The effects of silorane composites on levels of cytokines and periodontal parameters

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Abstract

Aims: The purpose of this pilot study was to determine the effects of silorane composites on gingival crevicular fluid (GCF) levels of tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6) and IL-8, GCF volume and clinical periodontal parameters in patients with silorane composite restorations before and after restorative treatment. Materials and Methods: A total of 20 systemically healthy non-smokers, 12 female and 8 male (age range: 24-46 years), presenting with 25 instances of primary dentine caries with subgingival margins were selected for this study. Approval was obtained from the university ethics committee and treatment plans were approved by the patients. GCF samples were obtained with periopaper strips from relevant teeth for IL-6, IL-8 and TNF-α measurements. Each sample was stored at – 80°C and analyzed using the enzyme-linked immunosorbent assay (ELISA) kits. Cavities were prepared according to the common principles for adhesive restorations and restored with a silorane adhesive system (Silorane System Adhesive (3M ESPE) and silorane composite (Filtek Silorane, 3M ESPE). Cytokine levels were reassessed 2 weeks after restorative treatment. Data were analyzed using the independent t-test at a significance level of α =0.05. Associations between parameters were analyzed using Pearson correlation analysis. Results: A significant increase in gingival index (GI) and plaque index (PI) were observed after 15 days (P < 0.05). GCF volume, IL-6, IL-8 and TNF-α levels exhibited significant differences before and after restorative treatment (P < 0.05). There were strong positive correlations among parameters except for PI/GCF volume and GI/GCF volume. Conclusion: Within the limitations of this investigation, silorane composites may have some negative effects on cytokine levels, clinical parameters and GCF volume.

Keywords: Class II restorations, cytokine, gingival crevicular fluid, gingival index, plaque index, silorane based resin composite

Introduction

Cytokines are low molecular weight proteins synthesized in response to bacteria and their products, inducing and maintaining an inflammatory response. The presence of a large number of cytokines in gingival crevicular fluid (GCF) has been proposed as a potentially useful diagnostic or prognostic marker of periodontal destruction. Various proinflammatory cytokines, such as interleukin (IL-1), IL-8, IL-6 and tumor necrosis factor alpha (TNF-α), have been the most commonly studied in the GCF, gingival tissue and serum of healthy, gingivitis and chronic periodontitis patients.

Resin composites are used frequently, in all cavity classes, owing to their esthetics and tooth material saving preparation technique. They contain a wide variety of monomers and additives, which can be released because of non-optimal conversion and degradation. Certain components of the composites are known to release monomers due to incomplete polymerization and also by naturally occurring degradation processes in the oral cavity. The monomers have been shown to cause adverse effects in some individuals. There has been discussion whether components released from methacrylate-based composite resins and dentine-bonding agents, the monofunctional monomer 2-hydroxyethyl methacrylate or the bifunctional comonomer triethylene glycol dimethacrylate, for instance, can affect pulp tissues and cells in physiological concentrations.

In the last few years, a new class of low-shrinking composites based on silorane technology (Filtek Silorane, 3M ESPE, Seefeld, Germany) has been introduced. As the resin matrix of the silorane composite differs significantly from that of conventional methacrylate-based composites, a new adhesive needed to be designed and developed. The silorane matrix is formed by the cationic ring-opening polymerization of the silorane monomers. The silorane molecule represents a hybrid made of both siloxane and oxirane structural moieties.
Silorane technology has resulted in a highly hydrophobic restorative material with reduced polymerization shrinkage, more balanced volumetric stress, high ambient light stability and insolubility in biological fluids. Although recent studies have evaluated the physicochemical properties of silorane-based resins, research regarding their biological effects, mostly based on in vitro cell culture studies, has been quite limited. Until date, there are no studies evaluating the in vivo effects of inflammation and the compatibility of these new restorative systems with the connective tissue.

