# EFFICACY OF TWO DENTAL LOCAL ANESTHETICS ON THE ORAL HEALTH-RELATED QUALITY OF LIFE AFTER ENDODONTIC TREATMENT IN SYMPTOMATIC MANDIBULAR MOLARS: A DOUBLE BLIND RANDOMIZED CONTROLLED TRIAL

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| **Study Product Provider:** | New York University College of Dentistry |

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## Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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# List of Abbreviations

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| AAE | American Association of Endodontists |
| AE | Adverse Event/Adverse Experience |
| ASA | American Society of Anesthesiologists |
| CNS | Central Nervous System |
| CRF | Case Report Form |
| CTSI | Clinical and Translational Science Institute |
| FDA | Food and Drug Administration |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICF | Informed Consent Form |
| IRB | Institutional Review Board |
| IANB | Inferior Alveolar Nerve Block |
| IL | Intraligamentary Injection |
| LA | Local Anesthesia/Local Anesthetic |
| LLA | Long Lasting Anesthesia/Long Lasting Anesthetic |
| LOT-R | Life Orientation Test- Revised |
| LTF | Lost to Follow up |
| MAOI | Monoamine Oxidase Inhibitors |
| NRS | Numerical Rating Scale |
| NSAID | Non Steroid Anti-Inflammatory Drug |
| NYU | New York University |
| OHIP-14 | Oral Health Impact Profile 14 |
| PG | Post Graduate |
| PCS | Pain Catastrophizing Scale |
| PI | Principal Investigator |
| QA | Quality Assurance |
| QC | Quality Control |
| SAE | Serious Adverse Event/Serious Adverse Experience |
| SIP | Symptomatic Irreversible Pulpitis |
| SOP | Standard Operating Procedure |
| UP | Unanticipated Problems |
| USA | United States |

# Protocol Summary

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| Title | EFFICACY OF TWO DENTAL LOCAL ANESTHETICS ON THE ORAL HEALTH-RELATED QUALITY OF LIFE AFTER ENDODONTIC TREATMENT IN SYMPTOMATIC MANDIBULAR MOLARS: A DOUBLE BLIND RANDOMIZED CONTROLLED TRIAL |
| Short Title | Bupivacaine with OHIP14 |
| Brief Summary | In this randomized controlled double-blinded study, subjects will be assigned to one of two study groups to either be anesthetized with Bupivacaine or Lidocaine prior to needed treatment of pulpectomy/endodontic debridement on a symptomatic tooth.<br><br>Subjects' oral health related quality of life and postoperative pain resolution, pain medication use and numbness will be compared in two study groups. |

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| Objectives | The goal of this randomized controlled trial is to compare oral health related quality of life, postoperative pain resolution, also to evaluate pain medication use and duration of local anesthesia (LA) in subjects with a symptomatic mandibular molar tooth who either receive longer lasting anesthesia (LLA) (0.5% bupivacaine with 1:200,000 epinephrine) or anesthesia routinely used standard of care (2% lidocaine with 1:100,000 epinephrine) for pulpectomy/endodontic debridement at NYU Dentistry Endodontic Clinic.<br><br>Bupivacaine is a FDA approved dental anesthetic, which has been reported to provide anesthesia up to 7 hours following administration. It is FDA approved for use in dentistry both for infiltration and block anesthesia.<br><br>Primary Objective<br>Assess whether pulpectomy/endodontic debridement with 0.5% bupivacaine with 1:200,000 epinephrine (as a LLA) differs with respect to changes from preoperative baseline to postoperative day 1 or day 5 in oral health related quality of life (as measured by OHIP-14 questionnaire), than treatment with 2% Lidocaine with 1:100,000 epinephrine.<br><br>Secondary Objectives<br>1. Compare the pulpectomy/endodontic debridement treatment of 0.5% bupivacaine with 1:200,000 epinephrine, as a LLA, with pulpectomy/endodontic debridement treatment of with 2% Lidocaine with 1:100,000 epinephrine, as a LLA, with respect to changes in postoperative pain over days 1-5.<br><br>2. Compare the pulpectomy/endodontic debridement treatment of 0.5% bupivacaine with 1:200,000 epinephrine, as a LLA, with pulpectomy/endodontic debridement treatment of with 2% Lidocaine with 1:100,000 epinephrine, as a LLA, with respect to the duration of pain medication use over days 1-5<br><br>3. Compare the pulpectomy/endodontic debridement treatment of 0.5% bupivacaine with 1:200,000 epinephrine, as a LLA, with pulpectomy/endodontic debridement treatment of with 2% Lidocaine with 1:100,000 epinephrine, as a LLA, with respect to duration of anesthesia (numbness) after treatment.<br><br>Exploratory Objective<br>Explore whether of 0.5% bupivacaine with 1:200,000 epinephrine provides pulpal anesthesia success and onset which is equal to 2% lidocaine with 1:100,000 epinephrine. |
| Methodology | Randomized controlled double blind study |

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| Endpoints | Primary Study Endpoint<br>• Oral health related quality of life OHIP-14 score changes from preoperative to postoperatively on day 1 and day 5.<br><br>Secondary Study Endpoints<br>• Postoperative pain intensity during 5 days<br>• Number and type of pain medication use<br>• Duration of LA in hours (numbness) after receiving pulpectomy/endodontic debridement<br><br>Exploratory Endpoints<br>• Cold test results (+/-)<br>• Number of supplemental injections<br>• Duration until adequate lip numbness is obtained (in minutes)<br>• Duration until negative cold response is obtained (in minutes) |
| Study Duration | The estimated duration of this study is 1 year |
| Participant Duration | 4 weeks ± 10 days (until the second appointment with the subject) |
| Duration of IP administration | The duration of administration of either Bupivacaine or Lidocaine as an inferior alveolar nerve block (IANB) lasts up to two minutes.<br><br>The duration of anesthesia following administration is up to 7 hours for Bupivacaine and up to 4 hours for Lidocaine. |
| Population | Patients presenting to the NYU Dentistry Department of Endodontics for endodontic care for a symptomatic mandibular molar tooth, aged between 18-85 years, any gender, all demographic and ethnic groups and ASA I or II. |
| Study Sites | NYU College of Dentistry Department of Endodontics |
| Number of Participants | We plan to enroll 50 subjects in each group; approximately 100 participants will be enrolled. 20% dropout rate is expected, with an expected 40 subjects in each group. |
| Description of Study Agent/Procedure | Bupivacaine is an FDA approved anesthetic drug, commercially available (0.5% Bupivacaine with 1:200,000 epinephrine) routinely administered intraorally by IANB. |
| Reference Therapy | Lidocaine is an FDA approved anesthetic drug, commercially available (2% Lidocaine with 1:100,000 epinephrine) routinely administered intraorally by IANB. |
| Key Procedures | Preoperative data collection, administration of an IANB (Bupivacaine or Lidocaine), followed by standard of care 1st visit endodontic procedure; pulpectomy/endodontic debridement. Postoperative data collection during 5 days after treatment. |

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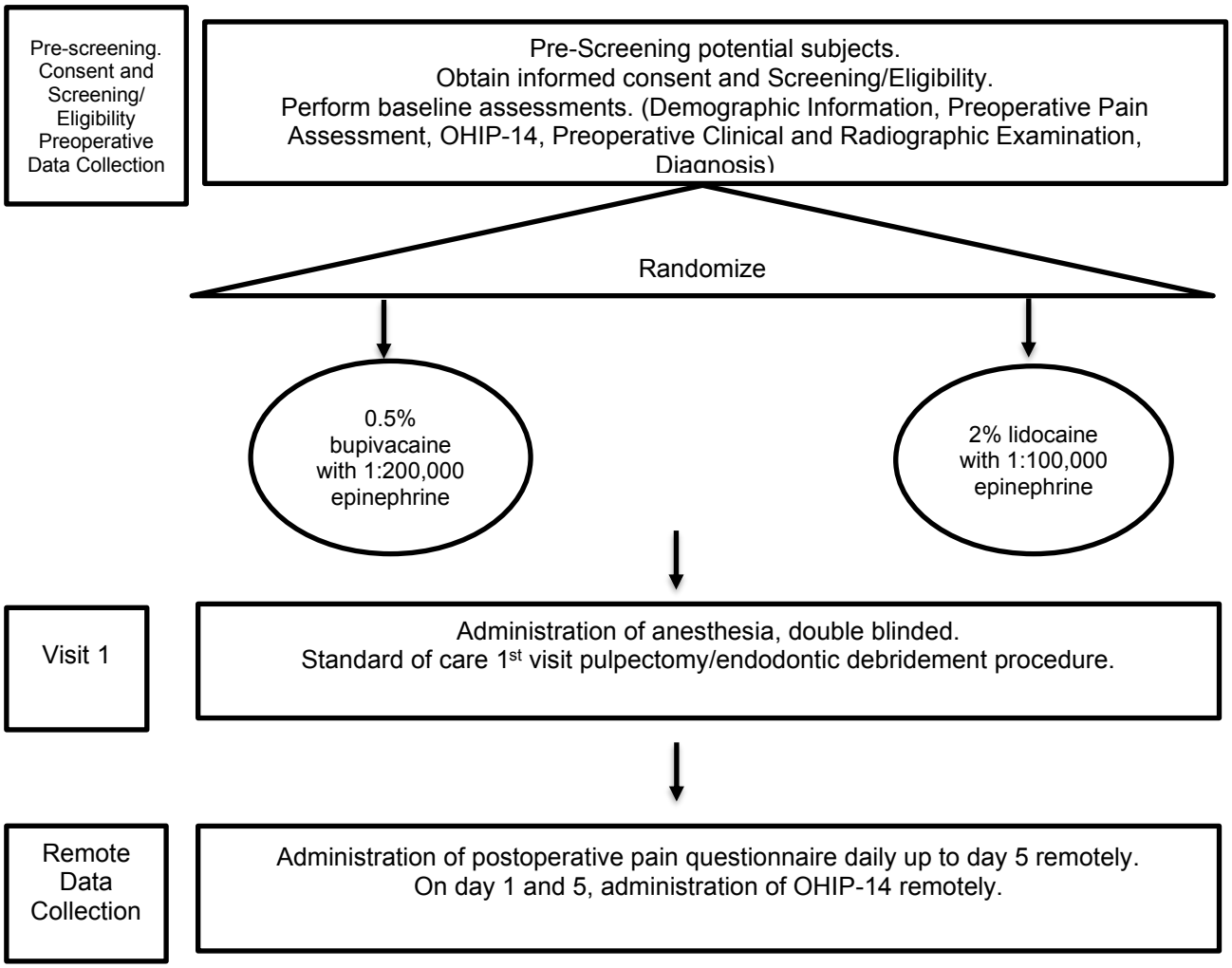
| Statistical Analysis | For the primary objective we will compare the oral quality of life OHIP-14 score change from preoperative baseline to day 1 postoperatively and the change from preoperative baseline to day 5 postoperatively between the 2 arms using a Wilcoxon Rank Sum test for each comparison individually at 2.5% significance level (2-sided) adjusted for the two comparisons using a Bonferroni correction. If at least one of the changes, either from baseline to day 1 postoperatively or from baseline to day 5 postoperatively, is significantly different between the 2 groups, the null hypothesis will be rejected.<br><br>For each of the 7 sub-domains of OHIP-14 we will calculate the mean change from preoperative baseline to day 1 and to day 5 in both arms.<br>For the secondary objective we will compare the efficacy of bupivacaine with that of lidocaine over the postoperative 5 days using mixed models for longitudinal data. The efficacy will be compared in terms of the following measures:<br><br>1. postoperative pain resolution<br>2. pain medication use<br>3. numbness (duration of LA) after receiving endodontic treatment<br><br>The success of LLA will be determined by the cold test results (+/-) and the number of supplemental injections. The onset of LLA will be determined by the duration until adequate lip numbness and the duration until negative cold response after IANB.<br>For the exploratory objective we will compare the success and onset of LA in the two study arms. For comparison of success of LLA between the 2 arms we will use Fisher's exact test. For comparison of onset of LLA between the 2 arms we will use a Wilcoxon Rank Sum test.<br><br>Ad Hoc Stopping Rule<br>After 40 patients are accrued (approximately 20 subjects in each arm) an ad-hoc analysis will be performed to assess and compare the success of LA in both groups. If the proportion of subjects who are excluded intraoperatively in the study arm is twice as large as that of the control arm, the study will be terminated. The reasons for being excluded intraoperatively are if adequate lip numbness is not obtained with 2 inferior alveolar nerve block anesthesia and/or adequate pulpal anesthesia is not obtained after 2 times of supplemental anesthesia. Although, this is not a safety issue, we do not want to create more risks of intraoperative pain than routine endodontic practice. This analysis will be done by the study statistician. The investigators will remain blinded to the subjects' treatment arm. |

