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Changes in serum interleukin-6, C-reactive protein and thrombomodulin levels under periodontal ultrasonic debridement

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Abstract

Aim: This study aimed to compare the effect of single-visit full-mouth mechanical debridement (FMD) and quadrant-wise mechanical debridement (QMD) on the levels of serum interleukin (IL)-6, C-reactive protein (CRP) and soluble thrombomodulin.

Material and Methods: Thirty-six subjects with chronic periodontitis were randomly allocated to three groups: undergoing QMD, single-visit FMD with povidone iodine or with water. Serum IL-6 and soluble thrombomodulin were measured by enzyme-linked immunosorbent assay, and serum CRP was measured by the latex-enhanced nephelometric method.

Results: Serum IL-6 level increased significantly immediately after debridement in all the three groups, with this increase being greatest in the full-mouth groups. However, the increase in the full-mouth groups was not significantly higher than that of quadrant-wise group. In the quadrant-wise group, serum IL-6 level decreased significantly 1 month after debridement compared with baseline. Serum-soluble thrombomodulin decreased significantly in the full-mouth groups but not in the quadrant-wise group. Changes in CRP level were not significant at baseline or after debridement in all the three groups.

Conclusions: FMD increased serum IL-6 and reduced serum-soluble thrombomodulin to a greater extent than QMD, suggesting that the former technique has stronger transient effects on systemic vascular endothelial functions than the latter.

Key words: CRP; IL-6; periodontitis; single-visit full-mouth debridement; soluble thrombomodulin

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Conflict of interest and source of funding statement

There is no conflict of interests.
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Periodontitis is a chronic inflammatory disease caused by periodontopathic bacteria, and is the leading cause of tooth loss in the adult population. Patients with periodontitis are exposed to periodontopathic bacteria and their components including lipopolysaccharide through the periodontal pockets (Beck et al. 1996). Lipopolysaccharide, an endotoxin component of the outer membrane in gram-negative bacteria, acts as a potent stimulus to a variety of host cells, resulting in the expression of cytokines, adhesive proteins and pro-inflammatory molecules (Raetz 1990, Tapping & Tobias 1997).

Bacteremia or endotoxemia has been reported after subgingival debridement (Ide et al. 2004, Takai et al. 2005, Forner et al. 2006a). Several researchers have noted bacteremia and short term increase in serum interleukin (IL)-6 following scaling (Ide et al. 2004, Forner et al. 2006b, Tonetti et al. 2007).

IL-6 is known to increase hepatic levels of C-reactive protein (CRP) (Steel & Whitehead 1994), and elevation of IL-6 and CRP has been associated with cardiovascular disease (Rattazzi et al. 2003).

The von Willebrand factor (vWF) and soluble thrombomodulin are circulating markers of endothelial function in cardiovascular disease (Constans & Conri 2006). Bizzarro et al. (2007) reported that more peiodontitis patients had elevated levels of vWF than periodontally healthy subjects. Soluble thrombomodulin can be released from injured endothelial cells, and is a specific marker of endothelial cell damage (Ishii et al. 1991). However, little is known about soluble thrombomodulin in periodontitis.

Full-mouth disinfection was introduced by Quirynen in 1995, based on the hypothesis that conventional quadrant scaling and root planing might cause re-infection of the treated pockets with periodontopathic bacteria from the untreated pockets (Quirynen et al. 1995). To eliminate periodontopathic bacteria and avoid re-infection, scaling and root planing of all periodontal pockets is completed in a short period of time (within 24 h) in the full-mouth disinfection approach. Various effects of this novel treatment have been recently reported (Quirynen et al. 2000, 2006, Apatzidou & Kinane 2004, Koshy et al. 2005, Wennström et al. 2005, Jervoe-Storm et al. 2006). Quirynen et al. (1999, 2000) reported that patients treated with full-mouth mechanical debridement (FMD) frequently had fever and pain, and they suggested that these symptoms were caused by transient bacteremia during subgingival instrumentation.

