Study Title: **Randomized Trial of Bupivacaine as Adjuvant for Post-operative Pain in Mohs micrographic surgery**

Document Date: **May 13, 2020**

NCT# **04362566**

TITLE: **Randomized Trial of Bupivacaine as Adjuvant for Post-operative Pain in Mohs micrographic surgery**

1. Abstract

Mohs micrographic surgery (MMS) is regarded as the gold standard for the treatment of high-risk nonmelanoma skin cancer (NMSC) (1). Pain after MMS peaks on the day of surgery and slowly decreases thereafter. The most common post-operative analgesics include acetaminophen, ibuprofen and narcotics (2-3). Lidocaine is the most commonly used anesthetic in MMS, but bupivacaine has been shown in other surgical specialties to be an effective adjuvant to reduce post-operative pain and opioid use when injected locally in the immediate postoperative period (4-5). Bupivacaine has also been shown to reduce intra-operative pain during MMS (6). We plan a single-blinded prospective, randomized, controlled trial to determine if post-operative wound infiltration of bupivacaine versus normal saline improves post-operative pain and decreases need for post-operative pain medications including both narcotic and nonnarcotic analgesics.

2. Objectives

Perform a prospective randomized controlled trial to determine the effect of adding bupivacaine injection versus injection of normal saline (control) at end of Mohs micrographic surgery on:

1. Use of narcotic medication in the first 24 hours after surgery
2. Postoperative pain levels, amount and type of narcotic and non-narcotic pain medications used in 48 hours following surgery

3. Background and Significance

Mohs micrographic surgery (MMS) is the first-line treatment for high-risk nonmelanoma skin cancer (NMSC) and is increasingly used for melanoma and other cutaneous neoplasms. The surgical technique involves multiple stages of surgery followed by reconstruction and is typically performed under local anesthesia in the office setting in one day (1).

MMS is generally well tolerated, but post-operative pain is common (7). Pain peaks on the day of surgery and slowly declines in subsequent days (2-3). Risk factors for increased pain may include flap or graft repair type, location on scalp, lip, nose, or ear, younger age, and increased number of lesions treated (2, 8-9). Post-operative pain medication is not standardized in dermatological surgery, but often includes non-narcotic analgesics including acetaminophen and ibuprofen, and less commonly narcotic analgesics such as tramadol and oxycodone (9-11). Given the current national trend to reduce opioid use, a multimodal approach to pain management has been adopted by many surgical specialties to optimize analgesia perioperatively (12).

The most commonly used anesthetic in MMS is local subcutaneous infiltration of lidocaine 0.5 – 2% with 1:100,000 – 1:200,000 epinephrine (13-14). Lidocaine is quick-acting, can be buffered to reduce injection pain, and is well tolerated, but the duration of action is only two hours, making it less effective for post-operative pain (6, 12). Bupivacaine with epinephrine has a longer duration of action compared to lidocaine (up to four hours), but it is rarely used alone due to slower onset of action and more painful injection compared with lidocaine (12). Bupivacaine is used in many other surgical specialties, including general, plastic, and orthopedic surgery, as a peri-operative adjuvant and has been shown to reduce post-operative opioid use (4-5). It is generally well tolerated, carrying a class-effect risk of cardiac toxicity in high doses as does lidocaine, but has been shown to be safe in dermatologic surgery when used for wound infiltration (6, 14). A newer formulation of liposomal bupivacaine has been shown to be even longer lasting and safer, with pain control up to 72 hours and no reported cardiac toxicity (15-16). In addition, a recent study has showed subcutaneous infiltration of bupivacaine with epinephrine to be an effective intra-operative pain adjuvant during MMS compared to lidocaine alone (6).

Pain control post-operatively in MMS may be optimized by including bupivacaine injections at the end of the surgical procedure given its long-lasting anesthetic effects. There are currently no studies addressing the use of bupivacaine as an

adjuvant to control post-operative pain during MMS. We propose a prospective randomized controlled trial to evaluate the effectiveness of bupivacaine injection at the conclusion of surgery for reducing post-operative pain and analgesic use.