The specific aim of this short-term clinical study was to determine the effects of silorane composites on GCF volume, plaque index (PI), gingival index (GI) and GCF levels of TNF-α, IL-6 and IL-8 not in paranthesis in patients with silorane composite restorations before and after restorative treatment.

Materials and Methods

Patients and study design
A total of 20 volunteers (12 female and 8 male; mean age 38 years, range: 24-46) with 25 Class II subgingival primary dentine caries were selected and the PI, GI and GCF were analyzed before restoration procedure and 15 days after restoration. The Atatürk University Ethics Committee granted ethical approval for each assessment phase. Subjects gave informed consent before participating. Personal information related to subjects’ medical and dental history was obtained using a questionnaire.

Inclusion criteria
At least one Class II decay cavity with subgingival margins, systemically healthy, no use of anti-inflammatory drugs in the 2 months preceding the study, no antibiotic therapy within the previous 6 months, clinically healthy, with generalized probing depths ≤ 3 mm and no radiographic evidence of periodontal bone loss. Exclusion criteria were any form of tobacco consumption, diabetes, immunocompromise, pregnancy and breast-feeding in women, use of orthodontic devices, ongoing dental or periodontal treatment 12 months prior to the beginning of the study or use of antibiotics within 6 months prior to clinical examination or medication that might lead to decreased salivary flow.

Radiographic examination and clinical periodontal assessments, including GI and PI, were performed at baseline and the end of the experiment (15 days later). All patients were motivated and exhibited good oral hygiene techniques.

Periodontal examination and GCF sampling
PI, GI and GCF were analyzed. The same trained examiner (SM) recorded PI and GI at the restorative surface using a periodontal probe. PI and GI evaluation criteria was given in Table 1. Gingival inflammation was assessed by visual inspection and by gentle drawing of a pocket probe along the entrance of sulcus. Plaque was assessed on the experimental surface. The reproducibility of these measurements using k statistics resulted in k - 0.86.

GCF was collected from the mesial or distal surface of relevant teeth, which has Class II decay cavity. After PI was assessed, supragingival plaque was removed and sites to be sampled were isolated with cotton rolls, carefully sprayed with water to remove saliva and finally gently dried with an air syringe. A saliva ejector was used to avoid salivary contamination. A paper strip (Periopaper, ProFlow Inc., Amityville, USA) was inserted intracreviculer 1 mm below the gingival margin and left in place for 30 s. One periopaper strip was used for each parameters the procedure was repeated once more with the second and third strips. Totally 3 paper strips sampled. Later 15 days, GCF, PI, GI were reassessed and the paper strips were then transferred for volume determination to a chairside electronic gingival fluid measuring device (Periotron 8000, Oratflow Inc., Plainview, USA), calibrated using known volumes of phosphate-buffered saline. The paper strips were then immediately placed into three labeled Eppendorf tubes (Microcentrifuge tubes, ISOLAB, Wertheim, Germany) with IL-6, IL-8 and TNF-α containing 300 µl of 0.9% of physiological saline solution, isolated with Parafilm M, (SPI Supplies Inc., West Chester, USA) to avoid evaporation and sent to the laboratory. After 15 min of shaking at room temperature, the strips were removed and the eluates centrifuged (20 min, 3000 × g) to remove plaque and cellular

| Scores | Criteria                                      |
|--------|----------------------------------------------|
| 0      | No plaque in the gingival area               |
| 1      | A film of plaque adhering to the free gingival margin and adjacent area of the tooth. The plaque may only be recognized by running a probe across the tooth surface |
| 2      | Moderate accumulation of soft deposits within the gingival pocket, on the gingival margin and/or adjacent tooth surface, which can be seen by the naked eye |
| 3      | Abundance of soft matter within the gingival pocket and/or on the gingival margin and adjacent tooth surface |

| Scores | Criteria                                      |
|--------|----------------------------------------------|
| 0      | Normal gingiva                               |
| 1      | Mild inflammation: Slight change in color, slight oedema No bleeding on probing |
| 2      | Moderate inflammation: Redness, oedema and glazing. Bleeding on probing |
| 3      | Severe inflammation: Marked redness and oedema. Ulceration. Tendency to spontaneous bleeding |
elements. The samples were stored at −80°C for subsequent assays. The procedure was repeated at baseline and 2 weeks after placement of the restorations.