As soluble thrombomodulin is a specific marker for endothelial cell damage, monitoring of soluble thrombomodulin together with IL-6 and CRP might effectively indicate systemic vascular endothelial cell damage following subgingival debridement. To date, little is known about the effects of full *versus* quadrant-wise debridement on serum IL-6, CRP and soluble thrombomodulin. The purpose of this study was to compare the effects of FMD with quadrant-wise debridement on serum IL-6, CRP and soluble thrombomodulin in periodontitis patients. The effects of FMD with water on serum IL-6, CRP and soluble thrombomodulin were also compared with the effects of FMD with povidone iodine, tongue brushing and chlorhexidine (CHX) rinsing on those parameters.

Material and Methods

Selection of subjects

A total of 36 systemically healthy, non-smoking patients, aged 34–66 years (23 women and 13 men, mean 50.4 ± 8.4 years), were recruited from the Periodontics Clinic of Tokyo Medical and Dental University. All the patients exhibited moderate-to-advanced chronic periodontitis, based on clinical and radiographic findings. Each subject had at least five teeth and two pocket sites with probing depth $\geqslant 5$ mm in each quadrant, and radiographic evidence of alveolar bone loss. Subjects had not undergone antimicrobial therapy, subgingival periodontal debridement or periodontal surgery in the preceding 6 months. Patients were not included in the study if they were suffering from any chronic inflammatory or immunological conditions such as arthritis, gastrointestinal disorders, skin conditions, or bronchitis or other chronic obstructive airway disease. None of the subjects were pregnant or lactating or had known allergy to iodine. The study protocol was approved by the Ethics Committee of Tokyo Medical and Dental University, and experiments were undertaken with the informed written consent of each subject and in accordance with the principles outlined in the 2002 Declaration of Helsinki.

Treatment protocol

The demographic details, clinical study design and treatment protocol are described in our earlier report (Koshy et al. 2005). The trial design and the timing of clinical interventions and sampling are summarized in Fig. 1. Briefly, the present study compared conventional quadrant-wise mechanical debridement (QMD), FMD with water in a single visit (FMD+water) and FMD with povidone iodine in a single visit (FMD+povidone).

Mechanical debridement consisted of supra- and subgingival ultrasonic instrumentation. This was performed by two experienced and trained periodontists, mainly with an ultrasonic scaler (Piezon® Master 400, EMS, Nyon, Switzerland) equipped with a Perio Slim tip. Local anaesthesia was administered during debridement, if necessary. In both the FMD+water group and the FMD+povidone group, mechanical debridement was completed in a single visit. The irrigant was distilled water in the former group and 1% povidone iodine (Popiyodon Gargle®, Yoshida, Tokyo, Japan) in the latter. Subjects in the FMD+povidone group were advised to rinse with 15 ml of 0.05% CHX mouthwash (Concool®, Weltec, Mie, Japan) twice a day for 1 month and to practice tongue brushing in order to delay re-colonization from other intraoral niches during the initial healing period. Subjects in the FMD+water and QMD groups were not advised to use any mouth rinse or perform tongue brushing.

