Nanodiamond Modified Gutta Percha (NDGP) Composite for Non-surgical Root Canal Therapy (RCT) Filler Material

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Summary:

Non-surgical root canal therapy (RCT) represents a standard of treatment that addresses infected pulp tissue in teeth and protects against future infection while preserving the tooth for the patient. RCT involves removing dental pulp comprising blood vessels and nerve tissue, followed by the placement of filler material to occupy the naturally occurring space where the pulp was removed. Currently, standard of care treatment for RCT utilizes gutta-percha (GP) as the root canal filling material. Tooth extraction is necessary if the RCT fails or if the tooth fractures. The need for extraction after failed RCT might be reduced by increasing the strength of the canal filling material closer to that of dentin. Nanodiamonds (NDs) may offer unique advantages due to their favorable properties, particularly for dental applications. In this prospective pilot study, we will utilize gutta-percha modified with nanodiamonds 5 wt % (NDGP) as the root canal filling material. Our research group has previously demonstrated NDGP's improvement in tensile strength compared to those of gutta-percha. We hypothesize that NDGP will not have a negative effect on clinical outcome for the patient compared to the GP. Additional potential positive benefits include decrease in void space and better clinician handling of NDGP during the canal filling procedure. NDGP with its increased mechanical properties, potential decrease in void space between the NDGP and the tooth's root, and the ease of handling by clinician of NDGP during vertical obturation procedure may result in a decrease in the pain experienced by the NDGP patients compared to those experienced by the control (GP) patients. Patients will be recruited and randomized into two RCT filler material patient groups for this study: 15 patients for the control, 15 patients with NDGP. For all the patients into the control arm of the study, the root canals will be filled with GP at the bottom third up to and including the top third, using a standard procedure involving vertical condensation obturation. For all the patients into the treatment arm of the study, the root canals will be filled with GP at the bottom third, NDGP in the middle third, and again with GP at the top third, using the vertical condensation obturation technique. The tooth will be restored with a crown for posterior teeth, or a composite filling for anterior teeth. There will ideally be a total of four visits: consultation appointment (~1 hour), RCT appointment (~2-3 hours), 6 month follow-up appointment (~1 hour), and 1 year follow-up appointment (~1 hour). Additional follow-up appointments (~1 hour) prior to the 6 month and 1 year follow-up appointments may be required in the event of infection or persistent pain of the root canal. Patient data will be categorized by age, weight, gender, and use of other drugs which may alter the pain assessment and pilot study success indicators. This study investigates a new type of filler, gutta-percha modified by the addition nanodiamond material (NDGP), which may be stronger and prevent complications of RCT such as tooth fracture to improve treatment outcomes.

Study Protocol:

Dr. Kang will recruit the patient for this study after the patient's referral to the UCLA endodontics department for root canal therapy. Informed consent will be obtained by Dr. Kang from all the patients that will be able to be taken home for patients to consider being part of this pilot study. We will stress to the patient that there will be an intended benefit and that we will be providing an incentive for joining this study (parking vouchers). The sample population will be screened and collected Dr. Mo Kang, M.S.,

Ph.D., D.D.S. All of the patients must be over 18 years of age when the treatment commences. Teeth will be excluded from this study if they had preoperative periodontal disease, prior non-surgical and surgical endodontic treatment, or if the apex/apices under investigation is/are not discernible in any of the periapical radiographs. The teeth that will be excluded from the analysis of the 'periapical status following treatment' are if: (1) they were not followed-up for at least 6 months, (2) if they were extracted for reasons not related to endodontic problems (for e.g. periodontal disease), (3) information on the periapical status during the time of extraction was not available.

Patients will be excluded if they are currently taking medications used to treat osteoporosis or currently taking any form of IV bisphosphonates, allergic to dental materials, have dental phobia, have MD consult/medically compromised/prophylaxis needed, have any developmental/congenital disorders, have mentally unstable/psychological issues, have any craniofacial disorder/syndromic cases or have a low pain tolerance/inquire about past dental experience. Patients will be also excluded if they had any of the following periodontal complications: current moderate to severe periodontitis (history is ok), greater than 4mm pocket depths, mobility of the tooth, furcation involvement, less than 4 month recall status, periodontal surgery needed and poor periodontal diagnosis around tooth of concern (ie. tooth may need to be extracted). Patients will also be excluded if they had any of the following restorative complications: tooth is non-restorable, has severe abfraction, has severe attrition, severe bruxism or history of severe bruxism and insufficient tooth structure (ie. post is needed). Patients will be excluded if they have any of the following endodontic complications: endodontic treatment needed on third molars, open apices, complicated root canal anatomy including sharp curvature, C-shaped canal, pulp stones/calcification, previous RCT/initiated pulp therapy, previous apical surgery, lateral lesion, root fracture, severe crown fracture (requiring post), perforations, non-endodontic related pathology, periapical radiolucency (minimum size to be determined by Dr. Kang), external/internal root resorption and surgical root canal procedure. Patients will be excluded if they have poor oral hygiene, diet, history or current drug use, and complicated dental history.