Cavity preparation and restoration
Class II cavities for silorane composite restorations were prepared in accordance with adhesive cavity principles. Preparation was limited to the removal of decay, preserving the sound tooth structure. Rubber dam isolation was used for each patient. The adhesive Silorane System Adhesive (3M ESPE) with the silorane composite Filtek Silorane (3M ESPE) was then applied, strictly according to the manufacturer’s instructions [Table 2].

Analysis of cytokine production
Cytokine assay levels of IL-6, IL-8 and TNF-α in samples were determined using appropriate commercial enzyme-linked immunosorbent assay kits (Biosource, Europe SA, Nivelles, Belgium), again according to the manufacturer’s instructions. The results were read using a microplate reader at a wavelength of 405 nm. Levels of IL-6, IL-8 and TNF-α were expressed as pg/mL. Data were analyzed using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA). The independent t-test was used for analysis at a significance level of α = 0.05. Associations between parameters were analyzed using Pearson correlation analysis.

Results
Clinical parameters and cytokine levels were also evaluated at baseline and 15 days after. GCF volume and GCF IL-6, IL-8 and TNF-α levels (mean ± standard deviation) in all groups are presented in Table 3. The mean GCF IL-6, IL-8 and TNF-α levels and GCF volume values were higher in Group II compared with

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**Table 2: Restorative materials properties which are used in the study**

| Materials | Components (wt%) |
|-----------|------------------|
| Silorane system adhesive | 15-25% 2-hydroxyethyl methacrylate; 15-25% bisphenol a diglycidyl ether dimethacrylate; 10-15% water; 10-15% ethanol; 5-15% phosphoric acid-methacryloxy-hexylesters; 8-12% silane treated silica; 5-10% 1,6-hexanediol dimethacrylate; <5% copolymer of acrylic and itaconic acid; <5% (dimethylamino) ethyl methacrylate; <3% dicamphorquinoxine; <3% phosphine oxide |
| Self-etch primer | | |
| Lot N 285058 3M, ESPE, Seefeld, Germany | Dimethacrylate; <5% copolymer of acrylic and itaconic acid; <5% copolymer of ethyl methacrylate; <3% dicamphorquinoxine; <3% phosphine oxide |
| Silorane system adhesive bond | 70-80% substituted dimethacrylate; 5-10% Silane treated silica; 5-10% triethylene glycol dimethacrylate; <5% phosphoric acid–methacryloxy–hexylesters; <3% dl-camorphoxquinone; <3% (1,6-hexanediol dimethacrylate) |
| Lot. N 285057 3M ESPE | | |
| Filtek Silorane composite | 5-15% 3,4-epoxycyclohexylethylcyclopolyemethylsiloxane; 5-15% bis-3,4 epoxycyclohexylethylphenylmethylsilane; 15-25% 2-hydroxyethyl methacrylate; 15-25% bisphenol A diglycidyl ether dimethacrylate; 20-25% water; 15-25% 1,6-hexanediol dimethacrylate; | | |
| Lot. N 279893 3M ESPE | Camorphoxquinone |

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**Table 3: Clinical and laboratory measurements mean and standard deviation values and independent t test results before and after restorative treatment**

| Periodontal parameters/cytokines | Before restoration | After restoration | P |
|---------------------------------|-------------------|------------------|---|
| PI                              | 0.60±0.44         | 1.38±0.6         | 0.05 |
| GI                              | 0.56±0.42         | 1.41±0.84        | |
| GCF (µL)                        | 0.13±0.02         | 0.17±0.03        | |
| TNF-α (pg/mL)                   | 5.38±0.25         | 7.15±0.7         | |
| IL-6 (pg/mL)                    | 71.69±15.8        | 131.9±17.4       | |
| IL-8 (pg/mL)                    | 525.0±78.35       | 1251.3±72.94     | |

