Title: Lidocaine Versus Bupivacaine in Orthognathic Surgery

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A. Specific Aims/Objectives

Aim 1: To assess patient experiences with pain, numbness, light touch perception, temperature sensation and narcotic and pain medication consumption following administration of bupivacaine and lidocaine in orthognathic surgery.

Aim 2: To determine if differences exist in patient-reported outcomes regarding the use of bupivacaine and lidocaine in orthognathic surgery.

B. Background and Significance

Lidocaine (known as lignospan commercially) and bupivacaine (known as marcaine or sensorcaine commercially) are two local anesthetics used ubiquitously for procedures in the oral cavity.[1-3] Lidocaine is known for its fast-acting properties, which can take effect within one to two minutes of administration.[1,4,5] However, lidocaine also has a relatively short duration of action, typically lasting about one to two hours.[1,4,5] On the other hand, bupivacaine is slightly slower acting (takes effect in 10-15 minutes) but has a much longer duration of action (up to eight hours).[2-5] Both local anesthetics are used in orthognathic surgery (jaw surgery) and are within the standard of care for these procedures.[1,2] Lidocaine and bupivacaine are both administered with epinephrine as an additive to reduce bleeding in the operative field and improve the depth and duration of anesthesia.[6] Some patients may experience significant pain postoperatively if their local anesthetic is metabolized too quickly, while others may experience prolonged numbness and decreased sensation if their local anesthetic has too long of a duration of action.[1-4]

C. Preliminary Studies

The majority of preliminary studies that explicitly compare lidocaine and bupivacaine are in the context of third molar extractions.[7-10] However, in terms of orthognathic surgery, there has not been a study performed that replicates our proposed study design.

Shetty et al. (2019) published a double-blind RCT with 110 participants (split into two equal groups).[11] Subjects underwent orthognathic surgery (Le Fort I with or without segmental osteotomies and BSSO with or without sliding genioplasty).[11] The experimental group received lidocaine and bupivacaine intraoperatively, while the control group only received lidocaine.[11] Bupivacaine was found to significantly decrease postoperative pain, discomfort, and analgesic consumption.[11] Although similar to our proposed methodology, our study is unique in that we hope to demonstrate anesthetic superiority (in either anesthetic) in the same patient, as patients have varying pain tolerances.

KC et al. (2022) published a triple-blind, randomized, placebo-controlled trial to assess the clinical analgesic effect of bupivacaine for *postoperative* pain management.[12] Bupivacaine (experimental) and saline (control) injections were administered in 28 subjects (14 per group) following an orthognathic procedure (BSSO).[12] There were no significant differences found in pain perception between the bupivacaine and saline injections. This study utilizes bupivacaine postoperatively, while our study would utilize bupivacaine intraoperatively.[12]

The literature on bupivacaine in orthognathic surgery specifically is limited. Aside from third

molar extractions, the use of bupivacaine has been explored in the following categories (all do not fall within orthognathic surgery): periodontal surgeries of the mandibular and maxillary regions,[13-15] endodontic therapy,[13,16] mandibular and maxillary teeth with irreversible pulpitis,[13,17,18] impacted molars that are not third molars,[13,19] individual tooth extractions,[13,19] and individual tooth preparation for other dental procedures.[13,20-23]

Maben et al. (2023), Bouloux et al. (1999), and Danielsson et al. (1986) all also compare bupivacaine and lidocaine. The former was in the context of mandible fractures while the latter two were in the context of third molar extractions.[24-26] Maben et al. (2023) tested a combination anesthetic (lidocaine vs. lidocaine + bupivacaine) and found that the combination anesthetic had a longer duration of action and required less volume administered.[24] Bouloux et al. (1999) compared lidocaine and bupivacaine explicitly in 23 third molar extraction cases and found that bupivacaine significantly reduced postoperative pain at the 8-hour period, and no other time point.[25] Danielsson et al. (1986) compared lidocaine, bupivacaine, and etidocaine in the context of third molar extractions.[26] They found that all three were effective at blocking pain, but bupivacaine was the most effective.[24-26]

Khan et al. (2015) assessed bupivacaine and lidocaine in third molar extractions, similar to Bouloux et al. (1999) and Danielsson et al. (1986).[27] However, they found no significant differences in intraoperative pain experiences in their 40 subject cohort.[27]

Given the current literature, we believe this would be a meaningful study, especially given the opportunity to employ a novel approach and compare the two anesthetics in the same patient.

