Clinical Comparison of Vital Pulp Capping Restorative Protocols: a randomized controlled double-blind, prospective study
Trial registration NCT02635867
03/28/2016

Study Protocol

Study design: Prospective, randomized, controlled, double-blinded study with three treatment arms.

Sample size: 150 teeth with deep caries of subjects willing and able to return to UIC COD for recall purposes.

Eligibility criteria: Subject must meet the inclusion criteria to participate in the study.

Clinical inclusion criteria:

- Adults in good general health between 18 and 64 years of age;
- Active carious lesions deep into dentin (75% or more of dentin) involving occlusal/incisal and/or proximal surfaces of permanent teeth;
- Absence of clinical symptoms of irreversible pulpitis (spontaneous pain);
- Absence of periapical pathology, sinus tract, swelling or abnormal mobility;
- Restorable teeth.

Radiographic inclusion criteria:

- Extension of carious lesion close to potential exposure upon excavation (within the D3 region – lesion extending 2/3 within dentin); with the presence of a well-defined radiodense zone between the lesion and the pulp.
- Absence of periapical radiolucency;
- Absence of thickening of the periodontal ligament PDL;
- Absence of resorptive defects;

Exclusion criteria:

- Non restorable teeth;
- Teeth with:
    - Recent trauma (within 6 months);
    - Calcified root canals;
    - Periapical radiolucency;
- Patients experiencing spontaneous moderate to severe pain;
- Patients that are pregnant or planning to become pregnant in the next year.
- Patients taking analgesics, anti-inflammatory, or antidepressant medications;
- Patients with orthodontic treatment;
- Newly erupted teeth.

Subject management and recruitment process

Recruitment flyers (attachment #1) will be posted in different locations at the University of Illinois at Chicago campus.

Recruitment e-mails and messages will be sent to all the faculty and students attending predoctoral and postdoctoral clinics at UIC College of Dentistry. We will also send recruitment messages to all faculty, staff and students at the University of Illinois at Chicago using campus wide massmail listservs. In addition, medical records will be reviewed to determine subject eligibility.

Those subjects who will volunteer to participate will be asked to contact via phone the principle investigator or study coordinator, to comply with the inform consent process (attachment #3 – phone call script).

Once patients have been properly screened and approved for the study, the selection of the treatment that they will receive will be carried out randomly, using random integer generator (www.random.org/integers/). Teeth of subjects will be first stratified into those needing indirect pulp capping and direct pulp capping. Based on stratification, subjects will be randomized to one of three arms (indirect pulp capping) or one of two arms (direct pulp capping). Patients will be blinded to the treatment.

Subjects will be compensated in cash for their participation in the study.

Clinical Protocol:

Operators' calibration

The study will be carried out in the UIC College of Dentistry, Clinical Research Center. The investigators will be calibrated for case selection using bitewing and periapical radiographs representing different lesion depths. Initial radiographs will be evaluated independently for root maturity, bridge formation, and periradicular status by two examiners blinded to the technique, with forced consensus in cases of disagreement.

All restorative procedures will be performed by three calibrated clinicians, who will use the 3 different lining/sealers materials in equally distributed subjects.

Study schedule:

The principle investigator or study coordinator will be the initial contact. Potential subjects will be approved for screening through a brief interview and intraoral examination.

- **Screening appointment**: A screening appointment will be scheduled and potential subjects will be approved after a thorough interview and intraoral and x-ray examinations. Each subject will be provided with a written consent form to read and attest with his or her signature. Patients will be assured of the privacy of their data and will receive a 3 digit number ID. All data collected will be saved in password protected computer in the principal investigator office, room 531A (key access only). The screening process will include medical and dental history, demographics, current/concomitant medication, oral soft and hard tissue examination, and a review of all inclusion and exclusion criteria (attachment # 5 and 6). Pregnancy test will be provided to childbearing women subjects at screening appointment to rule out pregnancy (to meet inclusion/exclusion criteria). The pregnancy test to be provided is First Response Pregnancy Test Stick (Church & Dwight Co. Inc).
- Subjects who are found eligible through the screening process will be evaluated preoperatively through a periapical and bitewing radiographs **(Figure 1).** The penetration of the lesion will be assessed in the bitewing radiograph according to the inclusion criteria. To obtain period-identical x-rays, a specific film holder (Super-bite; Kerr) Rinn XCP film holder will be used. An acrylic resin (Duralay) pattern will be fabricated for each subject on the biteblock of the film holder to be able to reposition it when taking follow up radiographs. Also baseline pain assessment will be recorded via visual analogue scale (VAS); and pulp vitality assessment, using palpation, cold, percussion, and EPT tests, will be completed. Data will be collected in a form (attachments #7) and inputted into a secure, web-based Research Electronic Data Capture (REDCap) application.

