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## THESIS APPROVAL PAGE FOR MASTER OF SCIENCE IN ORAL BIOLOGY

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# **A Pilot Study on the effect of Liposomal Bupivacaine on Morphine Milligram Equivalents prescribed after third molar surgery at Carl R. Darnall Medical Center**

COL David R. Maxwell, DC USA

**Purpose:** The purpose of this Pilot Observational Retrospective Study was to assess if the use of Liposomal Bupivacaine (LB) as an adjunctive anesthetic to the surgical protocol in the extraction of partially bony and full bony impacted third molar teeth at Carl R. Darnall Army Medical Center (CRDAMC) Oral Maxillofacial Surgery (OMFS) Department significantly reduced the total Morphine Milligram Equivalent (MME) amount prescribed when compared to a surgical protocol that did not utilize LB as an adjunct.

**Methods:** An Observational Retrospective Cohort Longitudinal study was conducted via three collection methods: an archival dental chart review executed by the principle investigator; a collated opioid report provided by the Pharmacy DATA Transaction Service, and finally, the Surgeon's Log for services provided at CRDAMC. Data analysis was developed using a two-tailed T- Test and an established P value of 0.05.

**Results:** The statistical analysis demonstrated no significant difference in regards to the total MME prescribed when LB was routinely used as a surgical anesthetic adjunct in the extraction of partial/full bony third molar impacted teeth from 01 August 2020 to 31 August 2021, when compared to the time frame 01 July 2019 to 31 July 2020, when LB was not used as a surgical anesthetic adjunct. There was no significant difference in the number of pills dispensed in relation to the number of extracted teeth, nor the MME to the severity of the impacted teeth that were extracted.

**Conclusion:** In this study, the introduction of LB has not yet led to a decrease in post-operative opioid prescribing by the OMFS clinic at CRDAMC. More research is necessary to evaluate the effectiveness of LB as an adjunct for post-operative pain after third molar extraction. A randomized clinical trial that monitors real-time opioid prescribing and consumption would likely provide clinically relevant data.

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## **INTRODUCTION**

In the United States, opioid prescriptions exceed that of the other developed countries in the world. The role of dental providers and the ongoing opioid epidemic in the United States is well documented.<sup>1</sup> Dentists are a common source of opioid overexposure as dental clinician

prescribing accounts for 5% - 10% of all opioid prescriptions. One study showed that one in 23 people who initiated a dental prescribed opioid experienced persistent use, and persistence was associated with the type of opioid, number of days taken, and the dose of the prescription.<sup>1</sup> Lower prescription doses, shorter duration, and avoiding long-acting formulations could possibly mitigate the risk of opioid overuse.<sup>1</sup> It has also been suggested that the use of Liposomal Bupivacaine (LB) when used as an anesthetic adjunct via local infiltration could possibly reduce the need for opioid prescriptions after third molar extraction of at least (1) partial or full bony mandibular molar.<sup>2</sup>

The American Association of Oral Maxillofacial Surgeons published a white paper outlining certain criteria for the extraction of third molars. Among these criteria, the prophylactic extraction of third molars before the age of 25 is highly recommended to reduce the risk of disease and post-operative complications.<sup>8</sup> Many U.S. service members undergo surgery based upon this recommendation as well as frank pathology that is often associated with the presence of third molars, making third molar removal prophylactically and as a definitive treatment of pain and infection a large part of the military dentist workload.<sup>3</sup> The military population is one that is relatively young and healthy and dentists account for 31% of opioid prescriptions written for adolescents up to 19 years of age. It is documented that adolescent and young adult patients are 15 more times more likely to develop dependence within one year than the same population not prescribed opioids.<sup>4</sup> Many U.S. servicemen and women fall within the age category that puts them at a higher risk for opioid abuse, misuse, or dependence. In 2006, in the military population, opioids were routinely prescribed following third molar extraction.<sup>3</sup> Many U.S. servicemen and women fall within the age category that puts them at a higher risk for opioid abuse, misuse, or dependence. In 2006, The American Association of Oral Maxillofacial Surgeons published a white paper outlining certain criteria for the extraction of third molars. Among these criteria, the prophylactic extraction of third molars before the age of 25 is highly recommended to reduce the risk of disease and post-operative complications.<sup>8</sup> A large number of U.S. service members undergo third molar surgery based upon this recommendation as well as frank pathology that is often associated with the presence of third molars. In the military population, opioids are routinely prescribed following third molar extraction.<sup>3</sup>