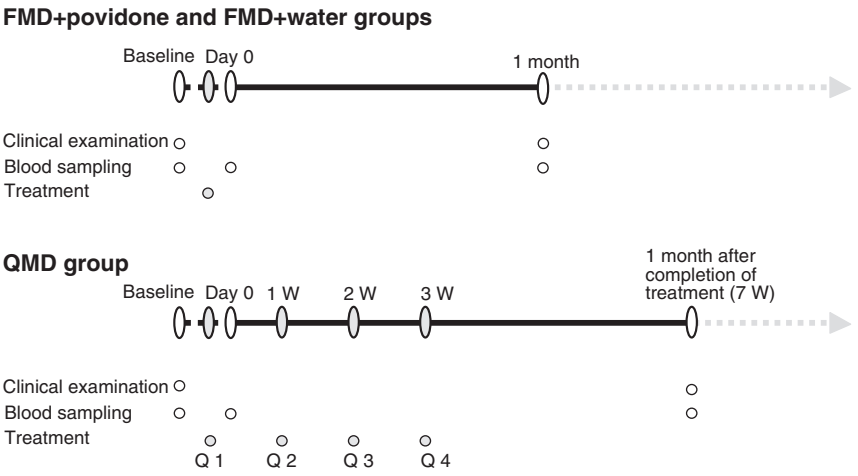

Fig. 1. Treatment schedule and blood sampling in the study groups: FMD+povidone, full-mouth mechanical debridement with povidone; FMD+water, full-mouth mechanical debridement with water; QMD, quadrant-wise mechanical debridement; TBI, toothbrushing instructions.

Measurement of serum IL-6, CRP and soluble thrombomodulin

Blood samples were collected in endotoxin-free tubes, at baseline (before treatment), immediately after treatment (approximately 5 h after the pre-treatment blood collection), and 1 month after treatment. All analysis was performed blinded, with no knowledge of the treatment administered.

Serum was isolated from the whole blood and stored at $-30^{\circ}C$ until use. The levels of serum IL-6 were determined using an ELISA kit (Biosource International, Camarillo, CA, USA for IL-6). The detection limit of the IL-6 ELISA kit was 0.104 pg/ml. Serum soluble thrombomodulin levels were determined using an ELISA kit (Prototype-Thrombomodulin ELISA kit; Diagnostica Stago, Asnieres, France). The detection limit of the soluble thrombomodulin ELISA kit was 0.3 ng/ml. The levels of serum CRP were determined with the latex-enhanced nephelometric method (Bio-Clinical Laboratories, Tokyo, Japan). Sensitivity of the CRP measurement was 40.0 ng/ml, and if the sample CRP was below the sensitivity of the assay, the CRP level was expressed as 0 ng/ml.

Statistical analysis

Comparisons of the changes in serum IL-6, CRP and soluble thrombomodulin levels between visits within group were performed with Friedman ANOVA and Wicoxon's signed-rank test for post hoc comparison. The p-values <0.05 were considered to indicate significant differences. All the statistical analysis was carried out with the aid of statistical software (StatView® for Windows, Version 5.0, SAS Institute Inc., Cary, NC, USA).