- **Clinical intervention**: As for any dental appointment for caries removal, the patient's medical history will be reviewed, vital signs will be taken, and standard procedures for caries removal and restoration will be done. These include local anesthesia and rubber

dam isolation. The caries will be accessed aseptically with conventional burs and high speed hand piece instruments.

- These preliminary procedures will be the same for direct and indirect pulp capping therapies. Three restorative protocols will be investigated in indirect pulp capping cases (see below protocols A, B, C) and two restorative protocols will be investigated for direct pulp capping (see below: protocol A and B). The protocol C is not indicated for direct pulp capping.
- Treatment protocols will be randomized and the subjects will be treated as follow:
    - Protocol A: Use of an intermediate layer of TheraCal LC between cavity floor and adhesive system/resin composite. Theracal LC will be applied directly to the cavity floor in increments of 1mm thickness. The layer will be light cured for 20 seconds, as recommended by the manufacturer's instructions.
    - Protocol B: Use of an intermediate layer of Dycal between cavity floor and adhesive systems/resin composite. Base and accelerator pastes will be equally dispensed, mixed, and immediately applied at the deepest portion of the preparation following manufaturers instructions. A thin layer of conventional glass ionomer (Vitrebond – 3M ESPE) will be applied over the Dycal and light cured for 30s as recommended by the manufacturer.
    - Protocol C: No placement of an intermediate material between cavity floor and adhesive system/resin composite.
- Following the above procedure, every tooth, regardless of the above protocol, will be restored following the traditional steps for resin composite restorations. The remaining enamel of the cavity wall will be selectively etched with Bisco's Select HV Etch. The acid will be rinsed thoroughly and excess water will be removed with high suction and/ or cotton pellets leaving the preparation visibly moist. Two separate coats of adhesive (All-Bond Universal) will be scrubbed into the preparation with a microbrush for 10-15 seconds per coat. The excess solvent will be evaporated and the adhesive will be light cured for 20 seconds.
- Resin composite (Aelite LS Posterior, Bisco) will be used incrementally (3-5 increments) to fill in the remaining cavity and each increment will be cured for 40 seconds. Patient's occlusion will be checked and adjusted if needed. Once patient is satisfied with the restoration, a bitewing radiograph will be taken as a baseline post-treatment documentation of the restoration and remaining dentin thickness (layer of dentin between the restoration and the pulp). Once the restoration is complete and the patient is satisfied, a bitewing radiograph will be taken. All subjects will be given post-operative instructions (attachment #5) and the following appointment will be scheduled. Post-operative instruction will be given to the patient.
- **Phone call follow up: 24h and 1 week:** Subject will be reached ~~interviewed~~ by phone (script) 24 hours and one week after the intervention to remind them to complete the pain assessment form. Electronic (via REDCap) or printed forms (with pre-stamped envelopes) will be provided to the subjects. Survey will ask the patient to assess their pain using the visual analog scale (attachment #8).
- **Follow up appointments at 3 months, 6 months, and 12 months after procedure:** At 3 months, only a clinical examination will be completed. At 6 and 12 months, periapical and bitewing radiographic evaluation will be performed for research purposes. Pulp vitality and

pain will be assessed at each follow up appointment using the respective forms. All gathered data will be inputted into the REDCap application. Pregnancy test will also be provided to childbearing women subjects at 6 months follow up (where x-rays will be taken for research purposes) and 12 month follow-up (where x-rays will be taken for research purposes). If pregnancy is detected during the trial, the subject will be immediately removed from the study**.**

All subjects will attend the College of Dentistry for a total of 5 times of approximately 1-2 hours each in a one year period for an approximate 6 hours. There will be a screening appointment for data collection and review inclusion and exclusion criteria for subject selection. The next appointment will be the intervention, where the patient's decayed tooth selected for the study, will be treated and restored. Treatment will be randomly assigned to each subject. The 3, 6 and 12 months appointments will be follow up appointments for data collection. (See above for further details of each appointment). On each appointment, medical history will be updated and oral examination will be performed.

Evaluation methods protocol

Clinical outcome measures will be carried out at the day of restorative procedures followed by 7 days, 3 month, 6 months, and 12 months following restoration placement (attachments 7 and 8).