4. Study Sites:

a. Lead site: The University of Missouri Dermatology and Skin Surgery Center will function as the lead site for this research
b. Participating sites:
    i. University of Pennsylvania Department of Dermatology
    ii. Columbia University Department of Dermatology
c. Research functions of each site:
    i. The lead site and participating sites will all perform similar research functions. All will enroll and consent patients, perform intervention and placebo injections, and collect and document data.
    ii. The lead site will be responsible for aggregation and statistical analysis of the data
d. Approvals per site:
    i. All sites will obtain approval from their respective IRBs.
    ii. Appropriate IRB approvals will be obtained prior to commencing patient enrollment at each particular site. Sites with approval will begin enrolling patients once their approval is obtained even if other sites have not yet obtained IRB approval.
e. Information management between sites:
    i. All sites will report information important to the protection of human subjects to one another by direct telephone communication as soon as possible in the case of unanticipated problems, protocol modifications and interim results.

5. Study Procedures

a. Study design:
    i. Prospective randomized controlled trial
    ii. Locations: University of Missouri at Columbia Dermatologic Surgery Unit (Columbia, MO), University of Pennsylvania Dermatologic Surgery (Philadelphia, PA), Columbia University Dermatologic Surgery (New York, NY).
    iii. Patients: All adult (18 years or older) patients presenting for Mohs micrographic surgery (MMS) and reconstruction for the treatment of melanoma or nonmelanoma skin cancer (NMSC) who fall into one of the following categories that have been identified as patients at increased risk of postoperative pain requiring narcotics in a recently published expert consensus in dermatology (17):
        a. Scalp rotation/transposition/advancement flap
        b. Ear rotation/transposition/advancement/interpolation flap or wedge repair
        c. Nose rotation/transposition/advancement/interpolation flap, cartilage alar-batten graft (ear donor site)
        d. Cheek Mustarde flap
        e. Lip rotation/transposition/advancement flap, wedge repair, Abbe flap
    iv. Consent:
        a. Consent will be obtained when a patient is offered the opportunity to participate in the study. Because we will not know who meets inclusion criteria for the study until Mohs surgery is completed, consent and randomization will occur midway through the patient's treatment. i.e. once the skin cancer has been completely removed with Mohs surgery, but before a reconstruction begins. During Mohs surgery, the patient is treated with local anesthetic. Mohs surgery and reconstruction are completed on the same say in the same encounter in most cases. Therefore, the most appropriate opportunity to obtain consent is if a patient is determined to need one of the above-described reconstructions, and this can only be done once Mohs surgery has ensured complete removal of the tumor.

v. Patients will be randomized into two arms once enrolled in the study and will be randomized by alternating group assignment as they are enrolled at each site. The study personnel will randomize patients to each group on day of surgery and patients and families will be blinded to intervention group assigned. One arm will serve as the control group and will receive wound infiltration injection of normal saline. A second arm will receive wound infiltration injection of 0.5% bupivacaine without epinephrine upon completion of MMS. These injections will occur once the reconstruction is completed before a bandage is applied. This dose and concentration were chosen because they were used in prior studies of bupivacaine in MMS (6). See below for protocol of injection volume by repair site, type and size.

   a. Scalp rotation/transposition/advancement flap: 2.5cc bupivacaine for 0-10cm2, additional 1cc for each additional 10cm2 up to max 5cc
   b. Ear rotation/transposition/advancement/interpolation flap or wedge repair: 2.5cc bupivacaine for 0-10cm2, additional 1cc for each additional 10cm2 up to max 5cc
   c. Nose rotation/transposition/advancement/interpolation flap, 2.5cc bupivacaine for 0-10cm2, additional 1cc for each additional 10cm2 up to max 5cc. Split volume between nose and donor site for melolabial interpolated flap
   d. Paramedian forehead flap: 5cc split between forehead donor site and nasal recipient site: 4cc forehead, 1cc nose
   e. Cartilage alar-batten graft (ear donor site) 1cc at auricular donor site in addition to bupivacaine used for nasal reconstruction, if any, that qualifies above
   f. Cheek Mustarde flap: 2.5cc bupivacaine for 0-10cm2, additional 1cc for each additional 10cm2 up to max 5cc
   g. Lip rotation/transposition/advancement flap, wedge repair, Abbe flap: 2.5cc bupivacaine for 0-10cm2, additional 1cc for each additional 10cm2 up to max 5cc

vi. All patients will receive standardized post-operative pain management instructions (see Appendix I) and be given prescription for tramadol 50 mg PO q6 hr prn #6 tabs.