## Schematic of Study Design



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# 2 Introduction, Background Information and Scientific Rationale

## 2.1 *Background Information and Relevant Literature*

Patients have been reported to suffer from moderate to severe pain after endodontic treatment for up to seven days, and of those the first 2 days pain is commonly the most severe (1). It has been shown that preoperative pain is the one of the major predictors of postoperative pain (2) which suggests that postoperative pain management becomes even more crucial for patients who report to the clinic with ongoing preoperative pain.

It has also been found that preoperative percussion hypersensitivity (mechanical allodynia) of an offending tooth has been shown to be one of the major predictors of severe postoperative pain after emergency treatments (3), 92% of the patients who attended emergency endodontic clinic had a painful response to percussion on the tooth in questions (4). Percussion hypersensitivity has been associated with central sensitization (5, 6) therefore, postoperative pain management can be an especially important in patients with a diagnosis of symptomatic apical periodontitis and painful percussion responses.

Postoperative management strategies have been suggested that usually include non-steroid anti-inflammatory drugs (NSAID) and/or acetaminophen (7), opioids (8), and corticosteroids (9). Alternatively, administration of LLA, bupivacaine, which can last up to 7-12 hours, has been suggested as a strategy to manage postoperative pain (10-12). A meta-analysis on efficacy and safety of bupivacaine versus lidocaine showed statistically significant better postoperative pain control with bupivacaine after dental treatment and no difference in safety when compared with lidocaine (10). It has been hypothesized that with the use of LLA, inhibits peripheral barrage from primary afferent neurons after the treatment and thereby significantly inhibit sensitization of second order neurons in the pain pathway that then will lead to reduction or elimination of central sensitization resulting in reduction of postoperative pain, not only during the LLA period but also after the resolution of the anesthesia (13).

There is a discussion about the toxicity of LLA bupivacaine in dental literature most of which are in vitro studies (13). However, a meta-analysis on safety of bupivacaine versus lidocaine in dental treatments showed no difference in safety when compared with lidocaine (10) and the use of LLA as a postoperative pain management strategy is being investigated and widely accepted in medicine, not only with bupivacaine, but also with extended release bupivacaine formulations which can last up to 3-4 days (14).

There is some controversy in the literature regarding the success of bupivacaine for pulpal anesthesia during the endodontic treatment (15-18). Some of those differences might be because of methodological differences and different inclusion criteria. The success rate of bupivacaine has been found inferior to lidocaine when anesthetic success rate has been determined by electrical pulp test (16) however, found comparable when success was measured as patient reporting no pain/mild pain during the treatment (15, 18). A recent Cochrane review suggests dental anesthetic success should not be measured with an electrical pulp test as it might not measure true clinical effect, rather the clinical success should be evaluated by patient reporting of pain or discomfort while being worked on (19). Another possible disadvantage of bupivacaine is found to be the delay in onset time. Although, the onset time has been found to delayed overall; in subgroup analysis when only molar teeth were analyzed, the onset time has been found comparable to lidocaine and without statistically significant difference (16).

It is also important to note that by the administration of bupivacaine, a longer period of soft tissue numbness along with a longer period of analgesia is likely to occur compared to the use of lidocaine. Some studies have indicated that some patients dislike longer term soft tissue numbness because it may alter orofacial function such as eating and speaking and thereby possibly affect their quality of life (11, 12).

Oral health-related quality of life, measured with Oral health Impact Profile (OHIP14) has been shown to be a reliable method to capture patients' oral quality of life and its change through endodontic treatment (20, 21). Not only does it capture physical pain, but also functional limitation, physical and psychosocial disability and psychosocial discomfort (22). Therefore, OHIP-14 could be a reliable candidate to measure the effect of LLA for postoperative pain management as a patient centered outcome because it will not only

capture effective analgesia, but also patient centered consequences of long lasting soft tissue numbness. To our knowledge, no study has been conducted to investigate the use of LLA by assessing subjects' oral quality of life in a patient-oriented manner.

In a response to the contribution of dentistry to the opioid crisis the President of American Dental Association, in a letter to the federal Pain Management Best Practices Inter-Agency Task Force, states that "federal efforts have not sufficiently addressed best practices for managing postoperative dental pain, which is more nuanced than managing pain in medical settings" (8). There is evidence that administration of LLA is a viable postoperative pain management modality in dentistry/endodontics, because it has been reported to lower the duration and intensity of pain (10) and thereby be an additional method in the fight against the opioid crisis. Of an interest is a recent guideline for the management of postoperative pain after general surgery that strongly recommends use of site-specific peripheral regional anesthesia with high quality level evidence, (23). However, to our knowledge no study has assessed the efficacy of bupivacaine as a postoperative pain management strategy using OHIP-14 in patients with symptomatic teeth who need pulpectomy/endodontic debridement with preoperative pain.

## 2.2 *Name and Description of the Investigational Agent*

Bupivacaine HCl is an FDA approved, commercially available local anesthetic. It is on the formulary of NYU Dentistry and routinely used. Although bupivacaine is not used as widely and frequently as lidocaine HCl with 2% concentration with epinephrine (1:100,00), it is preferred for longer duration procedures or for postoperative pain management and available in the clinic whenever preferred as the anesthetic choice. It is prepared as a sterile isotonic solution with epinephrine (as bitartrate) 1:200,000 for injection via local infiltration, peripheral nerve block, and caudal and lumbar epidural blocks.

Bupivacaine hydrochloride is (±) -1-Butyl-2′, 6′-pipecoloxylidide monohydrochloride, monohydrate, a white crystalline powder that is freely soluble in 95 percent ethanol, soluble in water, and slightly soluble in chloroform or acetone. Epinephrine is (-)-3, 4-Dihydroxy-α-[(methylamino)-methyl] benzyl alcohol.

Bupivacaine hydrochloride and 0.0091 mg epinephrine bitartrate, with 0.5 mg sodium metabisulfite, 7 mg sodium chloride, 0.001 mL monothioglycerol, and 2 mg ascorbic acid as antioxidants, 0.0017 mL 60% sodium lactate buffer, and 0.1 mg edetate calcium disodium as stabilizer. The pH of these solutions is adjusted with sodium hydroxide or hydrochloric acid.

Bupivacaine is related chemically and pharmacologically to the aminoacyl LA. It is a homologue of mepivacaine and is chemically related to lidocaine. All three of these anesthetics contain an amide linkage between the aromatic nucleus and the amino or piperidine group. They differ in this respect from the procaine-type LAs, which have an ester linkage.

Bupivacaine and Lidocaine are FDA approved marketed anesthetic drug and meets IND Exemption.

### 2.2.1 Clinical Data to Date

Bupivacaine stabilizes the neuronal membrane and prevents the initiation and transmission of nerve impulses, thereby effecting LA. The onset of action following dental injections is usually 2 to 10 minutes and anesthesia may last two or three times longer than lidocaine and mepivacaine in dental use, for many patients up to 7 hours. The duration of anesthetic effect is further prolonged by the addition of epinephrine 1:200,000. After injection of bupivacaine for peripheral nerve block in man, peak levels of bupivacaine in the blood are reached in 30 to 45 minutes, followed by a decline to insignificant levels during the next three to six hours. It has also been noted that there is a period of analgesia that persists after the return of some sensation, during which time the need for strong analgesic is reduced. Because of its amide structure, bupivacaine is not detoxified by plasma esterases but is detoxified via conjugation with glucuronic acid, in the liver. When administered in recommended doses and concentrations, bupivacaine does not ordinarily produce irritation or tissue damage, and does not cause methemoglobinemia.

Systemic absorption of LAs produces effects on the cardiovascular and central nervous systems (CNS). At blood concentrations achieved with normal therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure. Recent clinical reports and animal research suggest that these cardiovascular changes are more likely to occur after unintended intravascular injection of bupivacaine. Therefore, incremental dosing is necessary. Following systemic absorption, LAs can produce CNS stimulation, depression, or both. Apparent central stimulation is manifested as restlessness, tremors and shivering progressing to convulsions, followed by depression and coma progressing ultimately to respiratory arrest. However, the LAs have a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior excited state.

