMC 2017-09-004) and Dankook University Dental Hospital (DKUDH IRB 2017-09-002). The research was conducted in accordance with the ethics principles of the World Medical Association Declaration of Helsinki [14]. The CONSORT flowchart of the study is presented in Figure 1 [15].

2. Sample size calculation

The minimum sample size required for this study was based on a previous clinical study comparing treatment efficacy following the local antibiotics delivery as an adjunct to mechanical debridement in peri-implantitis patients (Renvert et al., 2006) [16]. A minimum sample size of 108 patients was estimated for detecting a clinically relevant difference—a reduction in PPD of 0.3 mm—with a statistical power of 80% at a significance level of 5%. Considering a possible dropout rate of 10%, the total required sample size was determined

to be 122 patients.

3. Inclusion and exclusion criteria

Implants installed at least 1 year previously, with PPD ≥5 mm, BoP, SoP and the presence of peri-implant bone loss in a peri-apical radiograph were diagnosed as peri-implantitis [17]. Intraoral periapical radiographs taken at the screening was used to determine whether or not radiographic bone loss (RBL) was evident. The distance from the platform of the implant to the most-apical level of the radiographic bone-to-implant contact along the long axis of the implant was measured at the mesial and distal aspects. Patients with at least one implant diagnosed as peri-implantitis were included in the study. If multiple implants fulfilled the study criteria, all of these implants were treated equally, but only the one with the greatest severity was enrolled for the analysis.

The following exclusion criteria were applied: (1) subjects ongoing invasive dental treatments in the same sextant as the enrolled implant, (2) allergy to tetracyclines or metronidazoles, (3) uncontrolled medical conditions, (4) alcoholism, (5) smoking (≥10 cigarettes a day), (6) pregnant or lactating females, (7) taking antibiotics related to periodontitis during the previous 4 weeks, or (8) taking medications known to affect periodontal conditions (i.e. phenytoin, calcium-channel blocker, cyclosporin, coumarin, non-steroidal anti-inflammatory drugs or aspirin) during the previous 4 weeks.

After the subjects were screened, they signed an informed-consent form before being enrolled in the study.

4. Outcome variables

The primary outcome was the composite treatment success rate, including the absence of BoP, SoP and sites showing deep PPD (PPD≥5 mm) [18]. The secondary outcomes were the improvements in clinical parameters (PPD, BoP, SoP and plaque index [PI]) and the microbiological parameter, which was the amount of causative bacteria related to peri-

implantitis.

5. Randomization and group allocation

Sealed envelopes containing the information about group assignments and random numbers were generated using web-based software (sealedenvelope.com) and were given to the enrolled patients by an independent statistician. Researchers were blinded to assignment before opening the envelope. Patients were stratified according to the treatment centre and randomly allocated to one of the following three groups on 1:1:1 ratio:

1. MM group: treated by non-surgical mechanical debridement along with the local administration of metronidazole-minocycline ointment (MM).
2. MC group: treated by non-surgical mechanical debridement along with the local administration of minocycline ointment (MC).
3. NST group: treated by non-surgical mechanical debridement alone.

6. Local antibiotics ointments

The local antibiotic used for the MM group was a prototype ointment (YH26153, Yuhan, Seoul, Republic of Korea) composed of minocycline hydrochloride dehydrate (10.0 mg) and metronidazole benzoate (201.0 mg) in a total dose of 0.5 g. The pharmacologic and pharmacokinetic properties were based on the local antibiotics widely used as the therapeutic agent of periodontitis (Periocline, Sunstar, Osaka, Japan; Elyzol, Dumex, Copenhagen, Denmark). This gel was charged in a disposable polypropylene applicator, enabling intrasulcular application at the implants. For the MC group, a commercial minocycline hydrochloride gel (Periocline, Sunstar, Osaka, Japan) containing 10.0mg of minocycline hydrochloride dehydrate was used. It was charged in a disposable polypropylene applicator with a total weight of 0.5 g per dose.

7. Treatment procedure

At baseline, all subjects were provided with the same oral hygiene products (FX2

brush, Complete Care toothpaste, 1-min interdental brush and Ultra floss, Yuhan, Seoul, Republic of Korea), and non-surgical debridement was carried out using an ultrasonic scaler (EMS, Nyon, Switzerland). Then according to the group allocations, the ointments assigned for the MM and MC groups were applied into the peri-implant mucosal sulcus, with no local medication applied in the NST group.

For the MM and MC groups, local antibiotics delivery was performed at 1, 2 and 3 weeks after baseline, while no further treatment was applied in the NST group. At 4 and 8 weeks after baseline, mechanical debridement with the ultrasonic scaler was applied to all subjects, and the final visit occurred at 12 weeks after baseline.

8. Outcome measurements

8.1. Assessments of clinical parameters

Clinical parameters including the PPD, BoP, SoP and PI were measured at the six sites of enrolled implants with a periodontal probe (PCP-UNC-15, Hu-Friedy, Chicago, IL, USA). PI was measured using a 4-point scale from 0 to 3 [19]. BoP was recorded as 0 (no bleeding) or 1 (bleeding) based on whether or not bleeding was found within 10 seconds after probing [20]. SoP was recorded as 0 (no purulence) or 1 (purulence) based on the occurrence of purulence either spontaneously or after probing [21]. These measurements were performed at baseline and 4, 8 and 12 weeks after baseline [22, 23]. All the clinical measurements were conducted by the calibrated examiners. The Kappa coefficient for the inter-observed reliability was 0.915 (95% confidence interval), showing inter-examiner agreement for the clinical measurements.