vii. A standardized pain diary will be provided for each patient to record pain starting on postoperative day (POD) 0 and continuing in 8-hour increments until 48 hours, or six 8 hour increments, have passed. Study staff will need to complete the time intervals on the patient pain diary to facilitate patient logging of data for the correct times. Patients will record their worst pain rating for each time frame on a scale of 0 through 10, pain medication type(s) and dose taken, and whether they felt their pain was well controlled regardless of pain score (see attached). They will also be asked about potential bupivacaine-related post-operative adverse events (abnormal heartbeat or blood pressure, problems with level of alertness and need for hospitalization). The patient will be provided a pre-paid envelope to mail diary back to our department once complete.

viii. If a patient does not return survey in reasonable amount of time, the patient will be called once by study personnel to remind them to send it back or to verbally collect the data from the patient.

ix. Patient's medical chart will be reviewed for the following demographic and health history information:
   a. tumor type, location, number of MMS stages, deepest tissue type affected (fat, muscle, cartilage, bone, etc.), type/size of surgical repair
   b. amount and concentration intraoperative lidocaine used
   c. age, sex, depression/anxiety requiring medication, alcohol or other substance abuse, tobacco use

b. Study duration and number of study visits required of research participants.
   i. Duration sufficient to enroll 300 total patients combined from all treatment sites (approximately 150 per treatment arm). No additional patient visits will be required beyond the visit normally required for their procedure and/or suture removal.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.
   a. Single-blinded trial in which patients will be masked to which treatment arm they are assigned

d. Justification of why participants will not receive routine care or will have current therapy stopped.
   i. Care will be identical in both arms except for addition of bupivacaine vs normal saline at completion of MMS.

e. Justification for inclusion of a placebo or non-treatment group.

i. There will be a control group of patients who do not receive the intervention, bupivacaine injection, and instead will receive injection of normal saline in order to provide a blinded comparison to the intervention arm. This will prevent unconscious bias from affecting patient perception of postoperative pain. Saline is routinely used as a diluent for local anesthetic in Mohs surgery and does not represent a new or risky exposure for patients in the control group.

f. Definition of treatment failure or participant removal criteria.
   i. We do not foresee a scenario where treatment failure would be possible unless a patient declines bupivacaine injection intraoperatively, thus voluntarily leaving the study, or if a patient is unable to complete and return the pain diary post-operatively. Only patients who complete all steps of the study will be included in data analysis, but the number of enrollees who do not complete the study will be tabulated to track if there is a significant difference between the groups.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.
   i. There will be no effect on the patient.

6. Inclusion/Exclusion Criteria

a. Adult (18 years or older) patients being treated with Mohs micrographic surgery will be included in this study.
b. Surgical procedure must include one of the following:
   a. Scalp rotation/transposition/advancement flap
   b. Ear rotation/transposition/advancement/interpolation flap or wedge repair
   c. Nose rotation/transposition/advancement/interpolation flap, cartilage alar-batten graft (ear donor site)
   d. Cheek Mustarde flap
   e. Lip rotation/transposition/advancement flap, wedge repair, Abbe flap
c. Patients must not
   a. be known to be pregnant or breastfeeding
   b. be taking scheduled narcotic medications
   c. use narcotics as a drug of abuse
   d. have an allergy to bupivacaine or other amide anesthetics
   e. have a contraindication to tramadol
   f. have been given narcotic pain medications during the Mohs procedure or subsequent reconstruction
   g. have multiple surgical sites treated on the same day