The main operator will be Dr. Zhangrui Liang, DDS. He is a Resident in the Section of Endodontics. Eric C. Sung, D.D.S. will be an advisor to the study. He is a Professor of Clinical Dentistry and Chair of the Section of Special Patient Care and is the Vice Chair of the Division of Advanced Prosthodontics. Dr. Sung is the Program Director of the General Practice Residency Program at UCLA. He also received his undergraduate at UC Berkeley, and he received his dental and GPR degrees from UCLA.

Primary root canal treatment will be provided to teeth that did not have prior non-surgical and surgical endodontic treatment. Standard principles of primary RCT consistent with the American Dental Association Guidelines will be followed, and the treatment protocol will be consistent with UCLA Department of Endodontics treatment protocol. All treatments will be performed under both local anesthesia and rubber dam isolation to ensure absence of saliva leakage. Sodium hypochlorite solution will be used as an irrigant during the whole procedure. The location of the apical terminus will be aided by an electronic apex locator. The initial working length will be determined by taking a radiograph with the diagnostic file placed at the maximal extent achievable with the smallest file. The initial size of the file (recorded as Initial Apical File (IAF)) will be

the largest that could reach the radiographic apex without force to ensure good electrical contact and stability when taking the radiograph. The apical instrumentation will be determined by the operator as a distance equal or slightly shorter (<0.5mm) than the working length.

The operator, Dr. Zhangrui Liang, DDS will be choosing his own various types of instruments and techniques for canal negotiation and shaping. The instruments available for use include: (i) K-flex files (Dentsply Maillefer, Ballaigues, Switzerland), (ii) Flex-O-files (Dentsply Maillefer), (iii) Hedström files (Dentsply Maillefer), (iv) GT hand instruments (Dentsply Maillefer), (v) ProTaper hand instruments (Dentsply Maillefer), (vi) rotary GT instrument system (Dentsply Maillefer), (vii) rotary ProFile instrument system (Dentsply Maillefer), (viii) rotary ProTaper instrument system (Dentsply Maillefer) and (ix) rotary K3 instrument system (SybronEndo). The stainless steel instruments will be used in push-pull filing (Abou-Rass et al. 1980), stem-winding (Backman et al. 1992) or balanced-force (Roane et al. 1985) motions. Patency will be maintained during canal shaping and filing by placing a small file of size 8 or 10 passively to 0.5 mm beyond the apex, between each instrumentation step during the canal enlargement. The recommended minimum or optimal apical size of canal preparation is a size 30 with a taper of 0.06.

5.25% Sodium hypochlorite (NaOCl) solution will be the standard root canal irrigant. Root canal preparation cream (Premier, Plymouth Meeting, PA, USA) will be used as an intracanal lubricant if needed. Calcium hydroxide (Ca(OH)2) will be the standard interappointment medicament for teeth with acute pulpitis if removal of pulp tissues at the first visit was incomplete.

Patients will be randomized according to a predetermined order created by Dong Keun and Theodore Kee via Matlab. 30 patients will be assigned a number 1-30 according to the order of recruitment for this study 1 being assigned to the first patient recruited and 30 to the last patient recruited for this study. The randperm(30,15) function will be used to create a list of 15 numbers from the 30 (recruitment order number). This list of 15 numbers (recruitment order numbers) will be the Nanodiamond gutta percha (NDGP) group to receive the NDGP filler material. The remaining 15 numbers will be given the standard of care gutta-percha filler material. This list will be arranged accordingly for the clinicians' reference.