According to previously reported success criteria for the non-surgical treatment of peri-implantitis[18], the absence of sites with BoP, SoP or PPD ≥5 mm was considered as treatment success in the present study.

In order to evaluate the relationship between the severity assessed at baseline and the efficacy of the treatment, further analysis based on the clinical measurements was conducted between two subgroups: moderate and severe. If the implant had a deepest PPD

of ≥8 mm, the subject was assigned to the severe subgroup, while if the deepest PPD was ≥5 mm and <8 mm, the subject was allocated to moderate subgroup [23].

8.2. Assessments based on the microbiological parameter

Microbiological changes were investigated based on three red complex bacteria (*Porphyromonas gingivalis*, *Tannerella forsythia* and *Treponema denticola*) and seven bacteria that mainly comprised orange complex (*Fusobacterium nucleatum*, *Prevotella intermedia*, *Prevotella nigrescens*, *Peptostreptococcus micros*, *Eubacterium nodatum*, *Campylobacter rectus* and *Eikenella corrodens*) [24]. Samples collected using endodontic paper points from the deepest PPD sites at baseline and 4 and 12 weeks thereafter were immediately immersed in a buffer solution and stored at –80 °C until assayed. Microbial quantitative analysis was carried out using the real-time polymerase chain reaction similar to the previous study [25]. DNA extraction was carried out using the Exgene Clinic SV mini kit (GeneAll, Seoul, Korea). Subsequently, the samples were processed in a reaction volume of 20μL containing 2μL of template DNA, periodontal pathogen-specific primers (Periogen, Gyeonggi-do, Korea), and PCR reaction buffer solution. The PCR amplification was performed using the ABI 7500 Fast Real-Time PCR system (Applied Biosystems, Life Technologies, CA, USA). After an initial denaturation at 95◦C for 15 min, 40 cycles of amplification were performed at 95◦C for 30s, 55◦C for 30s, and 72◦C for 30s.

9. Statistical analysis

Statistical analysis was performed using SPSS software (version 25.0, SPSS, Chicago, IL, USA) and SAS software (version 9.1, SAS Institute, Carey, NC, USA). Normality of the data distribution was confirmed for clinical parameters using the Shapiro-Wilk test ($p > 0.05$), while this was not the case for the microbiological parameter ($p < 0.05$).

The clinical measurements were quantified as mean±SD values, and mixed models for repeated measures (including interactions between groups, visits, baseline value, groups×visits and baseline value×visits) were used to assess differences in efficacy over

time between the three treatment modalities. Intergroup comparison of treatment success rate was performed with multivariate logistic regression analysis. The independent factors which might have contributed to the treatment success were included:

- treatment-related factor: treatment modality decided by group allocation (MM, MC or NST group)
- treated site-related factors: PPD and RBL at baseline
- implant-related factors: type of the implant fixture and time elapsed after implant installation
- patient-related factors: age, sex and smoking history of the enrolled subjects

Microbiological results were quantified as median and quartile values based on the counts of colony-forming units. Intragroup pairwise comparisons were performed using the Wilcoxon test for each group. The chi-square test was used for intergroup comparisons of the detection frequency between the three treatment modalities. The criterion for significance was set as $p < 0.05$.

III. RESULTS

1. Demographic information

This study enrolled 118 patients, of which 114 finished the trial and were included in the analysis: 38, 39 and 37 in the MM, MC and NST groups, respectively. Four subjects were excluded for following reasons: one in the MM group due to withdrawing consent, one in the MC group at the investigator's discretion (due to the occurrence of pneumonia, the subject had difficulty in conducting visits) and two in the NST group who needed to take contraindicated medications. No adverse events related to any kinds of treatment modalities of medications were reported up to the end of the trial.

The baseline demographic characteristics of the subjects are summarized in Table 1. No apparent imbalance between the groups was found at baseline.

2. Baseline characteristics

The baseline measurements of clinical and radiographic parameters are shown in Table 2. No significant difference between the groups was found.

3. Treatment success rate

The ratios of subjects fulfilling the success criteria for non-surgical treatment at 4, 8 and 12 weeks after baseline are presented in Figure 2. In the MM and MC groups, the success ratios tended to increase from baseline to week 4. The success ratios were maintained from week 4 to week 12, reaching 31.6% and 20.5% at the final visit in the MM and MC groups, respectively. For the NST group, the success ratio did not increase throughout the study period. The success ratio differed significantly between the MM and NST groups at week 4 ($p = 0.017$) and week 12 ($p = 0.011$), and was significantly higher in the MC group than the NST group at week 8 ($p = 0.014$) and week 12 ($p = 0.040$).

4. Clinical measurements

The changes in clinical parameters between baseline and the final follow-up are presented in Table 3. The mean PPD and mean BoP differed significantly between the MM and NST groups (p = 0.0023 and 0.0381, respectively). The mean SoP values decreased from baseline to the final follow-up, by 0.12, 0.25 and 0.24 in the MM, MC and NST groups, respectively**.** The mean PI values also decreased from baseline to week 12, by 0.54, 0.42 and 0.35, respectively, showing improved oral hygiene for all treatment modalities.

4.1. Pocket probing depth

The changes in PPD at all time points are shown in Figure 3a. The PPD changes differed significantly at all time points after baseline between the MM and NST groups (p = 0.0032, 0.0359 and 0.0050 at weeks 4, 8 and 12, respectively), but not between the MM and MC groups.