7. Drugs/Substances/Devices

a. Active intervention group: injection of 0.5% bupivacaine HCl without epinephrine (volume varies by site, repair type and size, see Study Design iv for details).
b. Control group: Identically dosed injection of sterile normal saline

8. Study Statistics

a. Primary outcome variable.
   i. Determination of effects of bupivacaine injection on need for narcotic medication (Y/N) during first 24 hours post-surgery
      - Patient use of narcotics will be recorded by diary and compared across groups for all recorded time intervals
b. Secondary outcome variables.
   i. Determination of postoperative pain levels and amount/type of pain medication needed during 48 hours following operation

- Patient pain levels and pain medication use will be recorded from patient pain diaries and compared across groups

ii. Determination of adverse effects

- The severity, timing and number of adverse events recorded by diary will be compared across groups.

c. Statistical plan including sample size justification and interim data analysis

i. The statistical analysis will be done by the MU biostatistics group. The sample size is based on a power analysis based on pain variances from prior studies in this space. No interim data analysis is planned.

ii. Data will be analyzed on an intention to treat basis.

d. Early stopping rules.

i. None

9. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

i. Bupivacaine injection

1. Minor risk: Pain during injection (common)
2. Major risk: cardiac arrythmias or CNS excitation or sedation (uncommon and either from unintentional intravascular injection or dose-related).

ii. It is important to note that bupivacaine is already part of the standard of care postoperatively in Mohs surgery, so the use of bupivacaine in this setting is accepted practice and not experimental.

b. Steps taken to minimize the risks.

i. Pre-injection with lidocaine: shown to reduce pain of bupivacaine injection (15)

ii. Aspiration before injection to decrease unintentional intravascular injection (18)

iii. Low dosage: Maximum single dose recommended is 225 mg. We will be giving between 12.5 – 25 mg once. 12.5 mg is lower than recommended test dose of 15 mg (14)

iv. Subcutaneous injection only, which has been shown to be safer than IV or intrathecal dosing

v. Monitoring of patients post-injection for 10 minutes. If patients show sign of bupivacaine toxicity, they will be monitored longer in office setting up to 1 hour to be sure patient is safe for discharge home

c. Plan for reporting unanticipated problems or study deviations.

i. Will report all deviations and problems to IRB.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

i. Patient surveys sent via mail could be lost or sent to incorrect recipient, but the only patient identifier on the diary will be a randomly assigned study number.

e. Financial risks to the participants.

i. None.

10. Benefits

a. Description of the probable benefits for the participant and for society.

i. Patients may have reduced pain, reduced need for post-operative medication, and improved overall surgical experience if in the active arm

ii. If this intervention is helpful, then the findings will help to direct practice in our institution and possibly change current practices and protocols across the nation. This is of particular importance in the context of the narcotic use/abuse epidemic currently in the US. Research like this that may change the approach to narcotic prescriptions may have a positive impact on this issue.

11. Costs

a. An application for funding will be made for the MU Department of Dermatology Dyer research fund and from the MU MSDO Procedural Fellowship Endowment.