For all the patients into the control arm of the study, the root canals will be filled with gutta percha at the apical third up to and including the coronal third, using the vertical condensation obturation technique, also known as the modified Schilder's warm vertical compaction technique (Van Zyl et al. 2005). The root canal sealer used will be zinc oxide-eugenol (Kerr Corporation, Orange, CA, USA). After the root canal treatment is done, the patient will be treated by Dr. Eric Sung, a general dentist for the restorative aspect of the procedure. Depending on how much tooth structure is left, he will decide which kind of build-up material to use and if a post is needed. The tooth will be restored with a crown for posterior teeth, or a composite filling for anterior teeth.

For all the patients into the treatment arm of the study, the root canals will be filled with gutta percha at the apical third, Nanodiamond gutta percha (NDGP) in the middle third, and again with gutta percha at the coronal third, using the vertical condensation obturation technique, also known as the modified Schilder's warm vertical compaction technique (Van Zyl et al. 2005). The root canal sealer used will be zinc

oxide-eugenol (Kerr Corporation, Orange, CA, USA). After the root canal treatment is done, the patient will be treated by Dr. Eric Sung, a general dentist for the restorative aspect of the procedure. Depending on how much tooth structure is left, he will decide which kind of build-up material to use and if a post is needed. The tooth will be restored with a crown for posterior teeth, or a composite filling for anterior teeth.

The goal is to follow-up all treated teeth 6 months and 1 year post-RCT. Appointment letters will be mailed to the patients 1 month prior to the follow-up dates. Patients, who failed to attend for recall, will be contacted with a personal courtesy call by the study team member (dentist on study team) and a more detailed explanation letter will be mailed to encourage them to attend follow-up appointments. If patients continue to not attend for recall, then the reasons provided by each patient (if provided) will be recorded. Recall appointments can be made as necessary other than the 6-month and 1-year follow-up appointments. Recall appointments will have their own specific form detailing the patient's reason and required procedure. Possible complications will be communicated to the patient prior to the study and will be dealt with on a case by case basis.

Follow-up examination consists of updating the general and endodontic history of the treated teeth upon clinical and radiographic examination. All patients will be interviewed and examined by one individual from the study team to remain consistent and reduce sources of bias from involving multiple individuals. Extraoral examination will be performed, which includes palpation of masticatory, neck and shoulder muscles, lymph nodes, and palpation of the temporomandibular joint for tenderness or any abnormalities. Clinical examination of the treated teeth will be carefully noted in detail, including the following details: (1) tenderness to percussion of the tooth, (2) tenderness to palpation of adjacent soft tissues, (3) presence of sinus tract or abscess, (4) periodontal probing depths around the tooth, (5) type/presence of coronal seal and restoration. Further examination of the restoration will be done and classified into the following three categories: (A) visual or tactile exposure of root filling material, (B) clinical or radiographically detected marginal discrepancy but without visual or tactile exposure of root filling to the oral cavity, (C) satisfactory coronal restoration with good retention and margins.

The radiographs will be taken digitally with size 1 or 2 XDR Digital Intraoral sensors (XDR Radiology, Los Angeles, CA, USA). The images will then be transmitted and analyzed by the XDR program.

If the patient feels persistent discomfort from the treated tooth at follow-up, periapical radiographs at different horizontal angles will be taken to detect any radiolucent pathology that may be superimposed upon the root. If the patient is pregnant at the time of the follow-up appointment, the radiographic examination will be deferred until after delivery.

All the preoperative, immediate post-obturation, and follow-up radiographs will be viewed on the computer screen with the "caries" and "endo" detection feature and magnifying viewer tools in the XDR program as needed. The preoperative periapical status of each root will be classified into three categories: (1) intact periodontal ligament, (2) widened periodontal ligament or (3) periapical lesion. The diameter of the lesion preoperatively and at follow-up was measured using the measuring ruler tool in the XDR program. The diameter for widened periodontal ligament will be recorded as

0.5 mm. The quality of previous treatment will be judged satisfactory if a well-condensed root filling extends to within 2 mm of the radiographic root apex.

Treatment success will be evaluated based on two outcome measurements: (1) absence of apical periodontitis via clinical and radiographic evaluation, (2) tooth survival.

The assessment of treatment success will strictly be defined as absence of pain, clinical signs of inflammation or swelling, and radiographic measures of complete healing (i.e. presence of normal periodontal ligament space, intact lamina dura, etc). A potential consideration for treatment success will also include aspects from the patient such as the absence of pain and/or clinical signs of inflammation or swelling and radiographic measures of complete healing or *incomplete healing* (i.e. reduced size of periapical lesion without normal periodontal ligament space width).