Third molar extraction is associated with a defined period of short term pain and discomfort that traditionally leads to a prescription written for opioid analgesics. The median range in Morphine Milligram Equivalents (MME) is 30 following surgical extractions.<sup>1</sup> Opioid-naïve patients are at a higher risk for persistent opioid use following third molar extractions; therefore, new approaches to postsurgical analgesia are needed.<sup>2</sup>

One such approach to the opioid problem is the use of LB. Bupivacaine is the active compound in liposomal bupivacaine, which is an amide local anesthetic. Bupivacaine has a pKa of 8.1, and at a physiologic pH it is 83% ionized. Only the non-ionized form of anesthetic can cross the nerve membrane to proliferate the effect of anesthesia. This is why bupivacaine has a slower onset of action. The form of LB approved for use in the United States is based on DepoFoam technology. This technology consist of encapsulated drugs in a liposomal platform which can be released over a prolonged period of time, imparting the added benefit of prolonged duration alongside Bupivacaine's high lipid solubility. Liposomal Bupivacaine however decreases its toxic dose. In a study by Boogaerts et al., rabbits that were administered bupivacaine required more than twice as much LB to produce arrhythmia and seizure.<sup>5</sup> The manufacturer's recommendation is that LB be administered 20 minutes after lidocaine and any other forms of bupivacaine should not be used within 96 hours of LB infiltration.

EXPAREL is the common brand name of LB used in dentistry. The manufacturer recommended dosage of 133mg/10ml not to exceed a maximum dose of 266mg/20ml to be infiltrated at the third molar surgical sites approximately 30 minutes after the procedure.<sup>9</sup>

LB became of interest to the Oral Maxillofacial Surgery Clinic located at Carl R. Darnall Medical Center as a potential mitigating factor against the complaint of pain in the short term after an evidence-based article was assigned to the post graduate dental residents as a part of their monthly current literature review. The surgeon followed in this study was not consistently using LB post-operatively as a part of the third molar extraction protocol. Upon reading the evidence based article, the surgeon decided to consistently add LB to the third molar extraction protocol to ascertain whether its use would reduce the complaint of post-op pain.

The purpose of this study was to compare the total MME prescribed from July 2019 to July 2020, the time in which LB was not primarily used after third molar extraction to August 2020 to August 2021, the time when LB was primarily used after third molar extraction at the OMFS Clinic at CRDAMC.

Primary research question: Did the total number of MME prescribed decrease during the time period when LB was primarily used after third molar extraction versus the total MME prescribed when LB was not primarily used?

Null Hypothesis: There will be no significant differences between the total MME prescribed when LB was primarily used as a part of the third molar surgical extraction protocol versus the total MME prescribed when LB was not primarily used as a part of the third molar surgical extraction protocol.

## **MATERIALS & METHODS**

An observational retrospective cohort longitudinal study was executed by the principal investigator through an archival dental chart review. A collated opioid report was provided by the Pharmacy DATA Transaction Service, and the Surgeon's Log for services provided at CRDAMC Operating Room (OR) to differentiate clinic procedures from OR procedures was provided by the research mentor. Data analysis was developed by applying the two-tailed T-test to compare the total prescribed MME quantity for the time period of July 2019- July 2020 to the time period of August 2020- August 2021.

Only authorized personnel from the Department of Pharmacy Analytics Support Section (PASS) located in San Antonio, TX were granted access to the Composite Health Care System and Armed Forces Health Longitudinal Technology data repository system. These personnel were not a part of the study team. The report provided included all prescriptions written by a single provider for the two time periods and is limited to the drug prescribed, dosage, number of pills prescribed, and the number of patients without including any personal identifiable information (PII). The data was arranged in a spreadsheet format, by grouping variable using the specific Current Dental Terminology (CDT) Codes and segregated into year groups. **1st Year:** July 2019- July 2020, wherein LB was not primarily used as part of the surgical protocol and **2nd Year:** August 2020- August 2021; wherein LB was primarily used as part of the surgical protocol. The principal investigator extracted the controlled prescriptions written for the two time periods. The controlled prescriptions included: Oxycodone, Hydrocodone, Codeine, and Tramadol. The controlled prescriptions dosages were converted into Morphine Milligram Equivalents (MME) using the 2017 version of the Center for Disease Control's Opioid Oral Morphine Milligram Equivalent Conversion Factors Chart.<sup>6</sup>

The surgical procedures and LB information collected was a raw data summary obtained for one specific provider for the two year period of time concerned and was compiled by the Corporate Dental System (CDS) personnel located in San Antonio, TX. An ad hoc report included the following CDT codes: D7230- Removal of impacted tooth- partially bony (impaction), D7240- Removal of impacted tooth- completely bony (impaction), D9613- Infiltration of sustained release therapeutic drug- single or multiple sites.<sup>10</sup> CDS personnel were not a part of the study team.