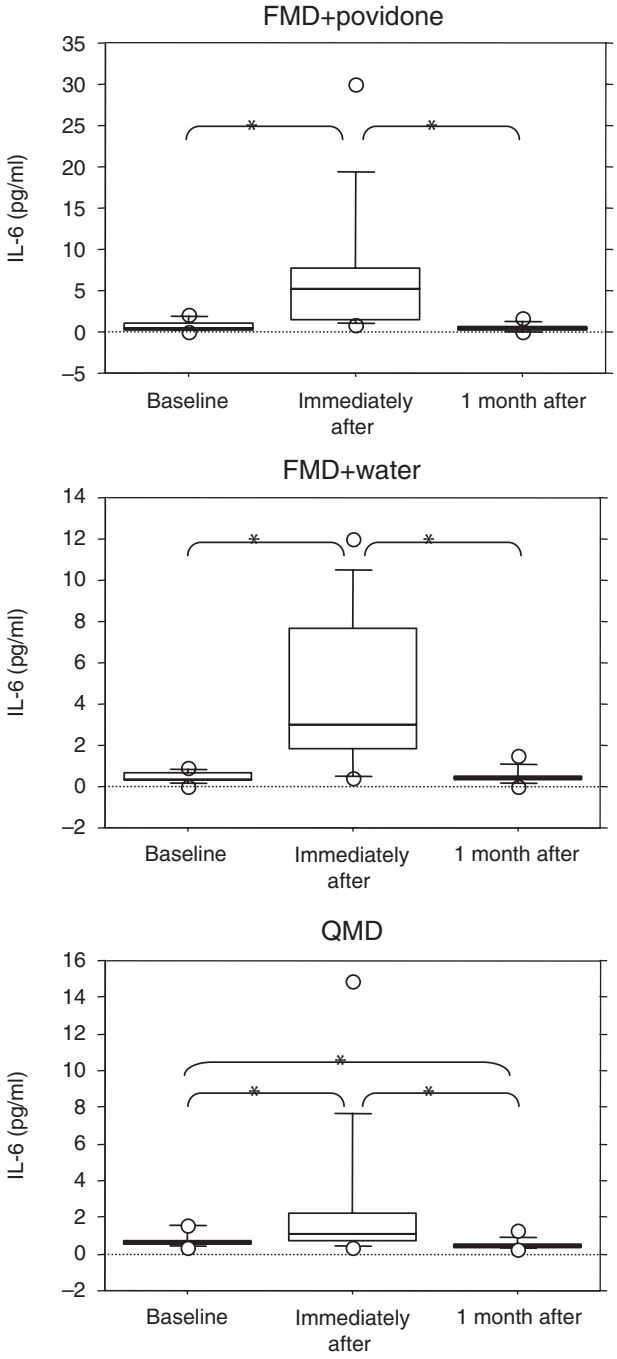

Fig. 2. Serum interleukin (IL)-6 concentration at baseline and after subgingival debridement: FMD+povidone, full-mouth mechanical debridement with povidone; FMD+water, full-mouth mechanical debridement with water; QMD, quadrant-wise mechanical debridement. Box plots show medians with 25th and 75th percentiles, whiskers represent 10th and 90th percentiles. Outlying values are shown as open circles. $^{*}p<0.05$ (Wilcoxon's signed-rank test).

Results

Serum IL-6 levels

Serum IL-6 levels at baseline (before treatment), immediately after treatment and 1 month after FMD and QMD are shown in Fig. 2. In the FMD+povidone group, serum IL-6 was significantly elevated immediately after treatment and reduced to the baseline level at 1 month after treatment. In the FMD+water group, serum IL-6 was also significantly elevated immediately after treatment, and it reduced to the baseline level 1 month after treatment. There were no significant differences between IL-6 levels at baseline and 1 month after treatment in the FMD+povidone and FMD+water groups.

Serum IL-6 in the QMD group was also significantly increased immediately after treatment, and it was significantly decreased at 1 month after treatment compared with baseline. The increase in serum IL-6 in the FMD+water and FMD+povidone groups immediately after treatment was greater than that in the QMD group.

Serum CRP levels

Serum CRP levels at baseline, immediately after treatment and 1 month after

FMD and QMD are shown in Fig. 3. In the FMD+povidone group, serum CRP levels did not differ significantly among the serum samples collected at baseline, immediately after treatment and at 1 month after treatment. Serum CRP levels also did not differ significantly among the three assessment points in the FMD+water and the QMD groups.

Serum soluble thrombomodulin levels

Serum soluble thrombomodulin levels at baseline, immediately after treatment and 1 month after FMD and QMD are shown in Fig. 4. In the FMD+povidone group, serum-soluble thrombomodulin levels were significantly decreased immediately after treatment, and they returned to the baseline level 1 month after treatment. In the FMD+water group, serum soluble thrombomodulin levels were significantly decreased 1 month after treatment compared with baseline. However, serum soluble thrombomodulin levels did not differ significantly among the three assessment points in the QMD group.