4.2. Bleeding on probing

Figure 3b presents the changes in BoP counts (at six sites per implant) from baseline to the 12-week follow-up. The BoP counts were 4.97±1.31, 4.88±1.44 and 4.79±1.49 in the MM, MC and NST groups, respectively (p > 0.05), at baseline, and they had reduced at the final follow-up to 1.92±2.14, 1.87±2.00 and 2.81±2.22, respectively. Complete resolution of mucosal inflammation (defined as the absence of BOP at all six sites) was detected in 42.1%, 33.3% and 18.9% of those in the MM, MC and NST groups, respectively.

5. Subgroup analysis

The PPD changes at the deepest sites in the two subgroups are summarized in Table 4. The baseline values in the severe subgroup were 9.08, 9.10 and 9.06 mm in the MM, MC and NST groups, respectively, and at the final follow-up they had reduced to 4.58, 6.05 and 6.73 mm, respectively. The PPD differed significantly between the MM and MC groups at weeks 4 and 12, and the reduction in the PPD was significantly greater in the MM group than the NST group at all time points. A similar analysis applied to the moderate subgroup did not reveal any significant differences between the treatment modalities.

None of the other clinical parameters (BoP, SoP and PI) differed significantly in either severity subgroup.

6. Microbiological analysis

The counts of red complex bacteria in all groups showed a decreasing tendency from baseline to week 4, and then slight rebounds at week 12 (Figure 4). At 12 weeks after baseline there were statistically significant decreases in the counts of *P. gingivalis*, *T. forsythia*, *T. denticola*, *P. intermedia*, *C. rectus* and *F. nucleatum* in the MM and MC groups. Except for *P. gingivalis* ($p < 0.05$), there was no significant difference between baseline and the final follow-up in the NST group.

Table 5 presents the detection frequencies of all pathogens for each group. The most frequently identified bacterial species in the submucosal biofilms were *P. gingivalis*, *T. forsythia*, *P. intermedia* and *F. nucleatum*. At the final follow-up, the detection ratio of *T. forsythia* was significantly lower for the MM group than for the MC group ($p = 0.038$).

IV. Discussion

The present RCT demonstrated that the combination of metronidazole and minocycline as a local adjunct to non-surgical debridement produced a significantly greater improvement in clinical and microbiological parameters compared to mechanical debridement alone, and showed comparable results to minocycline alone in terms of treatment success. This study has also demonstrated that this combined use of local antibiotics can contribute to greater PPD reductions compared to using minocycline alone in peri-implantitis lesions with deep PPDs.

Numerous studies related to surgical approaches for peri-implantitis treatment have evaluated treatment success using various metrics, including the absence of BoP, SoP and deep PPD sites, and no further peri-implant bone loss [26-28], with wide variations being detected. Carcuac (2016) found that 45% of implants were successfully treated by applying systemic antibiotics, whereas Jepsen (2016) found that only 23% of implants fulfilled the success criteria when applying open-flap debridement alone. More recently, Cha (2019) reported that 66.7% of implants were successfully treated after access surgery with repeated application of local minocycline.

As previously discussed in the consensus report, the treatment success of peri-implantitis should also be assessed for non-surgical modalities [18]. However, few studies have defined and evaluated treatment success for non-surgical modalities applied to peri-implantitis. A recent study performed non-surgical debridement of peri-implantitis using an ultrasonic device, hand curettes and air abrasive, after modifying the implant prosthesis into more cleansable profile [29]. Thereafter, systemic intake of metronidazole was applied every 8 h for 7 days, and peri-implant maintenance therapy was conducted every 3–6 months. After 12 months, 40.9% of subjects were consistent with the treatment success criteria. In the current study, the repeated use of local antibiotics produced success rates of 31.6% and 20.5% in the MM and MC groups, respectively, after 12 weeks, which are comparable to those observed in studies applying surgical and non-surgical interventions.

These relatively low success rates compared to that found by Nart (2020) can be attributed to the higher initial PPD (6.01±1.57 mm in the present study and 5.34±1.29 mm in that of Nart), a lower variety of modalities performed for mechanical debridement, the exclusion of prostheses modification after treatment and the allocation of the subjects being controlled better in this study than in the previous case series. Nonetheless, the present study found that the treatment success rate was significantly higher when administering local antibiotics (MM and MC groups) than in the negative control arm (NST group), and hence this study is the first RCT to have assessed the effects of local antibiotics on treatment success in peri-implantitis.

Little is known about the effect of local metronidazole in peri-implantitis, but several studies have investigated the benefits of local metronidazole in patients with periodontitis. Previous prospective studies found significantly greater improvement of PPD when using local metronidazole as an adjunct to SRP [30, 31]. Recently, a RCT with a split-mouth design found that the local delivery of 25% metronidazole gel resulted in improvements of PPD and BoP at a 4-week follow-up, with these outcomes maintained until 12 weeks after therapy [32].

The elimination of deep PPD sites is significant in peri-implantitis treatment. According to the protocol for supportive therapy of peri-implantitis presented in a consensus report, open-flap debridement should be considered when implants exhibit BoP combined with PPD >5 mm [33]. A recent review stated that the absence of sites with PPD >5 mm and concomitant BoP should be considered to indicate the successful treatment of peri-implantitis [2]. In the present severe subgroup (deepest PPD ≥8 mm), the use of MM reduced the deepest PPD to <5 mm after 12 weeks, whereas this was not achieved by applying minocycline or mechanical debridement alone (Table 4). These observations imply that the need for further treatment in peri-implantitis can be reduced by the local administration of metronidazole and minocycline, especially for lesions with deep pockets.

