Review Article

Liposomal bupivacaine: a literature review of applications in oral and maxillofacial surgery

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Objective: The purpose of this review is to examine the use of liposomal bupivacaine for postoperative pain management and opioid dose limitation following oral and maxillofacial surgery (OMS) procedures.

Background: In the United States, the consequences of the opioid crisis have been felt across all 50 states. This crisis has posed a challenge to oral and maxillofacial surgeons given the conflicting goals of adequate postoperative pain management and limitation of opioid doses. With the goal of limiting postoperative opioid exposure in mind, multimodal analgesic protocols and long-lasting local anesthetics have come into focus. Liposomal bupivacaine is a long-lasting local anesthetic that was granted approval by the United States Food and Drug Administration in 2011 for single-dose infiltration at the surgical site for postoperative analgesia.

Methods: An online review of scientific articles was performed using the medical databases PubMed, the Cochrane Library, and clinicaltrials.gov. A total of 9 relevant studies were included in this review.

Conclusions: Liposomal bupivacaine may be a promising tool to adequately manage postoperative pain and limit opioid doses following OMS procedures. Future studies investigating the effectiveness of liposomal bupivacaine following common oral and maxillofacial surgical procedures such as maxillofacial trauma surgery, orthognathic surgery, and temporomandibular joint surgery are needed.

Keywords: Opioid; liposomal bupivacaine; pain

Received: 20 November, 2021; Accepted: 11 February, 2022; Published: 31 March 2022.
doi: 10.21037/joma-21-22
View this article at: https://dx.doi.org/10.21037/joma-21-22

Introduction

Local anesthesia plays a vital role in virtually all surgical procedures, especially procedures involving the head and neck. The development of local anesthesia was a pivotal moment in surgical history that has had a profound impact on perioperative patient comfort. In 1884, Koller used a cocaine solution to achieve anesthesia of the globe for ocular surgery, which subsequently sparked the interest of cocaine as a local anesthetic (1). Halsted and Hall later went on to report the first successful nerve blocks with a local anesthetic (2). The early findings of Halsted and Hall revolutionized the field of dentistry and oral and maxillofacial surgery (OMS) as the first nerve blocks were of the infraorbital and inferior alveolar nerve for a dental procedure.

Since the introduction of local anesthesia, many different formulations have been used for various OMS procedures. In 1957, the local anesthetic bupivacaine was introduced. Bupivacaine is an amide local anesthetic with an onset of action of 2 to 10 minutes following local infiltration and an anesthesia time of up to 7 hours in some patients (3). Compared to other amides such as lidocaine, bupivacaine provides a significantly longer duration of

anesthesia. Further advancement of anesthesia duration was achieved with the introduction of liposomal bupivacaine. Liposomes were first discovered by Bangham in 1964 (4). In a suspension containing bupivacaine, liposomes are used to further prolong anesthesia duration by allowing slow release of bupivacaine over time. Liposomal bupivacaine was granted approval by the United States Federal Drug Administration in 2011 as a long-acting local anesthetic intended for single-dose infiltration at the surgical site for postoperative analgesia. By slowly releasing a consistent dose of bupivacaine, up to 96 hours of anesthesia has been reported following administration (5).

With the recent opioid crisis, long-acting local anesthetics have come into focus as a tool to limit postoperative opioid consumption. In the United States, the consequences of the opioid crisis have been felt across all 50 states. In 2018 alone, prescription opioids were misused by approximately 10.3 million Americans resulting in more than 47,000 deaths (6). Awareness of this crisis has led to a decrease in opioid prescriptions over the last several years with increased emphasis on multimodal analgesic modalities. However, the number of prescribed opioid morphine milligram equivalents (MME) is still about three times higher than it was in 1999 due to the differences in opioid drug type and strength (7). Of interest to oral and maxillofacial surgeons, recent studies have shown that opioid use after wisdom tooth extraction is associated with chronic opioid use (8,9). In addition, it has been demonstrated that inpatient opioid exposure correlates with opioid use after discharge (10).