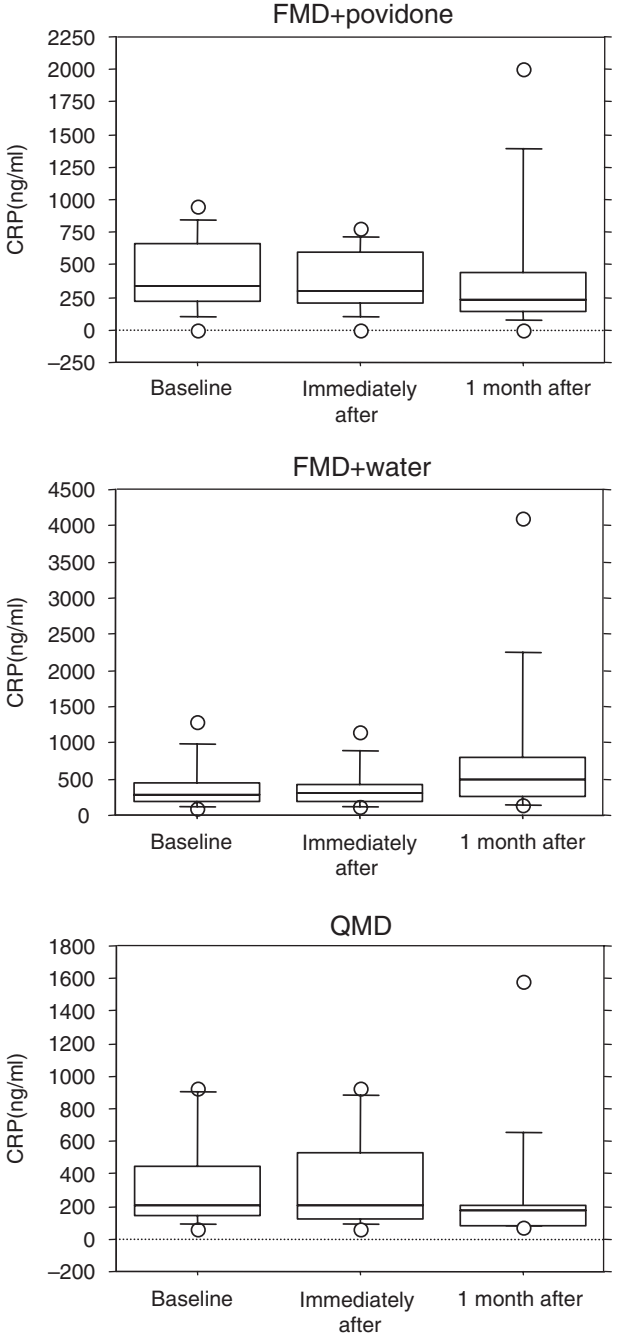

Fig. 3. Serum C-reactive protein (CRP) concentration before and after subgingival debridement: FMD+povidone, full-mouth mechanical debridement with povidone; FMD+water, full-mouth mechanical debridement with water; QMD, quadrant-wise mechanical debridement. Box plots show medians with 25th and 75th percentiles, whiskers represent 10th and 90th percentiles. Outlying values are shown as open circles.

Discussion

In the present study, serum IL-6 levels were significantly increased immediately after treatment in the FMD+povidone and FMD+water groups. The increase in serum IL-6 levels following debridement was smaller in the QMD group than in the FMD groups, but the differences were not statistically significant. Although we had collected blood samples soon after FMD, there was an interval of approximately 5 h between the initial blood sampling and the sampling after treatment (Koshy et al. 2005, Wang et al. 2006). Several investigators have found increased plasma IL-6 levels in patients with unstable angina, raising the possibility of IL-6 as a prognostic marker of cardiovascular disease outcome (Biasucci et al. 1999, Lindmark et al. 2001). Hence, elevation of serum IL-6 following FMD might increase the risk of cardiovascular events in periodontitis patients with cardiovascular disease. Alternatively, it is also possible that QMD may induce a stronger effect on systemic vascular endothelial functions than FMD, as QMD result in more frequent elevation of IL-6. In the present study, all the subjects were systemically healthy, and serum IL-6 returned to baseline levels 1 month after treatment. This transient elevation of IL-6 after periodontal treatment is consistent with the results of previous studies using healthy subjects (Ide et al. 2004, Forner et al. 2006b).