The clinical outcomes of the present study support that most of the reduction in BoP counts occurred during the first 4 weeks after baseline, at which adjunctive local drug

delivery was performed. Subjects treated with local antibiotics (either MM or MC) showed mean BoP reductions of more than 50% from baseline (from 82.8% to 32.0% for MM, and from 81.3% to 31.2% for MC), and showed significantly higher efficacy compared to subjects treated with mechanical debridement alone. This is consistent with previous studies related to repeated local drug delivery showing dramatic changes in the mean BoP percentage, from 86.5% to 48.1% [34], and the BoP counts, from 4.41 to 1.55 [35].

These marked improvements in clinical parameters were accompanied by lower counts of red bacterial complex for MM compared to MC, particularly for *T. forsythia* (p = 0.038). The results are in agreement with the previous study reporting a significant decrease in red bacterial complex after non-surgical treatment with the local delivery of minocycline [35]. These outcomes suggest that the additive use of metronidazole with minocycline at peri-implantitis is beneficial for disease resolution.

Several limitations have to be pointed out in this study. Firstly, the treatment protocol of the study shows some crucial differences between treatment modalities. Unlike the MM and MC groups with local antibiotics administration procedures, the delivery of placebo ointment was not included in the protocol of NST group. The difference in the number of visits between groups can also be a factor that might influence the results of the study. Second, the clinical endpoint of this study was 12 weeks, showing only the short-term benefits of the nonsurgical treatment of peri-implantitis. Further studies with longer term evaluations of the sustained effects related to the combined use of metronidazole and minocycline are still required. In addition, considering the previous consensus report [18], it would be better if the radiographic analysis is added to see if the maintenance of bone levels can be achieved.

V. Conclusion

Within the limitations of the study, it is concluded that the local adjunctive use of minocycline either with or without the addition of metronidazole result in significantly higher treatment success rates compared to NST in non-surgical treatment of peri-implantitis. Especially, the combination of metronidazole might enhance the PPD reduction in peri-implantitis with deepest PPD ≥8 mm.

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Figure legend

Figure 1. CONSORT flowchart of the study.

Figure 2. Composite treatment success. Numbers of subjects fulfilling composite treatment success criteria for peri-implantitis (absence of BoP, SoP and sites showing PPD ≥5 mm). Statistically significant differences between treatment modalities are indicated by ‡ (MM and NST groups) and † (MC and NST groups) ($p<0.05$). In the MM and MC groups, the success ratios tended to increase from baseline to week 4, which was the period during which local antibiotics were delivered on a weekly basis, and the ratios were maintained until the final visit. The treatment success rates at 12 weeks were 31.6%, 20.5% and 2.7% in the MM, MC and NST groups, respectively.

Figure 3. (a) Mean PPD and (b) BOP counts from baseline to 12 weeks. Statistically significant differences between treatment modalities are indicated by ‡ (MM and NST groups) and † (MC and NST groups) ($p<0.05$). (a) The baseline values did not differ significantly between the MM, MC and NST groups, at 5.71±1.33, 6.22±1.92 and 5.82±1.39 mm, respectively. Gradual decreases in the mean PPD were achieved in all groups. (b) Most of the reduction in the BOP counts were achieved at the first 4 weeks of the study.

Figure 4. Counts of red complex bacteria at all time points.

Tables

Table 1. Demographic data on patients.

	MM	MC	NST	Total
Patients	39	40	39	118
Age, y, mean (range)	60.7 (45 to 77)	61.2 (40 to 76)	61.2 (41 to 77)	61.1 (40 to 77)
Sex				
Male	18 (46.1)	21 (52.5)	21 (53.9)	60 (50.9)
Female	21 (53.9)	19 (47.5)	18 (46.1)	58 (49.1)
Jaw				
Maxilla	19 (48.7)	20 (50.0)	15 (38.5)	54 (45.8)
Mandible	20 (51.3)	20 (50.0)	24 (61.5)	64 (54.2)
Location				
Anterior (incisor to canine)	4 (10.3)	1 (2.5)	2 (5.1)	7 (5.9)
Posterior (premolar to molar)	35 (89.7)	39 (97.5)	37 (94.9)	111 (94.1)
Implant fixture type **				
A	8 (20.5)	8 (20.0)	10 (25.6)	26 (22.0)
B	3 (7.7)	6 (15.0)	7 (18.0)	16 (13.6)
C	24 (61.5)	26 (65.0)	21 (53.9)	71 (60.2)
Unknown	4 (10.3)	0 (0.0)	1 (2.6)	5 (4.2)
Implant surface				
Non-modified	8 (20.5)	8 (20.0)	10 (25.6)	26 (22.0)
Modified	27 (69.2)	32 (80.0)	28 (71.8)	87 (73.7)
Unknown	4 (10.3)	0 (0.0)	1 (2.6)	5 (4.2)
Implant duration (years)	8.7	9.0	9.2	9.0
Days of Peri-Implantitis	235.2	426.3	297.9	320.7

** A: bone-level, external connection; B: tissue-level, internal connection; C: bone-level, internal connection, with micro-thread design; if the fixture type could not be identified, it was referred as unknown.

Table 2. Radiographic and clinical parameters at baseline.