**Table 4: The parameters’ Pearson correlation coefficients (r values) between TNF-α, IL-6, IL-8, GCF volume, PI and GI**

| Parameter | TNF-α | IL-6 | IL-8 | GCF volume | PI | GI |
|-----------|-------|------|------|------------|----|----|
| TNF-α     | 0.688**| 0.823**| 0.542**| 0.508**| 0.448**|
| IL-6      | 0.686**| 0.824**| 0.479**| 0.430**| 0.503**|
| IL-8      | 0.823**| 0.824**| 0.519**| 0.617**| 0.560**|
| GCF volume| 0.542**| 0.479**| 0.519**| 0.80* | 0.256*|
| PI        | 0.508**| 0.430**| 0.617**| 0.80* | 0.567**|
| GI        | 0.448**| 0.503**| 0.560**| 0.256*| 0.567**|

**P<0.05; **P>0.05. PI: Plaque index; GI: Gingival index; GCF: Gingival crevicular fluid; TNF-α: Tumor necrosis factor alpha; IL: Interleukin**
Group I \((P < 0.05)\) Table 4 shows the correlations between GCF cytokine levels and GCF volume in the groups. There was a strong positive correlation between GCF cytokine levels and GCF volume in both (Groups I and II) \((P < 0.05)\). A strong positive correlation was observed between the parameters, except for PI/GCF volume and GI/GCF volume parameters. The levels of TNF \(\alpha\), IL-6 and IL-8 in GCF were significantly different between Groups I and II \((P < 0.05)\). Graph of change in the parameters shown in Figures 1-6.

**Discussion**

Low-shrinkage silorane resin composites have been developed as an alternative to conventional methacrylate-based resin material. Silorane technology is a highly hydrophobic restorative material with lower volumetric shrinkage and insolubility in biological fluids.\[13\] The biological properties of these new materials require discussion, as well as their physical properties. This clinico-biochemical pilot study was designed to estimate the clinical periodontal parameters, GCF volume and GCF levels of cytokines in patients with Class II silorane composite restorations before and after restorative treatment and to evaluate any correlation between these parameters.

Silorane monomers require the potential reactivity of the epoxy group to prevent polymerization shrinkage. \(\text{Oxiranes are reactive molecules and may thus have adverse biological effects on living organisms.}^{[14]}\) However, this can be resolved by a combination of silane and oxirane. Siloranes were developed as a result. From previous toxicological studies, epoxy groups in compounds are widely known to have genotoxic properties. One study which assessed the cell cycle distribution and deoxyribonucleic acid (DNA) damage in the human mammalian cell after exposure to different epoxy monomers showed that oxirane DNA interactions can cause DNA damage, mutations and cancer.\[15\]

Bacteria are able to survive and grow in the complex ecosystem of the microbial plaque. Bacterial products cause the inflammatory reaction and immune response.\[16\] The

**Figure 1:** Alterations in the volume of gingival crevicular fluid (\(\mu\)L) during the experimental period

**Figure 2:** Alterations in the gingival index during the experimental period

**Figure 3:** Alterations in the plaque index during the experimental period

**Figure 4:** Alterations in the total amount of IL-6 (pg/mL) during the experimental period
subgingival restorative margin frequently leads to gingival inflammation, clinical attachment loss and bone loss. This is thought to be due to the destructive inflammatory response to microbial plaque located in deeply buried restorative margins.\[17\] In our study, gingival tissue adjacent to Class II restorations exhibited more plaque retention and a higher GI than the control sides. Paolantonio et al.\[18\] used amalgam, glass ionomer cement and composite resin in the restoration of Class V cavities. Their results suggest that composite resin restorations may have some negative effects on the quantity and quality of subgingival plaque and lead to an increase in the total amount of bacteria. Schätzle et al.\[19\] researched the influence of restoration margins on the periodontal tissues for 26 years and determined that the degree of gingival inflammation adjacent to subgingival restorative margins was greater than that adjacent to the supragingival margin in each control subject. Peumans et al.\[20\] evaluated the effect of 5-6 years old direct composite restorations on marginal periodontal tissues. They reported that these direct composite additions have a negative impact on marginal periodontal health, involving increased plaque retention, gingival inflammation and periodontal destruction.