Bupivacaine has been tested in randomized control trials both for determining the onset time, duration efficacy and to determine the efficacy in postoperative pain management in patients who underwent endodontic treatment (11, 15, 16). Regarding the safety of bupivacaine, none of the studies in endodontics reported any unanticipated side effects. There has been one meta-analysis published which compared the safety of the drug, bupivacaine, with lidocaine and it did not find any significant difference in safety between the two (10). Though systemic absorption at toxic concentrations may create complications mentioned above, it is very unlikely to reach to those toxic concentration with systemic absorption when used for dental therapies.

### 2.2.2 Dose Rationale

As with all anesthetics, the dosage varies and depends upon the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, individual tolerance, and the technique of anesthesia. The lowest dosage needed to provide effective anesthesia should be administered.

The 0.5% concentration with epinephrine is recommended for infiltration and block injection in the maxillary and mandibular area when a longer duration of LA action is desired, such as for oral surgical procedures generally associated with significant postoperative pain. The average dose of 1.8 mL (9 mg) per injection site will usually suffice; an occasional second dose of additional 1.8 mL (9 mg) may be used if necessary to produce adequate anesthesia after making allowance for 2 to 10 minutes onset time. The lowest effective dose should be employed and time should be allowed between injections; it is recommended that the total dose for all injection sites, spread out over a single dental sitting, should not ordinarily exceed 90 mg for a healthy adult patient (ten 1.8 mL injections of bupivacaine with epinephrine). Injections should be made slowly and with frequent aspirations.

The dose that will be used in this study is one cartridge (1.8mL), of bupivacaine HCl with 0.5% concentration with epinephrine (1:200,000) for the experiment group. If adequate lip numbness is not achieved as reported by the subject and tested and compared with the contralateral side of the lip with a blunt instrument, after 15 minutes, a second injection of the same dosage will be provided.

For the control group, one cartridge (1.7mL) of lidocaine HCl with 2% concentration, with epinephrine (1:100,00) will be used. If adequate lip numbness is not achieved after 15 minutes, as reported by the subject, and tested and compared with the contralateral side of the lip with a blunt instrument, a second injection of the same dosage will be provided.

Those are the most commonly recommended initial doses that are used in routine endodontic practice for inferior alveolar nerve block (IANB (11, 16, 17). Though some clinical studies have recommended that initial the doses were set to be 3.6 mL (15).

Although adequate lip numbness is achieved, pulpal anesthesia at the same time is not always guaranteed for symptomatic teeth (17). Therefore, pulpal anesthesia will be tested with cold test, after a wait time of 10 minutes, after obtaining adequate lip numbness with (Endo-Ice, Coltene, USA) in the proposed study in an

attempt to test/confirm pulpal anesthesia. This is a routine procedure for the confirmation of pulpal anesthesia. This will be done to determine the success of IANB with either Lidocaine or Bupivacaine. All other injections, if needed, apart from the IANB, will be administered with Lidocaine only in both groups.

A supplemental buccal infiltration and intraligamentary (IL) injection will be given with Lidocaine HCI 2% 1:100000 to all patients, irrespective of their grouping. This approach is a routine and highly recommended for symptomatic teeth (24, 25). The effect of pulpal anesthesia will be tested with cold test (Endo-Ice, Coltene, USA). The algorithmic chart for anesthetic administration in Fig 1. will be followed as the guideline. Additional supplemental injections will be administered as portrayed in the chart, with Lidocaine HCI 2% 1:100000 if needed in order to obtain complete pulpal anesthesia.

Subjects who need supplemental injections more than 2 times will be excluded from the study because number of injections may also contribute to postoperative pain and discomfort.

The maximum recommended dose for lidocaine is 500mg per day, and it shouldn't exceed 7mg/kg of body weight. The maximum recommended dose for bupivacaine is 400 mg per day. There are no reported risks with these doses. All these supplemental injections will be performed with Lidocaine HCI 2% 1:100000 in both groups.

## 2.3 *Rationale*

Patients have been reported to suffer from moderate to severe pain after endodontic treatment for up to seven days, and of those the first 2 days pain is commonly the most severe (1). It has been shown that preoperative pain is the one of the major predictors of postoperative pain (2) which suggests that postoperative pain management becomes even more crucial for patients who report to the clinic with ongoing pain.

Endodontic pain is multifactorial and management of postoperative pain is important in terms of reducing both the peripheral and central components of the associated hyperalgesia through different approaches (26). Different postoperative management strategies that have been suggested including NSAID and/or acetaminophen (7), opioids (8), and corticosteroids (9). LLA has also been suggested for postoperative pain control and has been found to be effective up to 12 hours (11). It has also been hypothesized that with the use of LLA inhibits peripheral barrage from primary afferent neurons after the treatment and thereby significantly inhibit sensitization of second order neurons in the pain pathway that then will lead to reduction or elimination of central sensitization resulting in reduction of postoperative pain, not only during the LLA period but also after the resolution of the anesthesia (13).

However, LLA obviously will lead to longer period of soft tissue numbness. Studies have shown that some patients may not like the longer soft tissue numbness because it may alter orofacial function like eating and speaking and thereby possibly affect their quality of life (11, 12). OHIP-14 is a validated instrument that will be able to capture not only the intensity of pain, but also will be able to determine functional limitation, psychological discomfort, physical, psychological and social disability (22). These findings are significant because although bupivacaine may provide anesthesia up to 7 hours, and better postoperative pain management; it may create functional, psychological and social impairments during the time of anesthesia.

The null hypothesis of this study is that there is no difference between a group of subjects exposed to Bupivacaine, a LLA vs. a group exposed to Lidocaine for dental anesthesia regarding oral quality of life change in subjects with preoperative pain (at least 3/10 on Numerical Rating Scale (NRS)) and diagnosed with a pulpal diagnosis of either symptomatic irreversible pulpitis or pulp necrosis and periapical diagnosis of normal periapical tissues, asymptomatic or symptomatic apical periodontitis who will receive pulpectomy/endodontic debridement on a mandibular molar.

It is well established that one of the major predictors of postoperative pain is the preoperative pain associated with the offending tooth. (2). This fact is the rational why only subjects with symptomatic teeth (with preoperative pain at least 3/10) will be recruited from endodontic services on NRS. Bupivacaine or Lidocaine (chosen randomly) will be administered double blinded prior to the endodontic procedure to

anesthetize the pulp and surrounding bone with inferior alveolar nerve block (IANB) in lower molars with a dosage of one cartridge. This is a routine route of administration and dosage applied in routine endodontic practice. If the IANB fails, a second cartridge will be administered, again routinely recommended and done in clinical practice.

Some controversy exists in the literature regarding the success of bupivacaine for pulpal anesthesia during the treatment (15-18) because of methodological differences and different inclusion criteria. Also, delayed onset time may be a disadvantage of bupivacaine although, the onset time has been found comparable to lidocaine and there was no statistically significant difference, in mandibular molar teeth (16). However, because of these controversies in literature, success and onset of LA will be also captured and recorded and analyzed in the study without no additional interventions

## 2.4 *Potential Risks & Benefits*

### 2.4.1 Known Potential Risks

Reactions to bupivacaine hydrochloride and epinephrine injection, are the same as characteristic of those associated with other amide-type LAs such as the control agent in the study; 2% lidocaine with 1:100,000 epinephrine. Subjects who report allergies to LAs or any other component of the LA will be excluded from the study. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to over dosage, inadvertent intravascular injection or slow metabolic degradation.

Excessive plasma levels of the amide-type LAs cause systemic reactions involving the CNS and the cardiovascular system. The *CNS effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other CNS effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest. *Allergic reactions,* which may be due to hypersensitivity, idiosyncrasy, or diminished tolerance, are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value. Transient facial swelling and puffiness may occur near the injection site.

Small doses of LAs injected into the head and neck area, as small as nine to eighteen milligrams, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Confusion, convulsions, respiratory depression, and/or respiratory arrest, cardiovascular stimulation or depression and cardiac arrest have been reported. Reactions resulting in fatalities have occurred on rare occasions. In a few cases, resuscitation has been difficult or impossible despite apparently adequate preparation and appropriate management. These reactions may be due to intra-arterial injection of the LA with retrograde flow to the cerebral circulation. Patients receiving these blocks will have their circulation and respiration monitored and be constantly observed. Resuscitative equipment and personnel for treating adverse reactions will be immediately available. Dosage recommendations should not be exceeded. It is essential that aspiration for blood be done prior to injecting any LA, both the original dose and all subsequent doses, to avoid intravascular injection. However, a negative aspiration does *not* ensure against an intravascular injection. Reactions resulting in fatality have occurred on rare occasions with the use of LAs, even in the absence of a history of hypersensitivity.

The solutions, which contains a vasoconstrictor, should be used with extreme caution for patients whose medical history and physical evaluation suggest the existence of hypertension, arteriosclerotic heart disease, cerebral vascular insufficiency, heart block, thyrotoxicosis and diabetes, etc., as well as patients receiving drugs likely to produce alterations in blood pressure. Only subjects who are ASA I and II are included in the study.

Bupivacaine with epinephrine 1:200,000 or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, because a severe persistent hypertension may occur. Likewise, solutions of

bupivacaine containing a vasoconstrictor, such as epinephrine, should be used with extreme caution in patients receiving monoamine oxidase inhibitors (MAOI) or antidepressants of the triptyline or imipramine types, because severe prolonged hypertension may result. Subjects who use these drugs will be excluded from the study.

The solutions also contain sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence is very low. Subjects who have sodium metabisulfite allergies will be excluded from the study.

Any adverse reaction that could be caused by bupivacaine is similar, if not identical, to lidocaine because both have a similar chemical composition, both are amide type LA, and both are commonly and interchangeably used in dental practice (10, 27). With all routine precautions taken, exceeding the recommended plasma level and reaching toxic concentrations thus the occurrences of adverse events are reported to be rare during dental treatments.

When the study agent, bupivacaine HCl 0.5% with epinephrine, is used for dental injections, the long duration of anesthesia (7 hours) could increase the possibility of inadvertent biting trauma to tongue, lips, and buccal mucosa. Subjects will be advised not to chew solid foods or test the anesthetized area by biting or probing until normal sensation has returned. Subjects may have difficulty in eating, drinking, talking for a longer period of time, which might affect them physically and psychosocially. However, postoperative pain may also limit subjects' orofacial functioning and wellbeing, which is eliminated by LLA. Therefore, the information to be gained regarding the overall efficacy of bupivacaine by using OHIP-14 is significant and outweighs the risks involved.