D. Design and Methods

(1) Study Design

This is a prospective, randomized controlled trial. There will also be a small retrospective component of this study that involves data collection of demographic and clinical information. We aim to enroll 100 subjects.

(2) Patient Selection and Inclusion/Exclusion Criteria

Patients will be identified through an EMR search along with coordination with the surgical schedulers of the attending oral surgeons in the Department of Plastic and Oral Surgery at Boston Children's Hospital (Dr. Mark Green, Dr. Cory Resnick, and Dr. Bonnie Padwa). Inclusion criteria includes any patient undergoing orthognathic surgery between the ages of 15 and 35 years old weighing at least 40 kilograms. The data collection protocol (follow-up study visits) relies heavily on communication between the patient and the research personnel, which may be hindered if one party does not speak English. This could lead to a problem with protocol compliance that would be a confounding variable for this study and would not allow us to fully understand the patient experience following the use of lidocaine and bupivacaine in orthognathic surgery. Therefore, participants who do not speak English cannot be included. Other exclusion criteria includes any patient:

- Undergoing any other procedures in addition to their orthognathic procedure during the same sedation period (extraction, bone graft, etc.).
- With a history of chronic pain.

- With a history of an allergic reaction to bupivacaine or lidocaine.
- Any patient with known neurologic changes to the lip or chin.
- Any patient not enrolled in an Enhanced Recovery After Surgery (ERAS) Protocol.
- Known to be pregnant or with a positive pregnancy test prior to their procedure.

Whenever possible, patients and parents/guardians will first be approached by their clinical, followed by research staff, regarding their involvement in this study if they meet eligibility criteria. Patients and parents/guardians will be fully informed of the study, including its purpose, their involvement, and its risks. Patients and parents/guardians will be given time to ask questions regarding the study. Patients and parents/guardians will be approached regarding the study during their orthognathic work-up (OWU) visit, which is a part of standard care for patients undergoing orthognathic surgery and typically occurs four to six weeks prior to their procedure.

(3) Description of Study Treatments or Exposures/Predictors

Patients will be randomized into two equally sized groups. Group 1 will receive 6.8 cc of 0.5% bupivacaine hydrochloride and epinephrine 1:200,000 on the **left** side of their mandible and/or maxilla and 6.8 cc of 2% lidocaine hydrochloride with 1:100,000 epinephrine on the **right** side of their mandible and/or maxilla at the beginning of their orthognathic procedure. Group 2 will receive 6.8 cc of 0.5% bupivacaine hydrochloride and epinephrine 1:200,000 on the **right** side of their mandible and/or maxilla and 6.8 cc of 2% lidocaine hydrochloride with 1:100,000 epinephrine on the **left** side of their mandible and/or maxilla at the beginning of their orthognathic procedure. The use of bupivacaine and lidocaine are common practice in orthognathic surgery and are frequently used in conjunction with each other.

Email reminders will be sent to the oral surgeon reminding them that their patients is enrolled in this study. Following that email, another email will be sent to the oral surgeon by a member of the research staff (who is not performing the data collection visits) to inform them of which side they are able to administer which anesthetic. This allows the research staff member performing postoperative assessments, a different research staff member than the member who sent the email to the oral surgeon, to remain blinded. Research staff will not be aware of which side each participant received which anesthetic, which eliminates bias during the data collection visits. This information will be stored in a password-protected document that can be accessed if necessary.

(4) Definition of Primary and Secondary Outcomes/Endpoints

The primary outcome of this study is patient-reported pain. Secondary outcomes include numbness, perception of light touch and directionality, and temperature sensation. Covariates include narcotic and pain medication consumption postoperatively, procedure time, and procedure type.

