Clinical investigation of a new nanohybrid resin composite Venus Pearl in class 2 cavities– a multi-center study

NCT01925040

Study Protocol and Statistical Analysis Plan

Date 15.08.2013

Objective of the study

The objective of this study is to compare the performance of the composite resin Venus Pearl (a development based on the material "Venus Diamond", Heraeus Kulzer, Hanau-Germany) and the commercially available control material Filtek Supreme XTE (3M/ESPE, Seefeld-Germany- available for the study center in Germany) and its equivalent material Filtek Supreme Ultra (3M/ESPE, Seefeld-Germany- available for the study center in the United States) for the restoration of class II-cavities. Primary endpoints of the study are: loss of the restoration, fracture of the restoration, postoperative sensitivity, marginal discoloration and marginal gap or step formation. Secondary endpoints are the evaluation of secondary caries, plaque accumulation and gingival reactions.

Ethics

The study is in accordance with the declaration of Helsinki. The study protocol will be assessed and approved by the ethical committee of Hannover Medical School as well as by the Institutional Review Board of the Oregon Health and Science University (OHSU). Each patient will receive a detailed information leaflet and has to declare in writing her or his consent to participate in the study. This written informed consent can be cancelled by the patient at any time without justification.

Study design

The study will be executed as a multi-center, single-blinded and randomized clinical investigation.

Multicenter, single-blinded, and randomized clinical investigation. Study sites are the Department of conservative Dentistry, periodontology and Preventive Dentistry at the Hannover Medical School, Hannover, Germany, and the Department of Restorative Dentistry at the Oregon Health and Science University, Portland, Oregon, USA. Coordination of the study at both study sites is done by the Hannover Medical School.

General information

Time frame of the study: 2 years (with optional extension to 4 years)

Number of patients/ restorations: 90 comparable cavities per Institution (180 total), randomization

Test material: n=90 (n = 45 per site)

Control material: n=90 (n = 45 per site)

Recruitment of patients

Patients will be recruited by the Department of Conservative Dentistry, Periodontology and Preventive Dentistry of the Hannover Medical School and the Department of Restorative Dentistry of the Oregon Health and Science University (OHSU). Patients who require a class II restoration will be included in the study (see inclusion criteria). Each patient will be eligible to receive up to four restorations, with either a test or a control material. Patients will be given detailed information regarding the study before they are included in the study. Patients will receive an information leaflet and a copy of their signed informed consent form. Patients, who could not follow their examination appointments, will be contacted by phone to arrange a new appointment. Patients who miss three appointments will be classified as "drop-outs", which means that no further appointments will be scheduled for these patients regarding this study.

Inclusion criteria

- Patients should be 18 years and older.
- Study teeth should have an interproximal (Class II) carious lesion or an existing defective class II restoration requiring restorative therapy on premolars or molars.
- The maximum cavity depth determined by the radiograph will be D2 (Tyas classification).
- The teeth included in the study need to have a proximal contact with the adjacent tooth and be in occlusion with the opposing dentition.
- The teeth included in the study should be vital with no signs of pulpal pathology.
- Patients that report brushing regularly without severe gingival inflammation and/or extensive caries.
- Patients should have no allergies or systemic diseases which inhibit the treatment.
- Patients should have voluntary participation and sign a written informed consent form.
- Patients should be willing to participate in the recall/re-examination appointments.

Exclusion criteria

- Simultaneous participation in another study about dental restorative materials.
- Written informed consent form not signed.
- Nonvital pulp / periapical lesion.
- Insufficient oral hygiene despite detailed instructions.
- Pregnancy/ breast feeding before placement of the study restoration.
- Minors.
- Severe malocclusion/ malalignment/ traumatic occlusion/ bruxism.
- Known allergy to any components present in any of the materials that are used for this study.
- Unclear mucosal alterations, e.g. oral lichenoid reactions/lesions.
- Severe medical complications (organ transplants, cancer, immune-compromised, long-term antibiotic or steroid therapy).
- Infectious diseases such as HIV/Aids, Hepatitis, etc.
- Application of bleaching products less than 14 days before placement of the restoration.
- Orthodontic treatment during the study.
- Xerostomia.
- Untreated periodontal diseases.
- Rampant or extensive caries present.
- Systemic diseases with potential oral manifestation.
- Sufficient isolation according to the criteria of adhesive techniques not possible, e.g. application of rubber dam.
- Direct adhesive restoration not indicated.
- Replacement of more than one cusp indicated.
- Dental fears patients.
- Cracked tooth syndrome in study tooth.

Assessment of restorations

Restorations will be assessed by the evaluator per site at baseline (1 week after placement), as well as after 6, 12 and 24 months. Evaluations will be documented within the source data (patient's documentation) and in the Case Report Form (CRF).

Photographs of the teeth will be taken after the cavity preparation and after the restoration has been placed and finished as well as at each evaluation appointment.