	MM	MC	NST
Patients	39	40	39
Radiographic bone loss (RBL), mm			
Mesial	3.54±1.40	3.73±1.92	3.12±1.43
Distal	3.95±1.59	3.64±1.79	3.37±1.54
Probing pocket depth, mm			
At deepest site	6.92±1.80	7.55±1.93	7.49±1.52
Mean at 6 sites	5.71±1.33	6.22±1.92	5.82±1.39
Bleeding on probing, %			
At deepest site	0.95±0.22	0.98±0.16	0.97±0.16
Mean at 6 sites	0.83±0.22	0.82±0.24	0.80±0.25
Pus suppuration, %			
At deepest site	0.29±0.46	0.33±0.48	0.41±0.50
Mean at 6 sites	0.18±0.30	0.30±0.39	0.29±0.39
Plaque index			
At deepest site	1.15±0.74	1.03±0.53	1.00±0.56
Mean at 6 sites	1.02±0.61	0.92±0.43	0.98±0.49

Table 3. Changes in clinical parameters between baseline and 12 weeks follow-up.

	MM	MC	NST
Probing pocket depth, mm			
At deepest site at baseline	**-2.71±1.90** ‡	-2.51±1.82	**-2.03±1.38** ‡
Mean at 6 sites	**-1.95±1.28** ‡	-1.88±1.50	**-1.28±1.15** ‡
Bleeding on probing, %			
At deepest site at baseline	**-0.66±0.53** ‡	-0.59±0.50	**-0.38±0.49** ‡
Mean at 6 sites	**-0.51±0.32** ‡	-0.50±0.34	**-0.33±0.41** ‡
Pus suppuration, %			
At deepest site at baseline	-0.18±0.39	-0.31±0.46	-0.32±0.53
Mean at 6 sites	-0.12±0.25	-0.25±0.37	-0.24±0.37
Plaque index			
At deepest site at baseline	-0.71±0.80	-0.54±0.76	-0.35±0.89
Mean at 6 sites	-0.54±0.54	-0.42±0.54	-0.40±0.64

‡ (bold): significant difference between "MM" and "NST" group.

** p-value based on mixed model for repeated measures (including interactions between groups, visits, baseline value, groups * visits and baseline value * visits).

Table 4. Probing depth value of deepest site from baseline to 12 weeks follow-up at severe and moderate group.

Severe group (deepest PPD of ≥8 mm)	**MM**	**MC**	**NST**
N	12	20	15
Baseline	9.08±1.16	9.10±1.14	9.06±0.77
Change from baseline to week 4	-3.75±1.71	-2.30±1.75	-1.60±1.72
P value		**0.0252** †	**0.0015** ‡
Change from baseline to week 8	-3.67±1.23	-3.00±2.13	-2.40±1.72
P value		0.3396	0.0624
Change from baseline to week 12	-4.50±1.57	-3.10±2.17	-2.33±1.59
P value		**0.0471** †	**0.0024** ‡
Moderate group (deepest PPD was ≥5 mm and <8 mm)	**MM**	**MC**	**NST**
N	26	19	22
Baseline	5.96±1.02	5.84±0.90	6.39±0.72
Change from baseline to week 4	-1.35±1.26	-1.47±0.96	-1.14±1.55
P value		0.6739	0.2994
Change from baseline to week 8	-1.88±1.53	-1.84±1.01	-1.68±1.32
P value		0.9422	0.2593
Change from baseline to week 12	-1.88±1.42	-1.89±1.10	-1.82±1.22
P value		0.7963	0.3686

† (bold): significant difference between "MM" and "MC" group.
‡ (bold): significant difference between "MM" and "NST" group.

** p-value based on mixed model for repeated measures.

Table 5. Detection frequency at baseline and final visit.

	MM	MC	NST
P. Gingivalis			
Baseline	22 (58)	22 (56)	16 (43)
12 weeks	6 (16)	8 (21)	**15 (41) ‡**
T. Forsythia			
Baseline	14 (37)	19 (49)	16 (43)
12 weeks	3 (8)	**10 (26) †**	**12 (32) ‡**
T. Denticola			
Baseline	15 (39)	21 (54)	11 (30)
12 weeks	8 (21)	13 (33)	15 (41)
A.Actinomycetemcomitans			
Baseline	0 (0)	1 (3)	0 (0)
12 weeks	1 (3)	0 (0)	0 (0)
P. Intermedia			
Baseline	27 (71)	23 (59)	19 (51)
12 weeks	18 (47)	12 (31)	19 (49)
F. Nucleatum			
Baseline	28 (74)	32 (82)	24 (65)
12 weeks	25 (66)	27 (69)	21 (57)
P. Micra			
Baseline	1 (3)	1 (3)	2 (5)
12 weeks	0 (0)	0 (0)	**4 (11) ‡**
C. Rectus			
Baseline	7 (18)	6 (15)	6 (16)
12 weeks	1 (3)	2 (5)	3 (8)
E. Nodatum			
Baseline	7 (18)	11 (28)	10 (27)
12 weeks	1 (3)	1 (3)	5 (14)
P. Nigrescens			
Baseline	9 (24)	10 (26)	8 (22)
12 weeks	10 (26)	10 (26)	9 (24)
E. Corrodens			
Baseline	12 (32)	10 (26)	8 (22)
12 weeks	12 (32)	6 (15)	11 (30)

** Samples accounted as positive if more than 10^5 bacterial count is measured.
** Values are shown as number of implants accounted as positive and the ratios by percentage.
† (bold): significant difference between "MM" and "MC" group at 12 weeks follow-up. ($P < 0.05$)
‡ (bold): significant difference between "MM" and "NST" group at 12 weeks follow-up. ($P < 0.05$)