Subjects will be asked to spend time filling out questionnaires before and after treatment. We have limited the amount of questions per document to save the subject time. Subjects can complete these questionnaires alone if preferred, or if the subject feels uncomfortable answering any of the questions, they can tell the study coordinator or the PI. Although there is a minor risk for loss of privacy in this study, confidential data collected for research purposes will be labeled with a unique de-identified study subject number and stored securely.

### 2.4.2 Known Potential Benefits

There may be no direct benefits to subjects for participating in this research study.

Bupivacaine HCl lasts two to three times longer than lidocaine, in many patients up to 7 hours. This may be beneficial if the treatment duration is longer and it may also help managing postoperative pain (11) that might reduce the analgesic use.

The post-treatment pain monitoring involved in this study may help us to identify subjects needing additional or quicker follow up with their clinical provider than would routinely occur.

# 3 Objectives and Purpose

This is a double-blind randomized controlled single-site trial. The purpose of this trial is to compare oral health related quality of life change, postoperative pain resolution, and to evaluate pain medication use and duration of anesthesia in subjects with preoperative pain (at least 3/10 on NRS) and diagnosed with a pulpal diagnosis of either symptomatic irreversible pulpitis or pulp necrosis and periapical diagnosis of normal periapical tissues, asymptomatic or symptomatic apical periodontitis who either receive LLA (0.5% bupivacaine with 1:200,000 epinephrine) or LA used as standard of care (2% lidocaine with 1:100,000 epinephrine) for pulpectomy/endodontic debridement at NYU Dentistry Endodontic Clinic.

Bupivacaine is a FDA approved anesthesia, which provides anesthesia up to 7 hours following administration. It is approved for use in dentistry both for infiltration and block anesthesia. We will evaluate

oral quality of life change in subjects as well as the reported pain resolution and duration of postoperative pain in subjects who will undergo pulpectomy/endodontic debridement for a mandibular molar.

Controversies in literature regarding the success and onset of LA exist. This is why an exploratory objective will capture, record and analyze the success and onset of LA in two study arms in the study without additional interventions.

## 3.1 *Primary Objective*

Assess whether pulpectomy/endodontic debridement with 0.5% bupivacaine with 1:200,000 epinephrine (as a LLA) differs with respect to changes from preoperative baseline to postoperative day 1 or day 5 in oral health related quality of life (as measured by OHIP-14 questionnaire), than treatment with 2% Lidocaine with 1:100,000 epinephrine.

## 3.2 *Secondary Objectives*

1. Compare the pulpectomy/endodontic debridement treatment of 0.5% bupivacaine with 1:200,000 epinephrine, as a LLA, with pulpectomy/endodontic debridement treatment of with 2% Lidocaine with 1:100,000 epinephrine, as a LLA, with respect to changes in postoperative pain over days 1-5.

2. Compare the pulpectomy/endodontic debridement treatment of 0.5% bupivacaine with 1:200,000 epinephrine, as a LLA, with pulpectomy/endodontic debridement treatment of with 2% Lidocaine with 1:100,000 epinephrine, as a LLA, with respect to duration of pain medication use over days 1-5

3. Compare the pulpectomy/endodontic debridement treatment of 0.5% bupivacaine with 1:200,000 epinephrine, as a LLA, with pulpectomy/endodontic debridement treatment of with 2% Lidocaine with 1:100,000 epinephrine, as a LLA, with respect to duration of anesthesia (numbness) after treatment.

## 3.3 *Exploratory Objective*

Explore whether of 0.5% bupivacaine with 1:200,000 epinephrine provides pulpal anesthesia success and onset which is not different from 2% lidocaine with 1:100,000 epinephrine.

# 4 Study Endpoints

### *4.1.1 Primary Study Endpoints*

Oral health related quality of life OHIP-14 score changes from preoperative to postoperatively day 1 and day 5.

### *4.1.2 Secondary Study Endpoints*

- Postoperative pain intensity during 5 days
- Number and type of pain medication use
- Duration of LA in hours (numbness) after receiving pulpectomy/endodontic debridement

### *4.1.3 Exploratory Endpoints*

- Cold test results (+/-)
- Number of supplemental injections
- Duration until adequate lip numbness is obtained (in minutes)
- Duration until negative cold response is obtained (in minutes)

# 5 Study Enrollment and Withdrawal.

## 5.1 *Inclusion Criteria*

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Patients between the ages of 18-85 years old.
2. Patients with pulpal diagnosis of either symptomatic irreversible pulpitis or pulp necrosis and periapical diagnosis of normal apical tissues, symptomatic apical periodontitis or asymptomatic apical periodontitis.
3. Patients who only have one tooth with odontogenic pain at the time point of the screening.
4. Patients who are treatment planned, and have agreed to have, pulpectomy/endodontic debridement.
5. Patients with acute dental pain of at least 3/10 on NRS.
6. Patients must be able to comprehend and complete all study questionnaires.
7. Patients must be able to comprehend the description of the study protocol and written consent.
8. Patients must be available to be contacted by text messages, phone calls or email during 5 days after the pulpectomy/endodontic debridement.

## 5.2 *Exclusion Criteria*

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Medically complex patients with severe systemic diseases (ASA III or above). These may include uncontrolled diabetes, uncontrolled blood pressure and/or chronic renal failure, for example, and potential participants will be asked about these conditions during the screening process.
2. Pregnant patients.
3. Patients who have already been enrolled in the study. Patients can only be enrolled for treatment on one tooth. If a patient has been enrolled in the study and will receive additional endodontic treatment on a different tooth on a later date, they will not be enrolled again for the additional endodontic treatment on a different tooth.
4. Patients with a known hypersensitivity or allergy to any local anesthetic agent of the amide group, or any other components of the two anesthetic solutions such as epinephrine, sodium metabisulfite used in the study.
5. Patients who use ergot-type oxytocic drugs for uterine contraction, monoamine oxidase inhibitors, antidepressant of triptyline or imipramine types or patients who are planned to receive sedatives for the treatment.
6. Patients with additional elective dental treatments like extraction, implant placement, root canal therapy planned in the 5 days following the date of enrollment in this study.
7. Patients with pain whose examined tooth is planned for vital pulp therapies e.g. pulpotomy, retreatment, apical surgery or extraction.
8. Patients with a pulpal diagnosis of reversible pulpitis, previously treated, previously initiated therapy and periapical diagnosis of acute apical abscess or chronic apical abscess.
9. Patients who have multiple teeth with odontogenic pain at the time of the screening.
10. Patients who do not understand or are able to read the questionnaires.
11. Non-English speaking patients.

## 5.3 *Intraoperative Exclusion criteria*

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patients, whose endodontic treatment cannot be continued due to intra-procedural findings such as tooth fracture.
2. Any unexpected intraoperative procedural errors that might change the course of the treatment, such as separated instrument, perforation.
3. Patients whose adequate lip numbness is not obtained with 2 inferior alveolar nerve blocks.

4. Patients whose adequate pulpal anesthesia is not obtained after 2 supplemental injections of anesthetic.

## 5.4 *Vulnerable Subjects*

No vulnerable patients will be specifically targeted for inclusion in this study.

## 5.5 *Strategies for Recruitment and Retention*

Patients recruited in this study will be mostly those who present for emergency dental treatment at NYU Dentistry Endodontic Clinic. The dental providers are postgraduate students from the endodontic department and they work under the supervision of the NYS Dental Licensed faculty, listed as Co-Investigators, who will be overseeing the procedures and treatments which are part of the study. Study investigators (the PI, Co-PIs; ) will identify patients who need an emergency treatment either by inquiring directly to the dental providers at the start of the clinic session and through the day or by asking the front desk patient representatives in the Endodontic clinic if any emergency patients presented on that day. It is also possible that some patients who come for a treatment appointment might have a symptomatic tooth.

The potential participant's standard of care clinical and radiographic examination findings, diagnosis and treatment plan approved by the faculty will be prescreened by one of the study investigators after the standard of care clinical and radiographic examinations performed by the treating dentist to determine whether the patient is eligible in terms of diagnosis and treatment plan approved by the faculty by reviewing the gathered findings. This will be done in an effort to not to increase the wait time period for patients. After prescreening, potential participant will be asked by their dental provider if they are interested in discussing participation in a research study regarding postoperative pain with a research investigator. Interested subjects will be introduced to the study – this means the purpose of the study will be explained, details of what will be involved if they decide to participate will be described, duration of the study etc. by the PI or the Co-I; Ozge Erdogan. If they agree to participate, they will be consented by the PI or the Co-I; Ozge Erdogan.

Interested potential subjects will be screened for eligibility by one of the study investigators and will be enrolled if they meet all the eligibility criteria.

We estimate 80 subjects (randomized to 40 participants per arm) are required. We estimate that loss of subjects will be minimal due to a short follow up time of 1 week, however in order to anticipate a greater loss of subjects because of intraoperative exclusion criteria, we will increase our sample size to 100 to include 20% attrition (n=50 per treatment group).

We are unsure of how many cases will be screened in order to reach this approximate sample size but we will update the protocol as this information is obtained.

## 5.6 *Duration of Study Participation*

The duration of study participation will be from the 1st treatment visit, until the participant returns for their second routine endodontic treatment visit. At this second visit, compensation will be given and data collection will be finalized if necessary. This is in an effort to coincide the research visit with the routine and required dental visit. This visit will be scheduled by the treating dentist and can be scheduled up to several weeks after the first treatment visit. There will be no time limit for this research visit. If the patient will return to the school for an appointment in another department/clinic, they can inform the research team and efforts will be made to meet the patient then if the 5 days post-treatment data collection is complete.

## 5.7 *Total Number of Participants*

Recruitment will end when approximately 100 evaluable participants are enrolled, randomized to 50 subjects per group.

## 5.8 *Participant Withdrawal or Termination*

### 5.8.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), or other medical/dental condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation – this may include intra-operative factors outlined in the Intraoperative Exclusion Criteria including: fracture of the tooth, not having adequate lip numbness after 2nd inferior alveolar nerve block, or not having adequate pulpal anesthesia after two times supplemental injection.
- Failure of the subject to adhere to protocol requirements such as not completing the remote questionnaires after the treatment.

### 5.8.2 Handling of Participant Withdrawals or Termination

Efforts will be made prior to stating that a participant is lost to follow up (LTF) by contacting the participant with the contact information provided pre-operatively either by phone/text/email. We will also obtain a friend/family member's contact information to contact the subject in order to avoid LTF.