The principal investigator queried the clinic notes during the time frames of interest to assess what occurred during the surgical extraction of partial and full bony impacted third molars. The clinic notes revealed that the procedure was standardized without any demonstrable variation. An excerpt from a typical surgical clinic note describing the procedure is as follows:

### **CLINIC NOTE**

Bite block placed. Anesthesia started. A total of 144 mg of lidocaine local anesthesia was administered via bilateral inferior alveolar, long buccal, lingual, greater palatine blocks and maxillary local infiltrations. Throat screen placed and announced to room. Tooth #1 - Sulcular incision on buccal with distal paramedian release using #15 blade. Full thickness mucoperiosteal flap elevated on buccal with a #9 mucoperiosteal elevator. Bone removed with #9 elevator and #4 Molt curette to expose tooth. Tooth luxated with dental elevator and delivered with dental forceps. Manual compressions of extraction socket.

Hemostasis verified. Tooth #16 - Sulcular incision on buccal with distal paramedian release using #15 blade. Full thickness mucoperiosteal flap elevated on buccal with #9 mucoperiosteal elevator. Bone removed with #9 elevator and #4 Molt curette to expose tooth. Tooth luxated with dental elevator and delivered with dental forceps. Manual compressions of extraction socket. Hemostasis verified.

Tooth #17 - Sulcular incision with distal lateral hockey stick release using #15 blade. Full thickness mucoperiosteal flap elevated on buccal with #9 mucoperiosteal elevator. Bone removed with hand-piece and 702 fissure bur to expose crown under copious irrigation. Crown and roots sectioned with fissure bur and split completed with dental elevator. Crown and roots luxated with dental elevator and delivered with dental forcep. Irrigation with normal sterile saline, flap repositioned and secured with 3-0 chromic gut suture in figure-8 fashion. Hemostasis verified. Tooth #32 - Sulcular incision with distal lateral hockey stick release using #15 blade. Full thickness mucoperiosteal flap elevated on buccal with #9 mucoperiosteal elevator. Bone removed with hand-piece and 702 fissure to expose crown under copious irrigation. Crown and roots sectioned with fissure bur and split completed with dental elevator. Crown and roots luxated with dental elevator and delivered with dental forcep. Irrigation with normal sterile saline, flap repositioned and secured with 3-0 chromic gut suture in figure-8 fashion. Hemostasis verified.

5cc Exparel administered via buccal and lingual mandibular buccal infiltrations. Procedure completed.

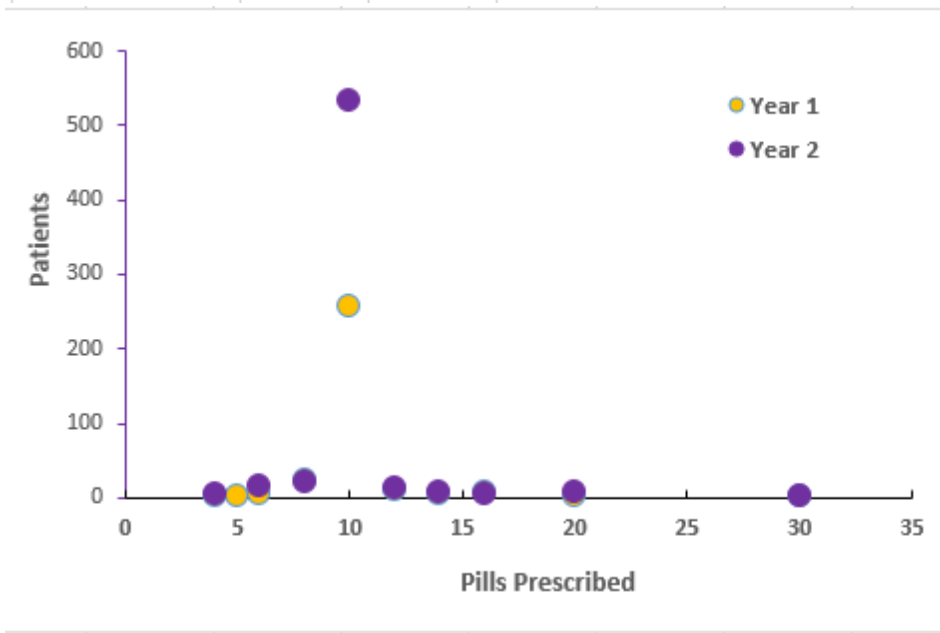
The Surgeon's Log was retrieved by the research mentor and forwarded to the principal investigator. The Surgeon's Log allowed the principal investigator to cross reference and exclude procedures that were performed exclusively in the Operating Room. This spreadsheet document was kept on a government computer assigned to the principal investigator. The computer is password and common access card (CAC) protected, and the system is firewall protected. There were no planned linkages with external databases. Data transferred from PASS, CDS, and the research mentor to the principal investigator was by encrypted email and secured against intentional or unintentional loss of confidentiality, integrity, or availability.