FIGURES

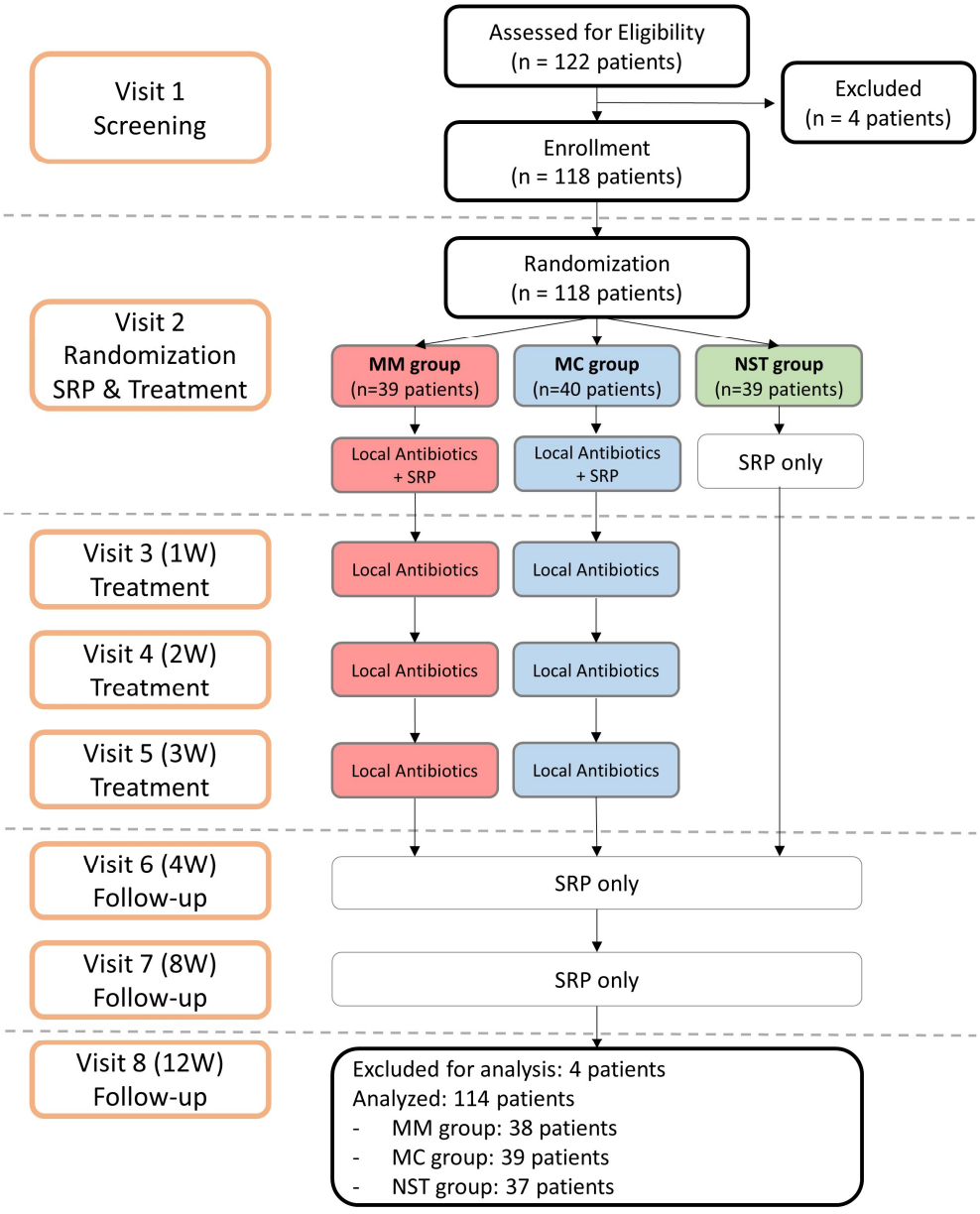

Figure 1

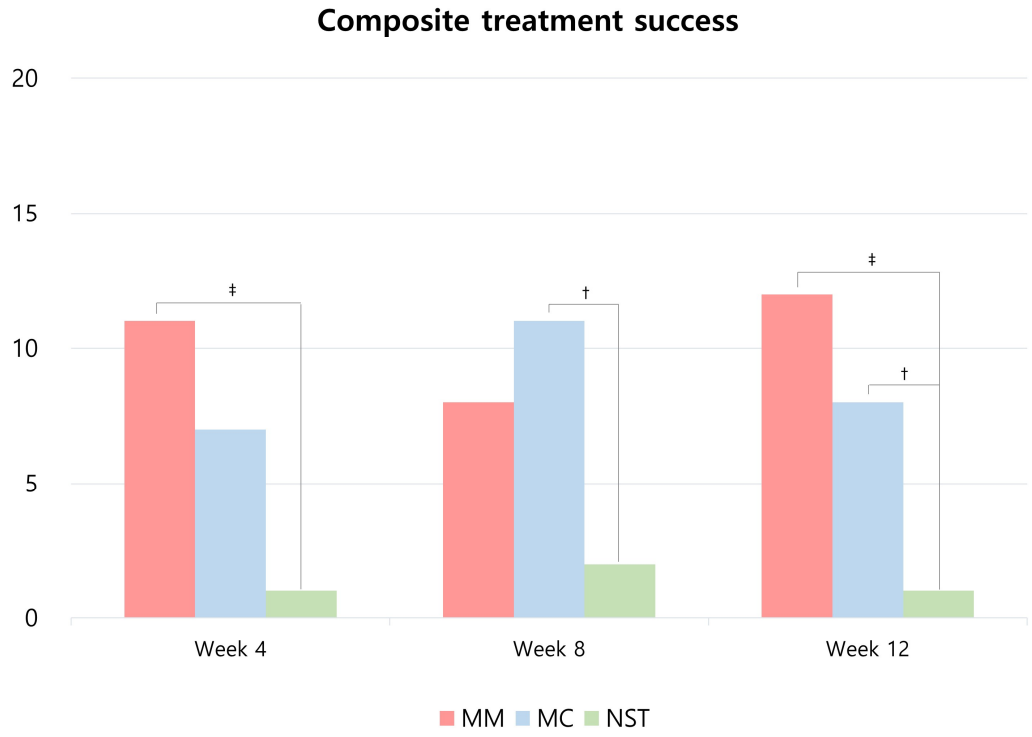

Figure 2

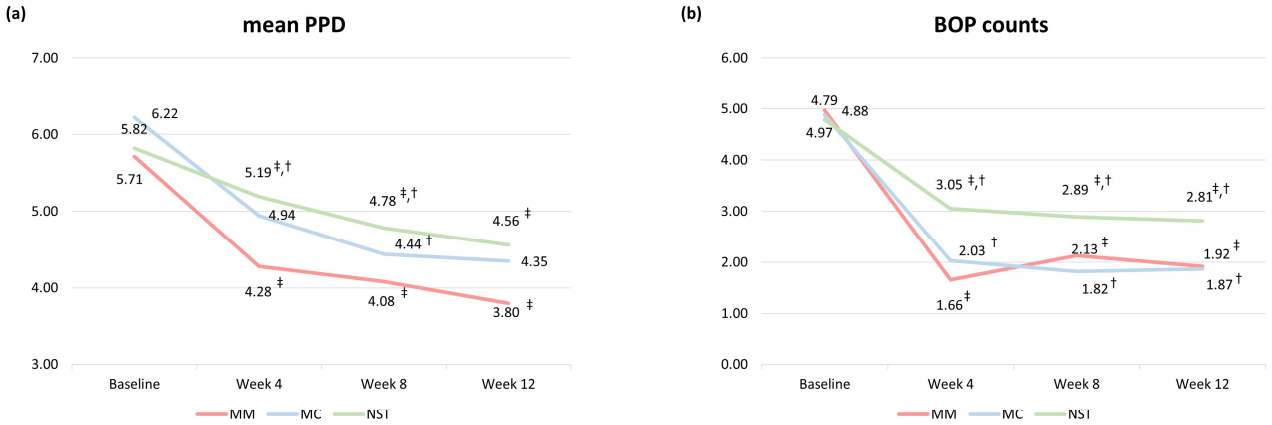
(a)
mean PPD
7.00
6.00
5.00
4.00
3.00
Baseline
Week 4
Week 8
Week 12
5.82
6.22
5.71
5.19 ‡,†
4.94
4.78 ‡,†
4.44 †
4.56 ‡
4.35
4.28 ‡
4.08 ‡
3.80 ‡
MM
MC
NSI
(b)
BOP counts