If the IANB fails to provide adequate lip numbness after the second injection and after a wait time of a further 15 minutes (total wait time 30 minutes), the subject will discontinue with the study agent/control agent, and will be excluded from the study. Also, subjects who need supplemental injections more than 2 times will be excluded from the study. The treating dentist will be unblinded and routine protocol will be followed; Lidocaine 2% with 1:100,000 epinephrine will be administered either with an IANB, infiltration or intraosseous anesthesia as decided by the treating dentist. Every failure for these reasons will be noted by the researchers and analyzed at later time to investigate possible difference in success of each of the two LA.

The study team will try to determine reasons for discontinuation and a subject disposition document will be completed to record reason for discontinuation. Subjects who decide to discontinue participation from the study will be provided with contact information of the PI and the study team if any questions or concerns arise at a later point. If the subject would like written confirmation of their discontinuation, a withdrawal letter will be given to them, signed by the PI. It will not be required for subjects to return to the clinic for any safety follow-up visits.

## 5.9 *Premature Termination or Suspension of Study*

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Data that are not sufficiently complete and/or evaluable
- Insufficient compliance to protocol requirements
- Determination of unexpected, significant, or unacceptable risk to participants
- Determination of futility
- Lack of funding

Study may resume once concerns about safety, protocol compliance and data quality are addressed and satisfy the sponsor, IRB and/or FDA.

# 6 Study Agent and Procedural Intervention

## 6.1 *Study Agent and Control Description*

Bupivacaine HCl (1.8mL) 5% concentration, with epinephrine (1:200,000) is the investigational product. It exists in liquid form in cartridges. Bupivacaine is a FDA approved marketed anesthetic drug and meets IND Exemption.

Lidocaine HCl (1.7mL) 2% concentration with epinephrine (1:100,000) is the control agent. It exists in liquid form in cartridges. Lidocaine is a FDA approved marketed anesthetic drug.

### 6.1.1 Acquisition

Both the study agent and the control product exist in clinical supply (NYU Dentistry Formulary) available as standard of care and will be obtained from the clinical supply on 7th floor in the Endodontics Department (7W), purchased by the Endodontic department.

### 6.1.2 Formulation, Appearance, Packaging, and Labeling

Bupivacaine HCl (1.8mL) 5% concentration, with epinephrine (1:200,000) is the investigational product. Lidocaine HCl (1.7mL) 2% concentration with epinephrine (1:100,000) is the control agent. Both products exist in liquid form; available in cartons containing 5 blisters of 10X1.8 mL and 10X1.7 mL glass cartridges, respectively. Both products are commercially available. Products are available for human use in the form, route and dose planned in this trial.

### 6.1.3 Product Storage and Stability

Both products should to be stored at room temperature below 25°C (77°F) and should be protected from light until expiration date printed on each cartridge. One cartoon containing 5 blisters of 10X1.8 mL of Bupivacaine, in total containing 50 cartridges and one cartoon containing 5 blisters of 10X1.7 mL Lidocaine in total containing 50 cartridges will be obtained initially from the supply desk. Those initial cartoons will be stored in a locked cabinet on the 7th floor which will be only accessible by the study team. A study product log will be created. The number of used and remaining drugs will be registered in this study product log. Weekly, the remaining cartridges will be counted. New cartoons will be obtained again from the supply desk when necessary.

### 6.1.4 Preparation

Products are packaged for ready for use. No additional preparation is needed. However, the glass cartridges will be covered with opaque tape to mask content. Each masked cartridges with have unique number written on the masking tape and a separate log will be kept to ensure that correct anesthetic was used after the random assignment.

### 6.1.5 Dosing and Administration

The initial dose administered for both groups will be one cartridge of anesthetic (1.8 mL for Bupivacaine, 1.7 mL for Lidocaine). The dose rationale will be followed up as described in section *2.2.2 Dose Rationale and 6.1.7 Starting Dose and Dose Escalation Schedule.*

### 6.1.6 Route of Administration

IANB is the route of administration.

### 6.1.7 Starting Dose and Dose Escalation Schedule

The initial dose administered for groups will be one cartridge (1.8 mL for Bupivacaine, 1.7 mL for Lidocaine).

If adequate anesthesia is not achieved within 15 minutes determined by the treating dentist by;

1. Asking the subject for reporting of lip numbness

2. Testing and comparing with the contralateral side of the lip with a blunt instrument such as mirror handle, a second injection of the same dosage of the same drug will be provided.

If the IANB fails to provide adequate lip numbness after the second injection after a wait time of a further 15 minutes (total wait time 30 minutes), the subject will discontinue with the study agent/control agent, will be excluded from the study and the treating dentist will be unblinded and routine protocol will be followed; Lidocaine 2% with 1:100,000 epinephrine will be administered either with an IANB, infiltration or intraosseous anesthesia as decided by the treating dentist.

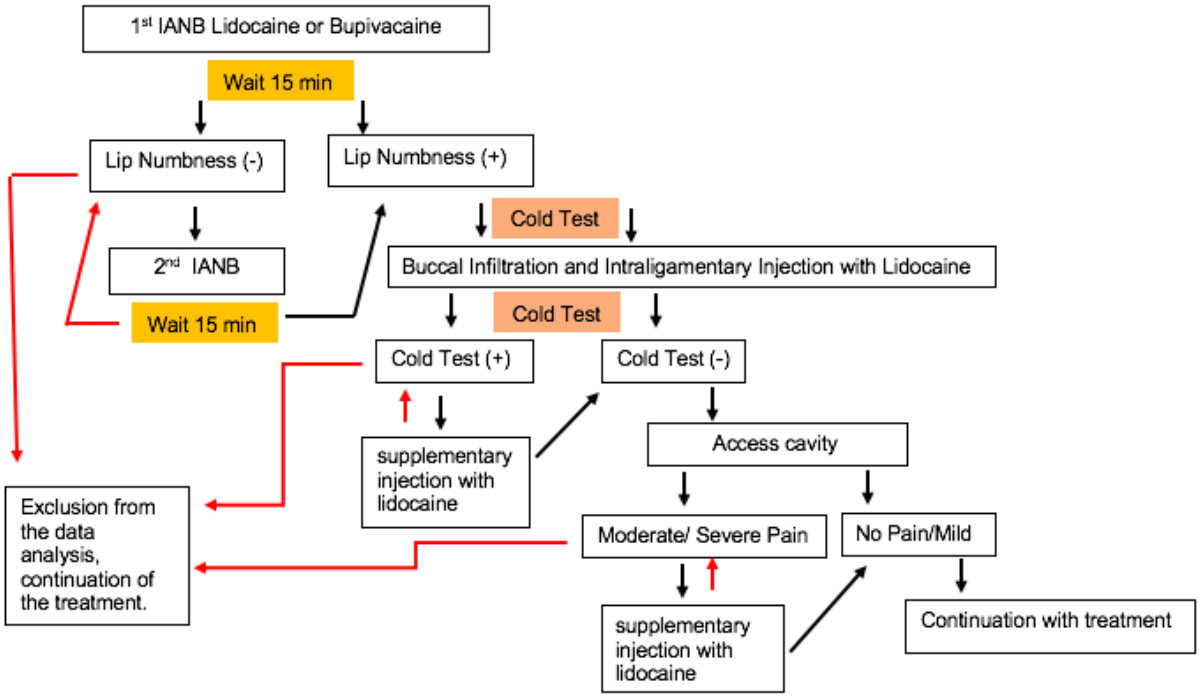
Whether the adequate lip numbness is gained either after the 1st or 2nd IANB, another 10 minutes will be waited to achieve pulpal anesthesia;

1. Cold Test - As per standard of care, Endo-Ice (Coltene, USA) will be administered to subjects to determine the success of pulpal anesthesia. This is a routine step in endodontic treatment. A cotton pellet is sprayed with the refrigerant spray and applied the tooth. A painful response will indicate inadequate pulpal anesthesia.

Subjects in each group will also receive a buccal infiltration and IL injection with Lidocaine which is highly recommended for symptomatic teeth. The Cold Test will be repeated to determine anesthesia. The algorithmic chart for anesthetic administration in Fig. 1 will be followed as the guideline. Additional supplemental injections will be administered as portrayed in the chart with Lidocaine HCl 2% 1:100,00 in both groups if needed, until pulpal anesthesia is obtained to initiate treatment or to continue with the treatment, without jeopardizing the maximum dose limit for the subject.

Subjects who need supplemental injections more than 2 times will be excluded from the study

**Figure 1: Algorithm to Follow Adequate Soft Tissue and Pulpal Anesthesia**



### 6.1.8 Duration of Therapy

The duration of the therapy begins with the administration of the IANB. The duration of the treatment is approximately 1-2 hours. The subject will then be followed remotely for 5 days.

The duration of study participation will be from the 1st treatment visit, until the participant returns for their second routine endodontic treatment visit. At this second visit, compensation will be given and data collection will be finalized, if necessary. This is in an effort to coincide the research visit with the routine and needed dental visit. This visit will be scheduled by the treating dentist and can be anywhere up to several weeks after the first treatment visit. There will be no time limit for this research visit. If the patient will return to the school for an appointment in another department/clinic, they can inform the research team and efforts will be made to meet the patient then if the 5 days post-treatment data collection is complete.

### 6.1.9 Tracking of Dose

The dose of anesthesia used both for IANB and for supplemental anesthesia will be recorded by a study investigator.

## 6.2 *Study Agent Accountability Procedures*

One carton containing 5 blisters of 10X1.8 mL of Bupivacaine, in total containing 50 cartridges and one cartoon containing 5 blisters of 10X1.7 mL Lidocaine in total containing 50 cartridges will be obtained initially from the Endodontic supply desk. Those cartons will be stored in a locked cabinet on the 7th floor, which will be only accessible by 2 post graduate (PG) students who are only delegated for study agent accountability procedures.
The two PG students who are only delegated for the study agent accountability procedures and blinding and randomization procedures will remove all drug cartridges from the blisters, wrap them with opaque tape and write a cartridge number assigned by Biostatistics prior to recruitment and place them in a container which will have the name of the drug. The same procedure will be done for the Lidocaine group. These two containers will be stored in a locked cabinet on 7th floor along with the blisters. This pre-wrapping will take place in order to not to waste time during the time of treatment.

A study product log will be created and maintained by these 2 PG students. The study product log will be signed and dated each time one of the two PG student removes a pair of cartridges. New cartons will be obtained from the supply desk when necessary and documented in the log. Unused product will be returned at the end of the treatment, if the cartridge is untampered. The two PG students will be responsible for maintaining this log and will reconcile the log each week assigned, to document drug consumed, and remaining.