In the FMD+povidone and FMD+water groups, a significant reduction in serum soluble thrombomodulin levels was observed. In systemically healthy subjects, low levels of soluble thrombomodulin have been associated with an increased risk of coronary artery disease and brain infarction (Olivot et al. 2004). In contrast, increased soluble thrombomodulin has been associated with recurrence in coronary artery disease patients (Blann et al. 1997). Soluble thrombomodulin, which acts as a natural anticoagulant, is thought to reflect thrombomodulin

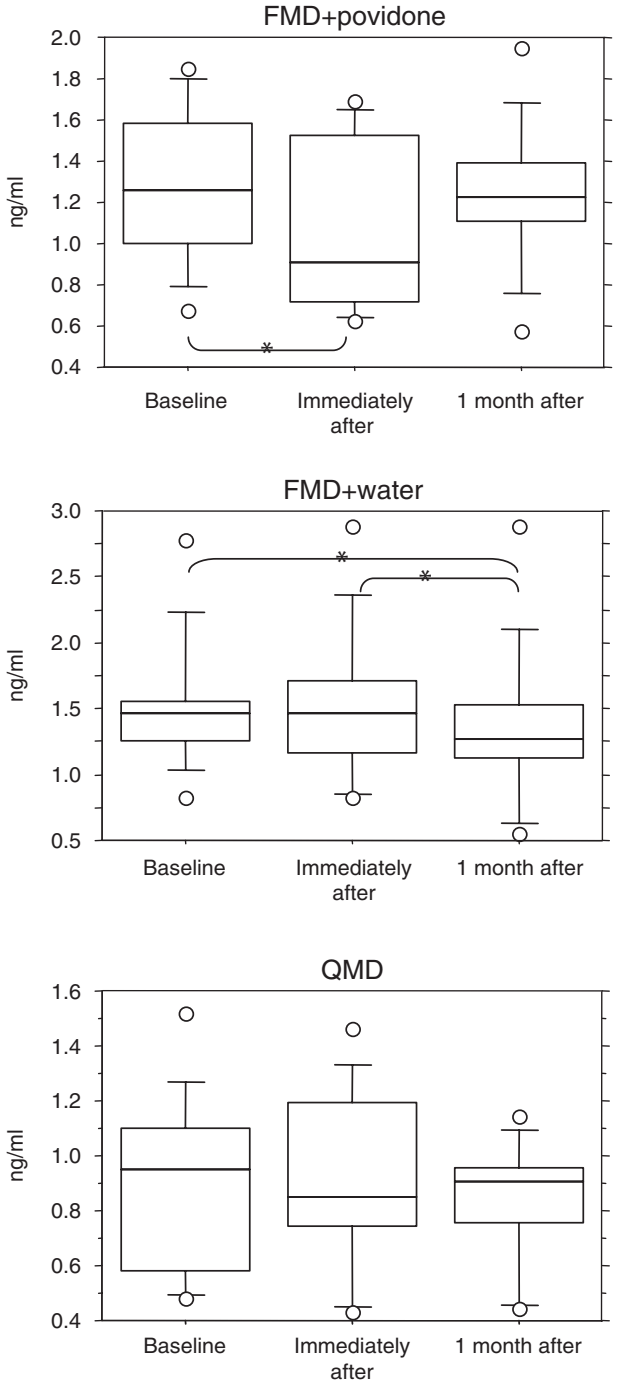

Fig. 4. Serum soluble thrombomodulin concentration before and after subgingival debridement: FMD+povidone, full-mouth mechanical debridement with povidone; FMD+water, full-mouth mechanical debridement with water; QMD, quadrant-wise mechanical debridement. Box plots show medians with 25th and 75th percentiles; whiskers represent 10th and 90th percentiles. Outlying values are shown as open circles. $^{*}p < 0.05$ (Wilcoxon's signed-rank test).