Pain will be measured by asking patients to rank their pain on a scale from 1-10 on each side of their mandible/maxilla. Patients will then be asked to subjectively describe their pain experiences on each side of their mandible/maxilla. Patients will be asked to describe their feelings of numbness on a scale from 1-10 on each side of their

mandible/maxilla. Patients will be tested regarding their perception of light touch using Von Frey hairs. Von Frey hairs are standardized plastic filaments that are numbered numerically representing the weight in grams that it takes to bend the filament. Von Frey's hairs will also be used to assess perception of directionality. Temperature sensation will be assessed by application of warm and cold water to mandible/maxilla using cotton tip applicators. Patients will be prompted to describe the temperature of the sensation they are experiencing. Pain medication and narcotic consumption data will be collected retrospectively from the subject's EMR.

(5) Data Collection Methods, Assessments, Interventions and Schedule (what assessments performed, how often)

Subjects will have data collected at four time points, with all four visits containing the exact same series of questions and tests (discussed in Section D4). Subjects will first be assessed at their orthognathic work-up (the same appointment in which they are consented). Then, subjects will be assessed one hour following their orthognathic procedure while they are in the Post-Anesthesia Care Unit (PACU). Next, subjects will be assessed four hours following their orthognathic procedure. Finally, subjects will be assessed when they visit the Plastic and Oral Surgery Clinic for their one-week follow-up appointment, which takes place approximately one week following the orthognathic procedure.

(6) Study Timeline (as applicable)

This study will be conducted over a period of approximately three months.

- **Approximately 4-6 weeks prior to procedure**: recruitment and consenting of participants and pre-operative study assessment
- **Approximately 2 hour after procedure**: first post-operative study assessment
- **Approximately 4 hours after procedure**: second post-operative study assessment
- **Approximately 1 week after procedure**: third and final post-operative study assessment

E. Adverse Event Criteria and Reporting Procedures

Monitoring and reporting of adverse events will comply with the Children's Hospital Committee on Clinical Investigation and Clinical Research Center requirements. An adverse event will be defined as any unfavorable, harmful, or pathological change in a research subject as indicated by physical signs, symptoms, and/or clinically significant abnormalities that occur during the treatment period, regardless of the suspected cause.

Serious adverse events will be defined as any adverse that: is fatal; is life-threatening (places subject at immediate risk of death); is persistently or significantly disabling; results in or prolongs hospitalization; is an event that, in the opinion of the principal investigator, may jeopardize that subject or may require medical or surgical intervention to prevent one of the outcomes listed previously.

F. Data Management Methods

Data will be organized on standardized data collection forms. Data will be managed by using REDCap, which is supported by the Boston Children's Hospital Clinical Research Program. REDCap is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.[28] Our REDCap database is only accessible to the research staff. The database will be checked monthly by the research coordinator and the PI for data accuracy. Each subject will be given a unique study code to identify them and will not incorporate or be derived from any PHI. The link between the study code and the medical record number will be kept in a locked/password-protected file. No patient identifiers will be revealed upon publishing or presenting these data. All data collected for this research study will be kept completely confidential in a locked cabinet or will be entered into a secure password-protected computer database on the secure hospital network accessible only to researchers directly involved in the study.

G. Quality Control Method

A limited number of investigators will be obtaining study consent or subject evaluation. The principal investigator will review study folders at regularly scheduled intervals. Statistical data will be reviewed by the research assistant with ad hoc biostatistician consultation. Additional data analysis and checking for data accuracy will be performed by research staff with prior data analysis experience.

H. Data Analysis Plan

Descriptive statistics will be calculated to provide demographic and clinical information whenever possible about the cohort (mean, standard deviation, median, range). A matched pair design will be used, with each subject being their own match. Pain scores will be assessed using a repeated measures ANOVA. All categorical and binary outcomes will be assessed using a McNemar's test for unadjusted comparisons. For adjusted modeling for the categorical outcomes, a conditional logistic regression model will be used.

I. Statistical Power and Sample Considerations

In a review of related studies, the effect size for the primary research question ranged from 0.54 to 1.32. Given that our sample will be a matched pair analysis rather than an independent sample analysis, we conservatively applied an effect size of 0.57, power of 80% and a significance level of 0.05, which resulted in a sample size of approximately 50 patients.

J. Study Organization

This study will be conducted primarily at the Boston location of Boston Children's Hospital. Patients will also be recruited from the Boston Children's Hospital – Waltham location. The data will be collected and analyzed under the direction of the principal investigator, Dr. Mark Green.

K. References

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