## 6.3 *Study Procedural Intervention Description*

IANB, which is the route of administration for obtaining anesthesia for mandibular molars, will be the interventional procedure with the study and the control agent in both groups. It will be followed by routine pulpectomy/endodontic debridement treatment.

### 6.3.1 Administration of Procedural Intervention

The study product in both treatment groups will be administered by the treating post PG student Endodontic student in the endodontic clinic. This treating dentist may be a study investigator. In this case, the investigator will be blinded to the randomization. Another study investigator will be present to provide assistance for the research visit. All study related interventions and standard of care treatments which become part of the research will be overseen by NYS Dental Licensed faculty who are listed as Co-Investigators.

### 6.3.2 Procedures for Training of Clinicians on Procedural Intervention

PG endodontic students who have been trained for at least 6 months in the Endodontic program at NYU Dentistry will administer both the IANB and the pulpectomy/endodontic debridement. PG endodontic students are actively treating patients and have had all relevant didactic lectures before they start to treat

patients with symptomatic teeth for providing a standardized endodontic care. Before the beginning of the trial, they will be reviewed about the steps to follow for anesthetic administration and treatment in order to standardize the treatment they provide.

### 6.3.3 Assessment of Clinician and/or Participant Compliance with Study Procedural Intervention

By direct observation, clinician and participant compliance will be assessed by the study PI routinely.

# 7 Study Procedures and Schedule

## 7.1 *Study Procedures/Evaluations*

### 7.1.1 Study Specific Procedures

**1. Screening, Consent and Preoperative Data Collection:**

The potential participant's standard of care clinical and radiographic examination findings, diagnosis and treatment plan approved by the faculty who are NYS Dental Licensed Co-Investigators, will be prescreened by one of the study investigators after the standard of care clinical and radiographic examinations performed by the treating dentist to determine whether the patient is eligible in terms of diagnosis and treatment plan approved by the faculty by reviewing the gathered findings. This will be done in an effort to not to increase the wait time period for patients.

After prescreening, potential participant will be asked by their dental provider who are PG students who work under the supervision of Co-Investigators, if they are interested in discussing participation in a research study regarding postoperative pain with a research investigator. Interested subjects will be introduced to the study by the PI or Co-I; Ozge Erdogan. If they agree to participate, they will be consented by the PI or Co-I; Ozge Erdogan.

Interested potential subjects will be screened for eligibility by one of the study investigators and will be enrolled if they meet all the eligibility criteria.

The following questionnaires will be completed to collect demographic information, psychological state information and trait characteristics, preoperative pain, and baseline oral quality of life information:

- Subject Demographic and Medical/Dental/Pain History Form
- Pain Catastrophizing Scale (PCS)
- Oral Health Impact Profile (OHIP14)

**2. Randomization and Blinding:**

Subjects will be assigned a de-identified subject number upon enrollment in the study. Subjects will be randomly assigned to one of two study groups in a 1:1 ratio just before receiving anesthesia; 0.5% Bupivacaine with 1:200,000 epinephrine OR 2% Lidocaine with 1:100,000 epinephrine.

The randomization schema will be provided by the unblinded statistician and will be implemented using the REDCaP randomization module. Two PG students (Austin Ramsey, Kyungsik Yang) who are part of the study team, but are only delegated for the study agent accountability procedures and blinding and randomization procedures will wrap all of the drug cartridges of Bupivacaine with opaque tape and write on the vials a cartridge number assigned by the statistician prior to recruitment and place them in a container which will have the name of the drug. The same procedure will be done for the Lidocaine group. These two containers will be stored in a locked cabinet on 7$^{th}$ floor. At the time when a subject is recruited by the treating resident and is found eligible and signs a consent, one of the 2 PG students will be notified and will log onto REDCaP and retrieve the randomization for the subject within the appropriate stratum (Lidocaine/ Bupivacaine), pick up a pair of 2 pre-wrapped cartridges in accordance with the randomization scheme, write on the wrapped cartridges the assigned subject number in the consult room on the 7$^{th}$ floor, privately in order to prevent unintentional unblinding, log electronically the subject number with the corresponding numbers of the pair of cartridges assigned to subject, and hand it to the treating resident.

**3. IANB Administration, Testing Pulpal Anesthesia:**

The initial dose administered for groups will be one cartridge (1.8 mL for Bupivacaine, 1.7 mL for Lidocaine).

If adequate anesthesia is not achieved within 15 minutes determined by the treating dentist by;

1. Asking the subject for reporting of lip numbness
2. Testing and comparing with the contralateral side of the lip with a blunt instrument such as mirror handle, a second injection of the same dosage of the same drug will be provided.

If the IANB fails to provide adequate lip numbness after the second injection after a wait time of a further 15 minutes (total wait time 30 minutes), the subject will discontinue with the study agent/control agent, the treating dentist will be unblinded and routine protocol will be followed; Lidocaine 2% with 1:100,000 epinephrine will be administered either with an IANB, infiltration or intraosseous anesthesia as decided by the treating dentist. This patient will be excluded from the study.

After the adequate lip numbness is gained, another 10 minutes will be waited to achieve pulpal anesthesia;

Cold Test – As per standard of care, Endo-Ice (Coltene, USA) will be administered to subjects to determine the success of pulpal This is a routine step in endodontic treatment. A cotton pellet is sprayed with the refrigerant spray and applied the tooth. A painful response will indicate inadequate pulpal anesthesia.

Subjects in each group will also receive a buccal infiltration and IL injection with Lidocaine which is highly recommended for symptomatic teeth. The Cold Test will be repeated to determine anesthesia. The algorithmic chart for anesthetic administration in the supplementary form *Pulpectomy/Endodontic Debridement Method* will be followed as the guideline. Additional supplemental injections will be administered as portrayed in the chart with Lidocaine HCl 2% 1:100,00 in both groups if needed, until pulpal anesthesia is obtained to initiate treatment, without jeopardizing the maximum dose limit for the subject.

Subjects who need supplemental injections more than 2 times will be excluded the study.

**4. Intra- and Immediate Post-operative Data Collection:**

- Pre-operative data obtained after clinical and radiographic examination which are performed as standard of care, before the treatment procedure, such as cold test response, percussion hypersensitivity, pulpal and periapical diagnosis will be collected by a study investigator by the end of the treatment, together with the intraoperative and immediate postoperative data.
- Intraoperative data such as number of cartridges used, time for adequate anesthesia, additional supplementary anesthesia will be collected.
- Intraoperative pain will be evaluated on a NRS by asking the subject directly after treatment.

**5. Remote Data Collection:**

Subjects will receive surveys remotely either by e-mail through REDCap, which will ask about their pain intensity reported on an NRS, analgesic medication use and numbness. REDCap surveys will be sent at 6, 12, 24, 48, 72, 96 and 120 hours after treatment. On day 1 and 5, subjects will be assessed by OHIP14.

If subjects do not have access to the Internet, a study team member will call them. Paper questionnaires will also be an option if no other methods are convenient for subjects. If they prefer to fill in the questions and questionnaire on paper, they will be asked to bring them to their second appointment.

### 7.1.2 Standard of Care Study Procedures

**Clinical and Radiographic Examination:** Routine clinical and radiographic examination will be completed. Diagnosis will be determined with American Association of Endodontists (AAE) criteria. Treatment plan for pulpectomy/endodontic debridement is determined as discussed and approved by the attending faculty; NYS Dental Licensed Co-Investigators, in the clinic.

**Access cavity Preparation, Working Length Determination, Cleaning and Shaping of the Canals, Intracanal Medication and Temporization of the tooth:** After obtaining soft tissue, periradicular and pulpal anesthesia, the tooth will be isolated with a rubber dam. Endodontic access cavity will be prepared. Root canals will be initiated by #10 K files and working length will be determined by electronic apex locator. Root canals will be cleaned by rotary instruments and irrigation with 3% sodium hypochlorite through the procedure. Root canal preparation will be completed a minimum size of 25/0.4 up to 40/0.4 depending on the size of the canals. Canals will be dried out with paper points and calcium hydroxide will be placed as an intracanal medicament. The teeth will be temporized with Cavit-G. Subjects will be scheduled for the completion of the root canal treatment. Subjects will attend their second visit for the completion of the treatment. They may need to come for 3rd time depending on the complexity of the tooth, post-operative symptoms or signs of ongoing infections. Those appointments will not dictate or affect the study as the subject's participation will be completed after the second visit.

## 7.2 *Study Schedule*

### 7.2.1 Screening

**Screening and Enrollment (Day 0)**

- Prescreening
- Obtain informed consent of potential participant verified by signature on written informed consent.
- Screening of potential participants for eligibility.
- Enrollment

### 7.2.2 Baseline

**Baseline (Day 0/Day 1)**

- Verify the diagnosis and the treatment plan for the tooth.
- Verify eligibility by reviewing inclusion/exclusion criteria
- Preoperative data collection: results of routine clinical and radiographic examination, endodontic diagnosis,
- Baseline OHIP14 questionnaire

**Treatment**

- Administer the study intervention and dental treatment
- Collect intraoperative pain with a questionnaire to the subject after the completion of the treatment.

### 7.2.3 Remote Data Collection

Subjects will be asked to rate their pain intensity on an NRS, report analgesic use and numbness:

- 6 hours after treatment
- 12 hours after treatment
- 24 hours after treatment
- 48 hours after treatment
- 72 hours after treatment
- 96 hours after treatment
- 120 hours after treatment

- Day 1 – OHIP14 questionnaire

- Day 5 – OHIP14 questionnaire

### 7.2.4 Final Study Visit

Subjects will attend the endodontic clinic for the completion/second visit of their treatment as scheduled by the treating post graduate student under the supervision of NYS Dental Licensed Co-Investigators. This visit may be several weeks after the first treatment visit. At this routine visit, compensation will be provided

by a study investigator. If remote questionnaires were completed on paper, subjects will bring these forms to this visit.

The treatment may require a third visit but for the study this will be the final visit.

### 7.2.5 Withdrawal/Early Termination Visit

Documentation will be completed regarding the reasons for early termination/subject withdrawal.

### 7.2.6 Unscheduled Visit

It is possible that subject may need to attend the endodontic clinic as an emergency again because of the continuation of the symptoms or exasperation of the symptoms like pain and swelling. If one of the study investigators is being contacted, and if it is found out necessary, an unscheduled dental visit will be scheduled for the next available time in the clinic, with the treating PG student or the subject will be seen by the treating dentist on emergency as soon as possible. Details regarding the visit will be recorded for research purposes including; symptoms, treatment performed, any medication prescribed to the subject will be obtained from the treating PG student with a questionnaire.