expression on the surface of endothelial cells in healthy individuals; however, it may also reflect the disease extent in patients with cardiovascular disease (Constans & Conri 2006). As the subjects in the present study were systemically healthy, decreased soluble thrombomodulin might be associated with reduced expression of thrombomodulin on endothelial cells. Endotoxin, IL-1 and TNF stimulate endothelial cells to internalize and degrade thrombomodulin expressed on their surface, and these substances also suppress transcription of the thrombomodulin gene within endothelial cells (Moore et al. 1987, 1989, Conway & Rosenberg 1988). As subgingival debridement induces transient bacteremia and release of inflammatory cytokines, the decrease in soluble thrombomodulin in the FMD+povidone and FMD+water groups might imply the internalization and degradation of thrombomodulin by endothelial cells following FMD. Tonetti et al. (2007) reported that vascular endothelial function was significantly lower in a periodontal treatment group than in a control group 24 h after treatment and that levels of CRP, IL-6, and the endothelial-activation markers soluble E-selectin and vWF were significantly higher in the periodontal treatment group. The endothelial damage following subgingival debridement in their study supports our hypothesis that the decrease in soluble thrombomodulin in the FMD groups might be caused by endothelial damage. The significant reduction in soluble thrombomodulin in the FMD groups suggests that damage to vascular endothelial cells is greater in FMD than in QMD. The patients were randomly allocated to each treatment group, and the baseline IL-6, soluble thrombomodulin and CRP were not significantly different among each groups. However, baseline IL-6, soluble thrombomodulin and CRP differed among groups, presumably due to the small sample size in this study. A further large-scale study might be necessary to exclude the possibility that significant differences between QMD and FMD groups could be attributed to differences in patients at baseline.

CRP is considered the major acute-phase reactant in humans, and IL-6 acts as the principal inducer of hepatic CRP synthesis. Elevated CRP level is a strong determinant of the risk of coronary heart disease, stroke, and peripheral arterial disease (Rattazzi et al. 2003). In the present study, serum CRP levels remained unchanged before and after debridement in both FMD groups. However, Yamazaki et al. (2005) have suggested that the distribution of serum CRP level is highly skewed toward lower levels in the Japanese population when compared with Western populations, and it might therefore be difficult to measure fluctuations of serum CRP in the Japanese population. A recent systematic review of CRP in periodontitis showed that periodontal therapy can lower the levels of CRP (Paraskevas et al. 2008). It is of note that the

reduction in serum CRP was greater in systemic or local antibiotics with standard periodontal treatment (intensive periodontal treatment) compared with standard periodontal treatment (D'Aiuto et al. 2005, 2006). As no antibiotics have been administered in this study, decrease of CRP did not reach statistical significance.

Serum IL-6 and CRP levels did not differ significantly between the two FMD groups, suggesting that use of povidone iodine, tongue brushing and rinsing with CHX did not effectively reduce systemic effects of FMD. This finding is supported by a previous report that irrigation with a 0.12% CHX gluconate mouth rinse did not affect the incidence of bacteremia after scaling and root planing (Lofthus et al. 1991). In addition, Quirynen et al. (2000) reported fever following FMD treatment both with and without antiseptics. These findings suggest that antiseptics have a limited role in suppressing bacteremia and systemic immune responses.

The present study suggested that FMD causes a transient elevation in serum IL-6 and decrease in serum-soluble thrombomodulin, and that these changes are more pronounced after FMD than after QMD. Accordingly, FMD appears to have a greater effect on systemic vascular endothelial functions than QMD, while QMD might repeatedly induce smaller amount of serum IL-6 than FMD in periodontitis patients. Although these systemic effects of subgingival debridement are unlikely to have serious consequences in systemically healthy subjects, caution should be exercised when using FMD or QMD in periodontitis patients with cardiovascular disease. Further investigations are necessary to determine the risks and benefits of FMD in periodontitis patients who are at increased risk of cardiovascular events.

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Clinical Relevance

Scientific rationale for the study: With emerging evidence of association between periodontitis and cardiovascular disease, it is important to clarify the effect of various periodontal treatments on systemic inflammatory markers.

Principal findings: Both single-visit FMD and QMD caused transient elevation of IL-6. Soluble thrombomodulin decreased following FMD.

Practical implications: FMD might induce higher serum IL-6 production than QMD and reduce soluble thrombomodulin levels in periodontitis patients. QMD might repeatedly induce smaller amount of serum IL-6 in periodontitis patients.