1- Pulp Vitality Tests

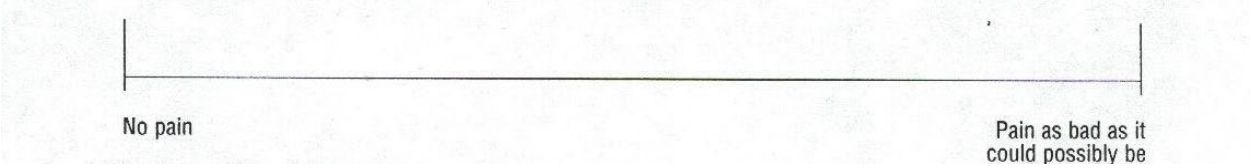
- Palpation test: finger pressure will be applied to the buccal and lingual mucosal areas adjacent to the root apices attempting to locate spots tender or painful to the patient.

- Cold test: cotton pellet will be sprayed with a refrigerant (Endo-Ice, Coltène Whaledent, Cuyahoga Falls, Ohio) and placed it on the crown of the tooth for approximately 15 seconds or until the patient raises a hand to indicate that s/he felt a cold sensation and with a two minutes interval between different tests.

- Percussion: will be done using the blunt end of an instrument applying light and gentle pressure on the teeth. The teeth should be first percussed occlusally and then if not difference is discerned, the test should be repeated, percussing the buccal and lingual aspects of the teeth.

2- Pain assessment using VAS scale

The **visual analogue scale** (**VAS**) is a psychometric response scale which is considered to be one of the best methods available for the estimation of the intensity of pain. The VAS provides a continuous scale for magnitude estimation of characteristics or attitudes that cannot be directly measured. When responding to a VAS, respondents specify their level of agreement to a statement by indicating a position along a continuous line between two end-points.



VAS is considered preferable to discontinuous methods, such as numerical and verbal rating scales. The main advantage of VAS has been claimed to be a high degree of 'sensitivity'. Indeed, it has a discriminating capacity superior to that of the numerical and verbal rating. In the present study, all the subjects will be asked to answer one question tracing a line on a hard copy visual analogue scale which will range from 0 to 10 (0 = no pain / 10 = pain as bad as could be). The question at the top of the visual analogue scale will be: "In a scale from 0 to 10 how would you define the pain relative to this particular tooth? Please draw a line". There will be a pain assessment at the baseline (during the initial exam), 7days, 3 months, 6 months, and 12 months (during the follow-up appointments). Each score will be kept in an excel file document and will not be shown to the subject at the time of the other pain assessments. All the data from the visual analogue scale will be classified and analyzed for statistical significance.

3- Radiographic outcome measures:

The criteria used to determine a successful radiographic outcome of the indirect pulp capping treatment is: (1) absence of interradicular or periapical radiolucencies, (2) absence of increased PDL space, (3) absence of resorptive defects all determined by periapical and bitewing radiographs. Radiographic assessment will be made through bitewings and periapical radiographs the day of intervention followed by the 6 and 12 months recalls as part of regular assessment and to collect research data. Teeth that present with clinical or radiographic signs or symptoms of irreversible pulpitis or necrosis will be assessed by an endodontist for proper endodontic treatment. Patient may be subjected to additional x-rays following pulp capping therapy for proper diagnosis of complications from treatment.
Radiographic research data collection: As part of research data collection, attempt will be made to assess changes to the remaining dentin thickness between recall appointments. To obtain period-identical x-rays, a specific film holder (Super-bite; Kerr) Rinn XCP film holder will be used to take bitewings. Software program (Dexis) will be used to measure digitally the remaining dentin thickness in 5-8 areas. The values will be averaged for estimated thickness.

Data handling and Interpretation

Data entry and database management will be done in an ongoing manner by project staff. All data will be entered in a timely manner once collected. The database will be password protected and housed in a secure location. The database will be backed up on a regular schedule with backup copies stored in a separate location from the primary file server. Quality of data entry will be enhanced by double entry data forms with field and range validation. Project management tools include graphical interfaces for tracking timeliness of data entry, missing data, graphical reports of actual recruitment versus recruitment goals on a real-time basis (i.e., updated as each participant is entered into the system), and other reports. The goal is 100% data accuracy.

Data and/or information which identifies the subject and the signed consent form may be looked at and/or copied for evaluation of the research protocol by: UIC Office for the Protection of Research Subjects, State of Illinois Auditors, State of Illinois Auditors and the research sponsor (Bisco Dental Products).

Statistical Analysis Plan: Descriptive data and rates of success will be calculated independently for indirect and direct therapies. Statistical analyses of proportions will done using Fisher's test and 95% confidence intervals (CI).