*STATISTICAL ANALYSIS:* The data analysis was conducted in conjunction with the biostatistics

analysis department at CRDAMC. Data analysis was developed with a two-pair T Test. The MME conversion factor that was used is intended only for analytic purposes where prescription data are used to calculate daily MME. The formula used was: Strength per Unit X (Number of Units/Days' Supply) X MME conversion factor = MME/Day. The MME conversion factors used were: Codeine (mg) 0.15; Hydrocodone (mg) 1; Oxycodone (mg) 1.5; Tramadol (mg) 0.1.<sup>6</sup>

**Figure 1**

# of Pills prescribed	1st Yr	2nd Yr
4	2	5
5	1	
6	5	15
8	23	22
10	258	533
12	9	12
14	4	7
16	8	6
20	2	8
30	1	3
10	258	533



**RESULTS**

Between both year groups 10 pills was the average number prescribed (figure 1).

The data collected in this study did not demonstrate any significant difference between the total MMEs prescribed when LB was used as a part of the surgical protocol in the extraction of third molars, as compared to when LB was not used as part of the surgical protocol (figure 2). Hydrocodone was the most common type of opioid prescribed during the two measured time periods.

**Figure 2**

	1st Year	2nd Year
Total prescriptions for pain	318	611
Total extractions	477	465
LB used	47	409
Average MME per prescription	29.97	30.01
P Value (Year 1 vs Year 2)	0.264	

## **DISCUSSION**

One shortcoming of this study was the selection bias of only reviewing a single provider's workload. The associated findings of this study could be coincident to the practice style of that one particular surgeon. While the data shows that the code for LB increased 10x fold from 2019 to 2021; there was not a commensurate reduction in the total amount of MMEs prescribed to patients. It is worth mentioning that during the time period representing Year Group 1, there were several months that the clinic was shut down as a result of the COVID-19 pandemic. As a result there was a reduced number of patients treated as compared to Year Group 2. Anecdotally, it can be deduced that the provider in this study did not have confidence that LB would be effective in eliminating short term (24-72 hours) pain; therefore, the amount of MME prescribed to patients were not reduced as one would expect. Also, this chart review did not indicate actual consumption of narcotics, rather it accounted for how many pills were prescribed to the patient. A future prospective cohort designed trial is needed. Potentially excluding OR cases could be useful due to the fact that the other drugs used to induce general anesthesia in the OR setting may have some effect on post-op pain. Observing the results of patients treated exclusively in the clinic setting where all patients receive the same moderate sedation protocol further reduce potential confounding variables. The actual tracking of opioid consumption is also needed versus opioids prescribed. Future studies can also serve as a touchstone for interdisciplinary partnerships. Some potential partners where information sharing would be mutually beneficial would include the Medical Center's addiction center; as well as the clinical pharmacy department, wherein an opioid return program after third molar extraction could be employed. Lines of effort in this regard addresses the Military Health System's Quadruple Aim by increasing readiness, providing better health, providing better care, and lowering per capita costs associated with the over use of opioids.

## CONCLUSION

The introduction of LB has not yet led to a decrease in post-operative opioid prescribing by the OMFS clinic at CRDAMC. More research is necessary to evaluate the effectiveness of LB as an adjunct for post-op pain after third molar extraction.

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