## 7.3 *Concomitant Medications, Treatments, and Procedures*

All concomitant prescription medications related to the study taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

## 7.4 *Prohibited Medications, Treatments, and Procedures*

Subjects who use ergot-type oxytocic drugs, MAOI, tricyclic antidepressant or subjects who are planned to receive sedatives for the treatment should be excluded from the study because of drug interactions unless discussed with and approved by the investigator.

## 7.5 *Prophylactic Medications, Treatments, and Procedures*

No prophylactic medications, treatments and procedures are planned for the study unless the subject needs any of those prophylaxis for his/her treatment predetermined by the primary care physician.

## 7.6 *Rescue Medications, Treatments, and Procedures*

Subjects will be provided instructions verbally and written regarding rescue medication of ibuprofen and/or acetaminophen. They will be instructed that they can use 400-600 mg ibuprofen and 500 mg acetaminophen every 6 hours if there is no medical contradiction for the use of these medications. These are the routine instructions given after every endodontic treatment. In order to make it standardized, the instructions will be given verbally and written. They will record their analgesic use on the questions that they will receive. If these medications also don't help they will be instructed to call the phone number of the PI and after the phone call, if it is found out necessary, an unscheduled dental visit will be scheduled for the next available time in the clinic, with the treating PG student or they subject will be seen by another available post graduate student, both of whom work under the supervision of NYS Dental Licensed Co-Investigators, on emergency as soon as possible.

# 8 Assessment of Safety

## 8.1 *Specification of Safety Parameters*

The agents used in this study are FDA approved, commercially available products. Therefore, safety parameters are not the main endpoints. If any adverse events (AE), serious adverse events (SAE) or any unanticipated problems (UP) occur, they will be recorded and reported for the protection of human subjects.

### 8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. The adverse events for the study and control agent can be found on the attachment of the agents' package insert. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

### 8.1.2 Definition of Serious Adverse Events (SAE)

The serious adverse events for the study and control agent can be found on the attachment of the agents' package insert.

**Serious Adverse Event**

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

### 8.1.3 Definition of Unanticipated Problems (UP)

**Unanticipated Problems Involving Risk to Subjects or Others**

Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- <u>Related or possibly related to participation in the research</u> (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- <u>Suggests that the research places subjects or others at greater risk of harm</u> (including physical, psychological, economic, or social harm).

## 8.2 *Classification of an Adverse Event*

### 8.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.

- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

### 8.2.2 Relationship to Study Agent

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

### 8.2.3 Expectedness

The information on the insert package for both the study and the control agent will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

## 8.3 *Time Period and Frequency for Event Assessment and Follow-Up*

The occurrence of an AE or SAE may come to the attention of study personnel during study visit or during the remote follow up period. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, unless the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

### 8.4 *Reporting Procedures – Notifying the IRB*

Any AE, SAE and UP will be recorded by the study PI and will be reported to IRB and other necessary sites immediately.

### 8.5 *Study Halting Rules*

The study will be halted when three grade 3 AEs determined to be "probably related" are reported and enrollment screens will stop accepting new study participants.

### 8.6 *Safety Oversight*

It is the responsibility of the PI and NYS Dental Licensed Co-investigators to oversee the safety of the study. NYS Dental Licensed Co-investigators who are full time faculty members of the department oversee every step of diagnosis, treatment planning and treatment on the PG endodontic clinic where this study will take place. PI and NYS Dental Licensed Co-investigators will be also overseeing the diagnosis, treatment planning, study interventional procedure and standard of care treatment process which is a part of the study by working closely with the treating PG students. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Appropriate reporting of AE as well as proper and ethical construction and implementation of the study sight and safety monitoring will be carried out by the PI. Proper data safety monitoring and oversight will be carried out by the Co-Investigator; Ozge Erdogan.

## 9 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s) by the PI on a regular basis, including all the steps in the study; data collection, data verification of endpoint, and safety.

### 9.1 *Data Safety and Monitoring Plan*

The sources of the documents are the preoperative questionnaires, immediate and follow-up postoperative questionnaire collected either on paper form or in REDCap. All source documents will be stored securely in REDCap. Paper forms or documents will be securely locked on 4$^{th}$ floor room 407 and will be only be accessible to study team. The PI will ensure safety of the subjects by regular data monitoring, giving the accurate access permissions in REDCap as well as to the securely locked drawer.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB, the government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.).

# 10 *Statistical Methods*

## *10.1 Sample Size Determination*

Based on a previous study, the mean change of overall OHIP-14 scores from baseline at 1 month follow up is 6 with a standard deviation of 13.3 (27). Assuming the mean change from preoperative baseline at day 1 and day 5 postoperatively in the lidocaine group is 6 and the standard deviation is 13.3 and assuming the standard deviation of the change from baseline at day 1 and day 5 postoperatively is the same in the bupivacaine group, then with 40 subjects in each of the 2 groups there is 80% power to detect a difference in the change from preoperative baseline of +/-9.3 between the 2 groups. Assuming significance level of 2.5% using a 2-sided 2-sample t-test (assuming the data are Normally distributed). The testing is done at 2.5% because the null hypothesis will be rejected if at least one of the changes, either from baseline to day 1 postoperatively or from baseline to day 5 postoperatively, is significantly different between the 2 groups.

Considering the dropout rate after randomization will be 20%, the total number of subjects need to be enrolled is 100. The dropped-out subjects are those who are needed to be excluded because of intraoperative exclusion criteria, and who are not compliant to complete postoperative questionnaires. NYU Dentistry, endodontic clinic is a busy clinic. We will most of the time recruit subjects from the endodontic emergency care where on a daily basis, on average 5 patients are being treated. However, we are unsure of how many cases will be screened in order to reach this approximate sample size but we will update the protocol as this information is obtained.

## *10.2 Statistical Analysis*

### 10.2.1 Analysis Dataset

The analysis dataset for study and control group will include subjects who receive IANB either with the study agent Bupivacaine or the control agent Lidocaine for the pulpectomy/endodontic debridement of symptomatic mandibular molar teeth diagnosed with either symptomatic irreversible pulpitis or pulp necrosis and periapical diagnosis of normal periapical tissues, asymptomatic or symptomatic apical periodontitis The dataset will consist of preoperative data (demographics, preoperative pain assessment, PCS, LOT-R), initial clinical examination (cold test, percussion hypersensitivity), diagnosis, intraoperative data, initial and follow up OHIP-14 scores and postoperative pain, medication use and numbness. All analyses will be intent-to-treat dataset that includes all randomized patients and will use the analysis dataset.

### 10.2.2 Descriptive Statistics

Within each randomized treatment group appropriate descriptive statistics including means and standard deviations for quantitative variables and frequency and percentages for categorical variables will be calculated. Wilcoxon Rank Sum test and Fisher's exact test will be used to compare the two intervention groups with respect to the following baseline variables:

- Demographics (age, sex, race, ethnicity)
- Initial pain intensity and duration
- Pain medication use
- Pain Catastrophizing Scale
- Initial diagnosis (symptomatic irreversible pulpitis with/without symptomatic apical periodontitis and pulp necrosis with symptomatic apical periodontitis)
- Initial clinical testing of cold response (positive/negative)
- Initial clinical testing of percussion hypersensitivity (painful/not painful)

Any variable deemed significant will be controlled for in the primary, secondary and exploratory analyses. All analyses will be done with significance level of 5% (2-sided) unless specified otherwise.

### 10.2.3 Primary Analysis

For the primary objective we will compare the oral quality of life OHIP-14 score change from preoperative baseline to day 1 postoperatively and the change from preoperative baseline to day 5 postoperatively between the 2 arms using a two-sample t-test (or a Wilcoxon Rank Sum test if data are not normally distributed) for each comparison individually at 2.5% significance level (2-sided) adjusted for the two comparisons using a Bonferroni correction. If at least one of the changes, either from baseline to day 1 postoperatively or from baseline to day 5 postoperatively, is significantly different between the 2 groups, the null hypothesis will be rejected.

For each of the 7 sub-domains of OHIP-14 we will calculate the mean change from preoperative baseline to day 1 and to day 5 in both arms.

### 10.2.4 Secondary Analysis

1. For the secondary objective we will compare the efficacy of bupivacaine with that of lidocaine over the postoperative 5 days using mixed models for longitudinal data. The efficacy will be compared in terms of the following measures: postoperative pain resolution,
2. pain medication use,
3. numbness (duration of LA) after receiving endodontic treatment

### 10.2.5 Exploratory Analysis

The success of LLA will be determined by the cold test results (+/-) and the number of supplemental injections. The onset of LLA will be determined by the duration until adequate lip numbness and the duration until negative cold response after IANB.

For the exploratory objective we will compare the success and onset of LA in the two study arms. For comparison of success of LLA between the 2 arms we will use Fisher's exact test. For comparison of onset of LLA between the 2 arms we will use a Wilcoxon Rank Sum test.

### 10.2.6 Ad Hoc Stopping Rule

After 40 patients are accrued (approximately 20 subjects in each arm) an ad-hoc analysis will be performed to assess and compare the success of LA in both groups. If the proportion of subjects who are excluded intraoperatively in the study arm is twice as large as that of the control arm, the study will be terminated. The reasons for being excluded intraoperatively are if adequate lip numbness is not obtained with 2 inferior alveolar nerve block anesthesia and/or adequate pulpal anesthesia is not obtained after 2 times of supplemental anesthesia. Although, this is not a safety issue, we do not want to create more risks of intraoperative pain than routine endodontic practice. This analysis will be done by the study statistician. The investigators will remain blinded to the subjects' treatment arm.

### 10.2.7 Adherence and Retention Analysis

Participation adherence, study retention/loss to follow-up, and frequency of and reasons for discontinuation of the intervention will be recorded and assessed.

### 10.2.8 Safety Analysis

None planned. The anesthetic solutions used in the study are FDA approved, commercially available products and readily available at NYU College of Dentistry. There are no specific safety endpoints for the study. However, if there are any reported AE, SAE or UP, they will be recorded and reported as per protocol.

## 10.1 *Measures to Minimize Bias*

### 10.1.1 Enrollment/Randomization/Masking Procedures

Subjects will be assigned a de-identified subject number upon enrollment in the study. Subjects will be randomly assigned to one of two study groups in a 1:1 ratio just before receiving anesthesia; 0.5%

Bupivacaine with 1:200,000 epinephrine OR 2% Lidocaine with 1:100,000 epinephrine. The randomization schema will be provided by the unblinded statistician and will be implemented using the REDCap randomization module.