12. References

1. Tolkachjov, SN, et al (2017). Understanding Mohs micrographic surgery: a review and practical guide for the nondermatologist. In *Mayo Clinic Proceedings* (Vol. 92, No. 8, pp. 1261-1271). Elsevier.
2. Saco M, Golda N. Postoperative Pain Management in Dermatologic Surgery: A Systematic Review. *Dermatol Clin*. 2019;37(3):341–348. doi:10.1016/j.det.2019.03.004
3. Saco M, Golda N. Optimal timing of postoperative pharmacologic pain control in Mohs micrographic surgery: A prospective cohort study. *J Am Acad Dermatol*. 2020;82(2):495–497. doi:10.1016/j.jaad.2019.07.077
4. Roy CF, Azzi AJ, Davison P. A Review of Wound Infusion With Local Anesthetics in Plastic Surgery. *Ann Plast Surg*. 2019;83(6):e110–e117.
5. Dasta J, Ramamoorthy S, Patou G, Sinatra R. Bupivacaine liposome injectable suspension compared with bupivacaine HCl for the reduction of opioid burden in the postsurgical setting. *Curr Med Res Opin*. 2012;28(10):1609–1615. doi:10.1185/03007995.2012.721760
6. Chen P, Smith H, Vinciullo C. Bupivacaine as an Adjunct to Lidocaine in Mohs Micrographic Surgery: A Prospective Randomized Controlled Trial. *Dermatol Surg*. 2018;44(5):607–610. doi:10.1097/DSS.0000000000001385
7. Merritt BG, Lee NY, Brodland DG, Zitelli JA, Cook J. The safety of Mohs surgery: a prospective multicenter cohort study. *J Am Acad Dermatol*. 2012;67(6):1302–1309. doi:10.1016/j.jaad.2012.05.041
8. Limthongkul B, Samie F, Humphreys TR. Assessment of postoperative pain after Mohs micrographic surgery. *Dermatol Surg*. 2013;39(6):857–863. doi:10.1111/dsu.12166
9. Firoz BF, Goldberg LH, Arnon O, Mamelak AJ. An analysis of pain and analgesia after Mohs micrographic surgery. *J Am Acad Dermatol*. 2010;63(1):79–86. doi:10.1016/j.jaad.2009.10.049
10. Sniezek PJ, Brodland DG, Zitelli JA. A randomized controlled trial comparing acetaminophen, acetaminophen and ibuprofen, and acetaminophen and codeine for postoperative pain relief after Mohs surgery and cutaneous reconstruction. *Dermatol Surg*. 2011;37(7):1007–1013. doi:10.1111/j.1524-4725.2011.02022.x
11. Evans T, Nicholas TA, Sutton AV, Wysong A. How We Do It: Postoperative Pain Control in Mohs Micrographic Surgery [published online ahead of print, 2019 Dec 4]. *Dermatol Surg*. 2019;10.1097/DSS.0000000000002279. doi:10.1097/DSS.0000000000002279
12. Lovich-Sapola J, Smith CE, Brandt CP. Postoperative pain control. *Surg Clin North Am*. 2015;95(2):301–318. doi:10.1016/j.suc.2014.10.002
13. Park KK, Sharon VR. A Review of Local Anesthetics: Minimizing Risk and Side Effects in Cutaneous Surgery. *Dermatol Surg*. 2017;43(2):173–187. doi:10.1097/DSS.0000000000000887
14. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/071168s020lbl.pdf
15. Kouba DJ, LoPiccolo MC, Alam M, et al. Guidelines for the use of local anesthesia in office-based dermatologic surgery. *J Am Acad Dermatol*. 2016;74(6):1201–1219. doi:10.1016/j.jaad.2016.01.022
16. Sorenson E, Chesnut C. Liposomal Bupivacaine: A Review and Applications to Dermatologic Surgery. *Dermatol Surg*. 2019;45(1):68–73. doi:10.1097/DSS.0000000000001628
17. McLawhorn JM, Stephany MP, Bruhn WE, et al. An Expert Panel Consensus on Opioid-Prescribing Guidelines for Dermatologic Procedures [published online ahead of print, 2019 Nov 1]. *J Am Acad Dermatol*. 2019;S0190-9622(19)32899-3. doi:10.1016/j.jaad.2019.09.080
18. Sepah Y, Samad L, Altaf A, Halim MS, Rajagopalan N, Javed Khan A. Aspiration in injections: should we continue or abandon the practice?. *F1000Res*. 2014;3:157. Published 2014 Jul 10. doi:10.12688/f1000research.1113.3

Appendix I: Postoperative Pain Management Instructions

Given verbally by clinical staff at conclusion of surgery:

If needed, take Acetaminophen 1000 mg and ibuprofen 400 mg immediately after surgery, then every 4 hours as needed thereafter to maximum 4 doses. Limit acetaminophen to 2000 mg daily if liver disease and avoid ibuprofen if kidney impairment.

Rest and elevate surgical site when possible

Cold compress (ice or bag of frozen vegetables) for 15 minutes every 1-2 hours

Opioid tramadol 50 mg PO q6 hr taken only as needed for pain not relieved by earlier discussed measures, 6 tabs given