The management of postoperative pain poses a challenge to the oral and maxillofacial surgeon given the conflicting goals of adequate postoperative pain management and limitation of opioid doses. The purpose of this review is to examine the use of liposomal bupivacaine for postoperative pain management and opioid dose limitation following OMS procedures. We present the following article in accordance with the Narrative Review reporting checklist (available at https://joma.amegroups.com/article/view/10.21037/joma-21-22/rc).

Methods

An online review of scientific articles was performed using the medical databases PubMed, the Cochrane Library, and clinicaltrials.gov. Databases were searched for articles in the English language from January 1st, 2010, to November 26th, 2021, using keywords dentoalveolar, orthognathic surgery, TMJ, temporomandibular, dental extraction, dental, dentistry, dental implant, craniofacial surgery, maxillofacial trauma, odontogenic infection, and liposomal bupivacaine. MeSH terms were also used where available. Papers not written in the English language were excluded. A total of 25 articles were available. Studies that assessed the use of liposomal bupivacaine in OMS procedures were included. All titles and abstracts were screened for relevancy by the first and second author (TWN, YH), with disagreements reviewed and decided upon by the senior author (TS). A total of 9 studies were identified and included in this review. One registered clinical trial was identified; however, no results were available, and the recruitment status was unknown. Dosage and administration information was gathered from manufacturer and United States Federal Drug Administration articles and labels. *Table 1* outlines the review specifications.

Narrative

Dose and administration

Liposomal bupivacaine is currently available in 266 mg/20 mL and 133 mg/10 mL single dose vials and is composed of 1.3% bupivacaine in a liposomal suspension. When compared to bupivacaine HCl, liposomal bupivacaine has been shown to have a similar side effect profile and time to initial onset (11,12). The advertised price by the manufacturer is $189.27 per 10 mL vial and $344.20 per 20 mL vial. It may be diluted with preservative-free normal saline or lactated Ringer's solution if administered within 4 hours of preparation. The maximum dose for local infiltration in adults is 266 mg. Recently, the indication was expanded to include patients 6 years and older with a maximum dose of 4 mg/kg. However, administration is still not recommended for pregnant patients. It is recommended that liposomal bupivacaine not be administered within 20 minutes of administration of other local anesthetics, as this could cause immediate release of the bupivacaine. For use in OMS, liposomal bupivacaine is injected as a local infiltration while withdrawing the needle so as to infiltrate all tissue layers (13).

Third molar removal

In the outpatient sedation setting, third molar surgical extraction is a common procedure performed by oral and maxillofacial surgeons. Depending on the degree of trauma

Table 1 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	November 26th, 2021
Databases and other sources searched	PubMed, the Cochrane Library, Clinicaltrials.gov
Search terms used (including MeSH and free text search terms and filters)	Dentoalveolar, orthognathic surgery, TMJ, temporomandibular, dental extraction, dental, dentistry, dental implant, craniofacial surgery, maxillofacial trauma, odontogenic infection, and liposomal bupivacaine
Timeframe	January 1st, 2010–November 26th 2021
Inclusion and exclusion criteria (study type, language restrictions etc.)	Inclusion: studies that assessed the use of liposomal bupivacaine in oral and maxillofacial surgery procedures
	Exclusion: papers not written in the English language
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	All titles and abstracts were screened for relevancy by the first and second author (TWN, YH) with disagreements reviewed and decided upon by the senior author (TS)
Any additional considerations, if applicable	Not applicable

to the surrounding soft tissue and bony structures, patients typically experience moderate to severe pain and are frequently prescribed opioid medications for postoperative pain management. In a study by Lieblich *et al.* of 59 patients that received liposomal bupivacaine following third molar extraction, cumulative pain scores were significantly lower when compared to 30 patients that received a placebo. However, there was no difference in postsurgical opioid consumption between the two groups in the measured 48-hour postoperative period (14). Contrary to this finding, a large retrospective study of 600 patients found that liposomal bupivacaine following third molar removal resulted in 59% fewer prescribed postoperative opioid MMEs (15). In a pilot study by Magraw *et al.*, of the 24 studied subjects that received liposomal bupivacaine as part of a multimodal analgesic regimen following third molar removal, 10 filled zero postoperative opioid prescriptions, and 8 filled only one (16).