If the study will be extended to 4 years, two additional assessments will be done, after 3 and 4 years (36 and 48 months) and patients will be informed of a possible request for recall at years 3 and 4 at the initiation of the study.

The evaluations will be based on the Recommendations for Conducting Controlled Clinical Studies of Dental Restorative Materials, Science Committee Project 2/98 - FDI World Dental Federation (J Adhes Dent 9 (1), 121-147 (2007).

Partial impressions of the study teeth will be taken at baseline and during all subsequent examinations of the restorations with an addition-type silicone material (Flexitime Putty and Correct Flow, Heraeus, Hanau-Germany) and a plastic inlay tray. These impressions will be used to determine the in-vivo wear of the restorations by means of replica using a resin material (DuroCit, Struers, Willich-Germany) by means of scanning electron microscopic-warden images.

Side effects that are associated with the treatment such as local inflammation due to an inadequately placed or polished restoration, and/or oral lichenoid reactions that are in direct vicinity to the study restoration, will be documented in detail and the patient affected will be excluded from the study. In this case, the restoration will be replaced by another material as soon as possible. In addition, a restoration that fractures due to a mechanical failure of the material will also be replaced as soon as possible. It is possible to have an irreversible pulpitis develop after placement of the restoration, as often times happens during routine dental treatment. In this case, the subject will be excluded from the study and will have to continue with the appropriate treatment at the dental office of their choice at their own expense.

Biostatistical analysis

Study design

The goal of this clinical trial is to show that Venus Pearl (a development based on the material "Venus Diamond", Hereaus Kulzer, Hanau – Germany) has a better score than the commercially available control material (Filtek Supreme XTE, 3M/ESPE, Seefeld – Germany and Filtek Supreme Ultra, 3M/ESPE, USA) for the restoration of class II-cavities. Patients older than 18 who show an interproximal (Class II) carious lesion or an existing defective restoration requiring therapy on premolars or molars will be included.

For the determination of the superior outcomes of both fillings a pre-specified evaluation scheme will be used.

The assessment of the replacement will be performed at four time points (1 week, 6 months, 12 months and 24 months after replacement). For the primary analysis the score will be considered 24 months after the replacement.

The primary endpoint will be a mean score calculated as following: There are three aspects to be assessed: aesthetic, functional attribute and biological parameters. For each aspect there are respectively four categories where each has to be assessed on a scale from 1 to 5. Thereby 1 means clinically excellent, 2 means clinically good and 3 means clinically disappointing. This assessment form is given in FDI World Dental Federation (J Adhes dent 9 (1), 121 – 147 (2007)). For each

patient the points of the 12 different evaluation criteria (four categories in the three parts) will be summed up resulting in a score that ranges from 12 to 60.
Secondary endpoints are the evaluation of secondary caries, plaque accumulation and gingival reactions and the comparison of the primary score at week 1, month 6, month 12 and month 24 after restoration. Beside this, the single components of the three categories of the primary endpoints will be compared.

Randomization, stratification and blinding

This is an observer-blind clinical trial, e.g. evaluators will not know the given treatment. Restorations will be distributed evenly between the control and the experimental groups using randomization lists.
The application of the two restorative materials is limited to premolars and molars and to achieve a uniform distribution of both tooth types, stratification with the strata premolar and molar will be performed in the randomization process. In addition randomization will be stratified by center.
Randomization will be performed centrally by the Institute of Biometrics to ensure admission before allocation. The randomization will not be based on patients' names, rather than on a scheduled visit, to avoid problems with patients that do not show up for the treatment.
In order to guarantee an objective evaluation at the different time points, the Case Report Form has separate sections for each evaluation, so that the evaluators only use the form for the present examination. Through this method, the evaluator cannot see which assessment he/she gave during previous examinations. These sections will only have the patient number information.
The treatment allocation and the corresponding patient ID will be kept in a separate file that is inaccessible for operators and evaluators.

Description of the primary analysis and key secondary analysis

In the primary analysis the superiority of Venus Pearl will be investigated. Therefore the primary analysis will be conducted on the ITT population, e.g. in all randomized patients. The missing values will be replaced as described below. For the comparison of the scores of the Venus Pearl and Filtek Supreme group an ANOVA will be performed 24 months after restoration. Here, center, tooth type and treatment will be incorporated as covariables. The study is successful if the 95 % confidence interval for the treatment effect (Venus Pearl – Filtek Supreme) is below 0.
In the secondary analysis, caries (yes/no), plaque accumulation (yes/no) and BOP/ Pocket depths, will be examined with logistic regression models including center and tooth type as independent variables. Sensitivity analysis will be applied using mixed models.
If the study is extended to 4 years, the additional appointments taking place 3 and 4 years after restoration placement (late follow-up) will be evaluated descriptively using the same line as described above for the primary analysis.

Missing values

Missing values may be recorded when patients miss examination appointments. In this case the missing values will be replaced by the "last observation carried forward", where the assessment of the previous examination will be carried over to replace the missing value.