6.00
5.00
4.00
3.00
2.00
1.00
0.00
Baseline
Week 4
Week 8
Week 12
4.79
4.88
4.97
3.05 ‡,†
2.89 ‡,†
2.81 ‡,†
2.03 †
2.13 ‡
1.92 ‡
1.66 ‡
1.82 †
1.87 †
MM
MC
NSI

Figure 3

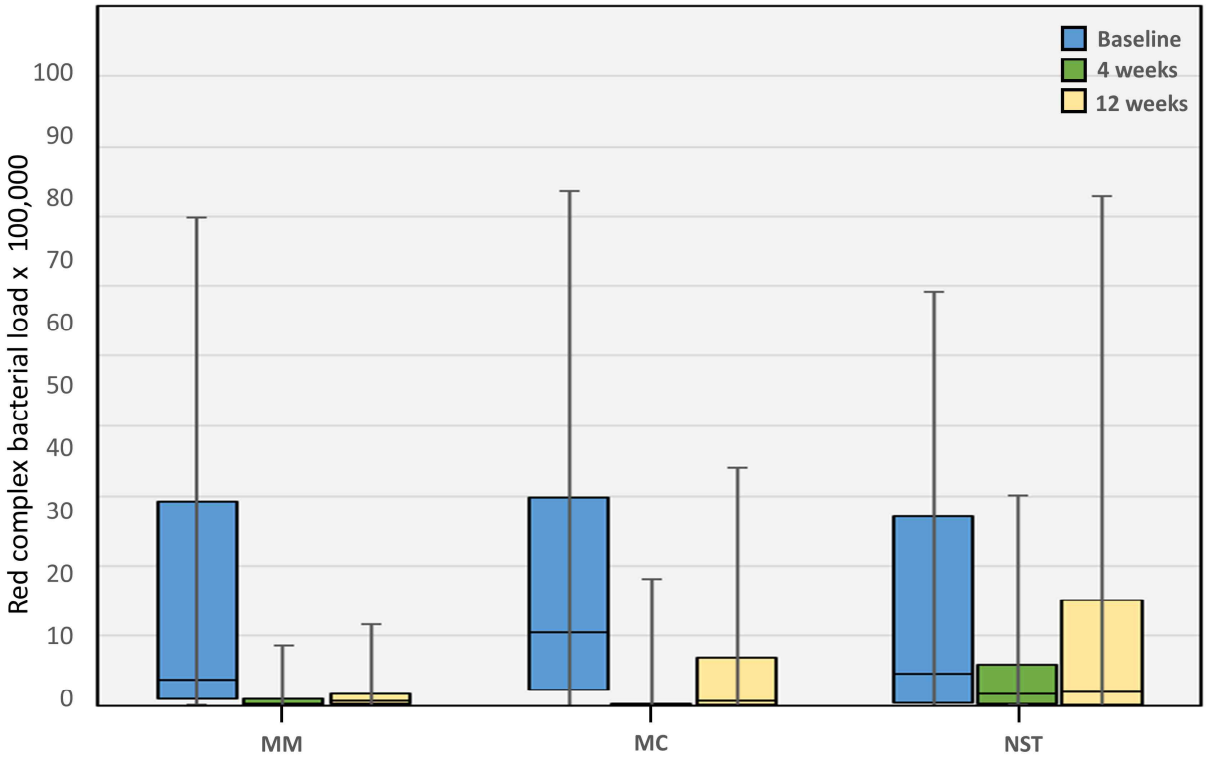
Baseline
4 weeks
12 weeks
Red complex bacterial load x 100,000
100
90
80
70
60
50
40
30
20
10
0
MM
MC
NST