Different clinical applications are used to collect GCF samples in the literature. The three basic methods involve gingival washing, capillary tubing or micropipettes and absorbent filter paper strips.\[21\] We used paper strips, the most common method, to obtain GCF in the final period. We chose to use paper strips because the technique is easy to use, the sampling time is short and the method can be easily tolerated by the patient. Paper strips were inserted into the gingival sulcus in the interdental area until mild resistance was felt. They were left in place for 30 s in order to avoid mechanical irritation triggering the release of cytokines. Strips contaminated with blood were discarded.\[22,23\]

GCF is an exudate of varying composition found in the sulcus between the tooth and marginal gingiva. The amount of GCF in the healthy sulcus is very low.\[24\] A relationship between GCF and gingival inflammation has previously been reported.\[25\] GCF provides a unique window for the analysis of periodontal condition. Konradsson and van Dijken\[26\] reported that low plaque and gingival indices were observed at the buccal surfaces of calcium aluminate cement and resin composite in individuals with ordinary oral hygiene. After 10 days of undisturbed plaque growth, a greater level of plaque was found on the restauratives compared with the enamel, as well as a tendency to an increase in the contiguous GCF flow. In our study, PI, GI and levels of GCF were also higher after restoration than before restoration.

Cytokines are important mediators of cell functions and make significant contributions to inflammatory responses. Some cytokines, such as IL-1, IL-6, IL-8, IL-12 and TNF, have pro-inflammatory functions, whereas others, such as IL-4, IL-10, IL-11, IL-13 and TGF-β, have anti-inflammatory functions.\[27\] High levels of IL-6 in biological fluids and blood have been determined in infections, trauma, chronic inflammatory disease and neoplasia, in addition, IL-6 may be a useful diagnostic marker for periodontal disease.\[28\] The production of IL-8 in gingival tissues is an important mechanism of polymorphonuclear neutrophils, this being the first step in immune defense.\[29\] Giannopoulou et al.\[30\] reported that periodontal disease is positively correlated with GCF IL-1 β, IL-6 and IL-8 levels. Annsofi et al.\[31\] examined the relationship between stress, plaque, GCF and IL-6. Plaque levels were significantly higher in patients compared to the controls and elevated levels of IL-6 were also determined.

Inflammatory cytokines, such as IL-1 β, IL-6 and TNF-α, have also been reported to be present in low levels in clinically healthy gingival tissues. This means that cytokines are prominently involved in normal tissue homeostasis.\[32\] In an aqueous environment, dental composites absorb water and release unreacted monomers. The release of unreacted monomers from resin composites may stimulate the growth

**Figure 5:** Alterations in the total amount of IL-8 (pg/mL) during the experimental period

**Figure 6:** Alterations in the total amount of tumor necrosis factor alpha (pg/mL) during the experimental period
of bacteria around the restoration.\textsuperscript{[13]} They may favor initiation of gingivitis by facilitating local plaque accumulation and/or, in contrast to healthy tooth tissues, by releasing toxic substances.\textsuperscript{[3]} It may therefore be inferred that fillings act as a foreign object and result in cytokine secretion. This raises the issue of an immune response against the chemical components.

**Conclusions**

Residual monomers are released from dental composite due to degradation processes or incomplete polymerization of the materials. It appears that the effect of this release may depend on the chemical nature of the various materials. The reactive epoxy group of siloranes may play a significant role in producing changes in the oral environment and may have a negative effect on gingival tissue health.

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