Two PG students, who are only delegated for the study agent accountability procedures and blinding and randomization procedures will wrap all of the drug cartridges of Bupivacaine with opaque tape and a cartridge number assigned by Biostatistics prior to recruitment and place them in a container which will have the name of the drug. The same procedure will be done for the Lidocaine group. These two containers will be stored in a locked cabinet on 7th floor.

At the time when a subject is recruited by the treating resident and is found eligible and signs a consent, one of the 2 PG students will be notified and will log onto REDCap and retrieve the randomization for the subject within the appropriate stratum (lidocaine/ Bupivacaine) pick up a pair of pre-wrapped cartridges in accordance with the randomization scheme, write on the wrapped cartridges the assigned subject number in the consult room on the 7th floor, privately in order to prevent unintentional unblinding, log in the subject number with the corresponding numbers of the pair of cartridges, and hand it to the treating resident.

### 10.1.2 Breaking the Study Blind/Participant Code

The blind will be broken for the individual, if IANB doesn't provide adequate soft tissue numbness after 15 minutes after the second cartridge of anesthesia was administered because the method of injection of LA might change if IANB doesn't provide adequate lip numbness after 2nd injection. The blind will also be broken for those subjects who need supplemental injections more than 2 times because of reporting of more than mild pain when being worked on as shown in the algorithmic chart for anesthetic administration in Fig. 1 The subject will be excluded from the study. If number of supplemental injections increases, the injections themselves may also contribute to postoperative pain and discomfort.

In case of AE, SAE or UP, the blind will be broken for the individual. It will be reported to the PI. If unblinding occurs because of an emergency situation such as AE, SAE or UP, the PI will be informed. If it is an emergency AE, SAE or UP, the attending faculty; NYS Licensed Co-Investigators on the floor may be the first one to reach out to before the PI can be present on the floor by the treating PG student. The Co-Investigator will call to access medical emergency if any such event occurs. Resuscitative equipment and personnel for treating adverse reactions will be immediately available. If it is a delayed AE, such as persistent anesthesia that lasted more than the expected period, the subject will inform the PI and PI will be responsible for any additional clinical examination and diagnosis and referrals.

# 11 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. The sources of the documents are the preoperative questionnaires, immediate and follow-up postoperative questionnaire collected either on paper form or in REDCap. Also, questionnaire regarding subject's preoperative clinical examination and diagnosis, intraoperative data will be collected in a questionnaire from the treating PG student. All source documents will be stored securely in REDCap. Paper forms or documents will be securely locked on 4th floor room 407 and will be only be accessible to study team.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB, the government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

# 12 Quality Assurance and Quality Control

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written standard operating procedure (SOP), the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol. The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

## 12.1 *Data Monitoring Regarding Drug Accountability*

One carton containing 5 blisters of 10X1.8 mL of Bupivacaine, in total containing 50 cartridges and one cartoon containing 5 blisters of 10X1.7 mL Lidocaine in total containing 50 cartridges will be obtained initially from the Endodontic supply desk. Those cartons will be stored in a locked cabinet on the 7$^{th}$ floor, which will be only accessible by 2 post graduate (PG) students who are not otherwise part of the trial.
The two PG students who are only delegated for the study agent accountability procedures.

A study product log will be created and maintained by the 2 PG students assigned (Austin Ramsey and Kyungsik Yang). The study product log will be signed and dated each time one of the two PG student removes a pair of cartridges. New cartons will be obtained from the supply desk when necessary and documented in the log. The two PG students will be responsible for maintaining this log and will reconcile the log each week assigned, to document drug consumed, and remaining.

# 13 Ethics/Protection of Human Subjects

## 13.1 *Ethical Standard*

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

## 13.2 *Institutional Review Board*

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

## 13.3 *Informed Consent Process*

### 13.3.1 Consent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. Each participant will be given a copy of the consent form to bring home. This will include contact information for the PI.

Potential subjects will be informed that the purpose of the study is to compare their oral quality of life and pain resolution with two different standard of care dental anesthetics postoperatively. They will be informed about possible, risks and benefits.

In order to successfully blind the subjects, they will not be informed of the names and differences in duration of two types of study product used in the study. Subjects will be informed that both products are FDA

approved, commercially available and routinely used in the NYU Dentistry clinics. They will also be informed that the products are used to provide soft tissue anesthesia between 3-7 hours.

It is important to blind the subjects in terms of the differences of duration of the two products because the outcome measures are patient centered and any bias could affect the study results and prevent objective data collection. When the participant returns for the second treatment visit for the completion of the treatment, they will be debriefed and told which product they received.

The following materials are submitted with this protocol:

- Screening and eligibility form
- Key information form
- Consent form
- Subject contact form
- Debriefing script

### 13.3.2 Consent Procedures and Documentation

Consent form will be presented to the eligible subject prior to any procedures being done specifically for the study in the consult room, or in an available dental chair, assuring subjects privacy. Consenting process will be completed either by the PI, Co-I; Ozge Erdogan. The consenting process will be carefully run and at the same time every effort will be made not to delay the patient's treatment taking into consideration that most of the patients are in pain and are waiting to receive treatment. Consenting process will take place in accordance with the NYULH SOP: Informed Consent Process and Documentation. The PI and the Co-I; Ozge Erdogan will be delegated for the consent process. Prior to recruitment, the PI and the Co-I; Ozge Erdogan will review the consent process in detail. Consent progress note for each subject will be completed, affirming that the appropriate procedures were followed.

Extensive discussion of risks and possible benefits of participation will be provided to the participants. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Consent forms describing in detail the study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. Each participant will be given a copy of the consent form to bring home. This will include contact information for the PI.

Potential subjects will be informed that the purpose of the study is to compare their oral quality of life and pain resolution with two different standard of care dental anesthetics postoperatively. They will be informed about possible, risks and benefits.

In order to successfully blind the subjects, they will not be informed of the names and differences in duration of two types of study product used in the study. Subjects will be informed that both products are FDA approved, commercially available and also available in the clinic. They will also be informed that the products are used to provide soft tissue anesthesia between 3-7 hours.

It is important to blind the subjects in terms of the differences of duration of the two products because the outcome measures are patient centered and any bias could affect the study results and prevent objective data collection. When the participant returns for the second treatment visit for the completion of the

treatment, they will be debriefed (verbally and by a written form) and told which product they received. They will receive information about all issues that was not completely shared with them during consent process (names of the LAs, duration of LAs) and why this information was not shared at that time.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. The other copy will be provided to the subject. A copy of the consent form can be found in the appendix.

### 13.4 *Posting of Clinical Trial Consent Form*

This section describes plans for ensuring compliance with Federal Regulations 45 CFR 46.116(h) for clinical trials. The PI will post the IRB-approved informed consent form used to enroll subjects on the publicly available Federal website.

The informed consent form will be posted on the Federal website after the clinical trial is closed to recruitment, **and no later than 60 days after the last study visit by any subject**, as required by the protocol.

### 13.5 *Participant and Data Confidentiality*

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Personal health information collected in this study includes the patient's name, and telephone number and email address. Participants will be identified via unique de-identified subject numbers, which link their personal information to the collected data. This will be kept in a master log in a locked cabinet on 4$^{th}$ floor room 407. Throughout the study, after de-identification, all personal information will be entered into a HIPAA compliant online storage system, REDCap.

### 13.6 *Data Collection and Management Responsibilities*

Data collection will be performed directly using REDCap surveys. All the hard copies will be kept in a locked cabinet on 4$^{th}$ floor room 407. The REDCap database will be accessible to the study PI and study team via a specific username and password.

### 13.7 *Study Records Retention*

Source Documentation and CRFs are considered Research Data under the NYULH Policy on Retention of and Access to Research Data. As such, since this project incorporates protected health information (PHI), research data of this study must be retained for the period mandated by New York State law (six years from the date of discharge), whichever is longer, or at least six years after death).

### 13.8 *Protocol Deviations*

The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation. Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

## 14 Study Finances

### 14.1 *Funding Source*

The costs associated with the study will be provided by the Department of Endodontics at NYU College of Dentistry.

### 14.2 *Costs to the Participant*

Subjects will be responsible for any payment related to the treatment received. Subjects will be informed that their participation in this study will not change the cost of their treatment.

### 14.3 *Participant Reimbursements or Payments*

Subjects will be given $25 in petty cash as an incentive after they complete the questionnaires sent to them for 5 days after the first treatment visit. This will be given when they attend the clinic for their second treatment visit several weeks later. Subjects will be able to obtain the petty cash from the bursar located on the sublevel of the NYUCD building.

## 15 Study Administration

**Principal Investigator:** Asgeir Sigurdsson, DDS, MS, Professor and Chair, NYUCD, Department of Endodontics

**Co- Investigator:** Ozge Erdogan, DDS, Instructor, NYUCD, Department of Endodontics

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**Other Investigators:**
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**Statistician:** Benjamin A. Levinson, PhD, NYU School of Medicine, Department of Population Health, Division of Biostatistics

## 16 Conflict of Interest Policy

Investigators have no conflict of interest.

## 17 References

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# 18 Attachments

Insert package for bupivacaine and lidocaine

- Screening and Eligibility Form
- Consent Form, Key Information Form
- Subject Contact Form
- Subject Demographic and Medical/Dental/Pain History Form
- OHIP-14
- PCS
- Preoperative Examination and Diagnosis Form to the PG Student
- Intraoperative Pain Evaluation Form to the Subject
- Intraoperative Evaluation Form to the PG Student
- 5 Day Pain and Medication Follow-up Questionnaires
- Debriefing Script

# 19 Schedule of Events

| Activity | Emergency Visit | Remote Data Collection | 2nd Visit |
|---|---|---|---|
| Pre-Screening | | | |
| Consent and Screening/Eligibility | | | |
| Preoperative Evaluation Questionnaires | | | |
| Clinical and Radiographic Examination | | | |
| Randomization | | | |
| IANB administration | | | |
| Treatment | | | |
| Collection of Questions to the Subject and the PG student | | | |
| 5 Day Remote Data Collection | | | |
| 2nd Visit Endodontic Treatment | | | |
| Collection of Remaining Documents | | | |
| Presentation of Compensation and Debriefing | | | |

Procedures completed by the study team.
Procedures completed by the treating PG student who can also be a study team member.

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