Figure 4

국문요약

임플란트주위염의 비수술적 처치시 메트로니다졸-미노사이클린의 국소 도포제제로서의 항미생물학적 효능: 다기관 무작위 대조 실험

<지도교수 **김 창 성**>

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박 승 현

임플란트주위염은 임플란트 주위에 나타나는 치태 기인성 염증과정으로 대표적인 특징으로 임플란트주위 치조골 소실, 깊은 치주낭, 탐침 후 출혈 혹은 화농 등의 양상을 지닌다. 현재까지 박테리아성 치태 제거를 위해 다양한 비수술적 치료방법들이 소개되어 왔으나 술자의 시야 제한 및 임플란트 표면 형태에 기인하여 완전한 치태의 제거는 용이하지 않다고 알려져 있다.

임플란트주위염의 비수술적 처치 방법들 중 국소 항생제 도포의 병행기법은 유의한 수준의 임상적 지표 개선을 가져옴이 여러 논문들을 통해 입증되어 왔다. 대다수 논문들은 미노사이클린 제제의 국소 항생제 사용을 통해 치주낭 깊이 및 탐침 후 출혈의 감소를 유도할 수 있음을 발표한 바 있으나, 완전한

염증 소실에 이르지는 못한다는 점과 미노사이클린 이외 전신체계에서 활용되는 다양한 종류의 항생제에 대해서 다루지 않았다는 점이 한계로 남는다. 본 연구에서는 중등도 이상의 임플란트주위염에서 발견되는 red complex bacteria를 비롯한 절대혐기성균에 효과적이라고 알려진 메트로니다졸, 그리고 현재 임상에서 임플란트주위염 치료에 항생제 중 가장 많이 활용되고 있는 미노사이클린을 임플란트주위염 치료목적으로 복합 사용하였을 때 임상학 및 미생물학적 지표의 개선 정도를 평가하고자 하였다.

임플란트주위염을 지닌 122명의 환자들을 대상으로 네 개 치료기관에서 12주간 무작위 대조 실험이 실시되었다. 환자들은 무작위적으로 다음 세 치료군 중 하나에 속하여 기계적인 세정 및 국소 항생제 도포 치료를 받았다: MM 군 – 기계적인 세정 및 메트로니다졸-미노사이클린 복합 연고 (MM 연고) 도포, MC 군 – 기계적인 세정 및 미노사이클린 연고 도포, NST 군 – 기계적인 세정만 진행.

최종적으로 118명의 환자들을 대상으로 결과 분석이 시행되었다. “치료 성공율” (탐침 후 출혈, 화농, 5mm 이상의 치주낭 완전 소실) 측면에서 12주차에 MM 군 (31.6%), MC 군 (20.5%)이 NST군 (2.7%)보다 통계적으로 유의하게 높은 비율을 보여주었다. 치료 시작 시 임플란트주위염의 경도에 따라 개체들을 나누어 부분군 분석을 시행하였을 때, 초기 치주낭 깊이 8mm 이상의 환자들의 경우 치주낭 깊이 감소측면에서 MM 군이 MC 군보다 4주차 (p =

0.025), 12주차 (p = 0.047) 때 통계적으로 유의하게 더 높은 지표 개선을 보여주었다. 미생물학적 지표 분석시 *T.forsythia* 균의 검출 비율 측면에서 MM 군이 MC 군보다 통계적으로 유의하게 더 낮게 계측되었다. (p = 0.038)

결과적으로 MM 혹은 MC 항생제를 사용 시 모두 단순 기계적 세정보다 통계적으로 유의하게 더 높은 치료 성공율에 도달함을 확인하였다. 아울러 미노사이클린 – 메트로니다졸의 동반 사용을 통해 깊은 치주낭 깊이를 보이는 중증도 수준의 임플란트주위염에서 더 빠른 치주낭 깊이 감소를 유도함을 관찰할 수 있었다.

핵심되는 말: 임플란트주위염, 비수술적 처치, 메트로니다졸, 미노사이클린, 다기관 무작위 대조 실험