In some of these cases where the failure is not due to an iatrogenic perforation, a secondary RCT, also called non-surgical endodontic retreatment, might be indicated to resolve any pulp tissue that may have been left behind. A secondary RCT may also be necessary if there is failure of primary RCT due to narrow or curved canals were not treated during the initial procedure, complicated canal anatomy went undetected in the first procedure, placement of the crown or other restoration was delayed following the endodontic treatment, inadequate seal during primary RCT and a radiolucency that still persists or expands. Furthermore, a secondary RCT is indicated if any infection from primary RCT causing persistent pain and or periapical lesion seen in the radiograph. This secondary RCT will still be done with NDGP in the middle third of the root, as the cause of failure in the first place would have been because of regular in-tact gutta percha extruding from the apex or insufficient instrumentation.

The root canal therapy (RCT) procedure has potential risks and complications associated with the procedure: possible pain swelling, separation of instrument, perforation, fracture/crack, requirement for permanent restoration, and extraction of tooth if persistent infection is observed. If the tooth is indicated for an extraction instead, the extracted tooth will be evaluated for other potential causes of failure (eg. cracked tooth, missed extra canals, difficult canal anatomy, etc.). Extractions should be considered upon the identification of a fractured and cracked tooth during an apicoectomy. After the root canal therapy, if pain or pressure persists for more than a few days after the RCT, the endodontist would need to evaluate the prognosis of the tooth and determine whether the tooth is viable or needs extraction due to inadequate infection control of the canal or damage to tooth structure during the RCT. An extraction may also be indicated several years after the RCT due to persistent infectious bacteria or microleakage of the endodontically treated tooth. Other indications for extractions include perforations, coronal breakdown, or periodontal disease. If a tooth were to be extracted due to endodontic problems, such as persistent pain, swelling, sinus or periapical lesion, the treatment will be considered as a failed outcome. Tooth extraction without any information on postoperative periapical status will be excluded from analysis. We have to keep in mind that even conventional RCTs do not have a 100% success rate. Most studies say that primary RCTs have about a 86% success rate - so when taking that into consideration, we cannot assume that if the procedure fails, it is due to the NDGP material.

Customized forms, recorded by endodontic postgraduate students, will be used for recording follow-up information and radiographic assessments. The patient's medical conditions will be self-reported onto a standard medical history form at the first appointment and will be verified and updated by interview prior to the both arms of control and treatment and at the follow-up appointment. While all conditions reported by the patient will be recorded, only those that will be common among the patients or previously reported to have significant association with treatment outcome will be further analyzed.

Relevant demographic data, medical history, preoperative pain history, diagnostic and treatment details of the tooth were recorded on collection forms and then entered electronically into a database (Microsoft Office Access software). Handling of patients' personal data will accordingly conform to the Data Protection Act 1998. All data will be made anonymous on the database.

Nanodiamonds (5 nm) will be purchased from the NanoCarbon Research Institute Co., Ltd. (Nagano, Japan) prepared as a 50 mg/mL aqueous ND stock solution. Unmodified gutta-percha points will be purchased from SybronEndo (Glendora, CA, USA).

Dean Ho's lab personnel (Dong-Keun Lee and Theodore Kee) will prepare the NDGP. First, the nanodiamond (ND) stock solution will be sterilized. The ND stock solution will then be mixed with ethanol. In a separate beaker, the unmodified gutta-percha tips will be dissolved in eucalyptol. Next, the previously prepared ND solution will be mixed with the eucalyptol solution containing the dispersed gutta-percha. This final solution will then be sonicated for 5-15 min to mix the ND with the gutta-percha in the solution. Next, the solution will be lyophilized overnight to get rid of all the solvents in the solution. After lyophilization, solid NDGP composite filler material will be heated at 70-90C allowing the NDGP to be manually rolled into the cylinder shape of the standard of care gutta-percha filler material used in non-surgical RCT vertical condensation obturation.

Statistical Analysis:

For the analysis of the elastic moduli, tensile strength, and percentage of elongation properties of the NDGP, a two-tailed Student's t test was used. α was set at 0.05, and P values <0.05 were considered statistically significant. All tests were performed in triplicate, and statistical analyses were conducted using MATLAB R2014a (MathWorks Inc.).