Dental implants

Implant placement for dental reconstruction is another routine OMS procedure. Mild to moderate pain is expected following implant placement depending on the amount of pre-prosthetic surgery required, the quantity of implants placed, and the experience of the surgeon. In a randomized prospective study following full-arch implant surgery, Iero *et al.* demonstrated that patients that received liposomal bupivacaine postoperatively reported significantly less cumulative pain levels than the control group at all study time points. However, there was no statistically significant difference in the usage of rescue opioid medication for severe breakthrough pain between the control and liposomal bupivacaine groups (17).

Orthognathic surgery

In a large study of 8,163 opioid naïve adults who underwent orthognathic surgery, Pakvasa *et al.* found that 45.6% filled a postoperative opioid prescription. This equated to an average daily MME of 66 and 17.9% of subjects that filled a prescription had persistent opioid consumption past 90 days (18). When evaluating inpatient opioid use of patients that underwent orthognathic surgery, Mobini *et al.* found the average opioid consumption was 106 MMEs (19). To date, there are no available prospective studies investigating the efficacy of liposomal bupivacaine following orthognathic surgery. Recently, our group retrospectively investigated MMEs of patients that received bimaxillary surgery from 2017 to 2019 at our institution. There were 19 subjects included, 10 of which received liposomal bupivacaine as local infiltration following bimaxillary surgery. Subjects that received liposomal bupivacaine following surgery had an average inpatient postoperative MME of 9.3, while subjects who did not had an average inpatient postoperative MME of 25 (20). There is a paucity of literature related to liposomal bupivacaine administration

following orthognathic surgery in comparison to its use following third molar surgery. Currently, there is a registered clinical trial investigating the effectiveness of liposomal bupivacaine following orthognathic surgery, but the results are not yet available.

Craniofacial

The anterior iliac crest has historically been used as an autogenous bone source to restore alveolar bone loss in patients suffering from facial trauma, congenital anomalies, pathology, and age-related resorption. Two recent studies have investigated the use of liposomal bupivacaine following anterior iliac crest harvest. In a retrospective cohort study of 38 patients that received either 0.25% bupivacaine or liposomal bupivacaine following anterior iliac crest bone graft, Patel *et al.* reported a significant difference in mean postoperative pain scores in the first 24 hours. There was also a significant difference in opioid consumption, as the liposomal bupivacaine group consumed a total MME of 4.7, while the control group consumed a total MME of 14.3 (21). Similar findings were reported by Crowley *et al.* in a study of 44 patients that underwent alveolar bone grafting using the anterior iliac crest. Subjects that received liposomal bupivacaine following surgery consumed an average MME of 3, while those that did not receive liposomal bupivacaine consumed an average MME of 18, and the difference was statistically significant. They also reported a significant difference in pain scores between the two groups (22).

The use of liposomal bupivacaine has been examined following pharyngoplasty and palatoplasty for the treatment of cleft palate. Given that liposomal bupivacaine was not approved for pediatric use in the United States until March of 2021, there are few reports of its use and effectiveness in this population specific to craniofacial surgery. In two studies by Day *et al.* liposomal bupivacaine was associated with less postoperative opioid consumption, shorter hospital stays, and earlier oral intake following palatoplasty and pharyngoplasty (23,24). *Table 2* provides a summary of articles reviewed.

Discussion

The purpose of this review was to examine the use of liposomal bupivacaine for postoperative pain management and opioid dose limitation following OMS procedures. From the available literature related to OMS procedures, it appears that liposomal bupivacaine may be a promising modality to modulate acute postoperative pain while also limiting opioid doses. Many studies using liposomal bupivacaine following OMS procedures report significantly fewer opioid doses consumed and decreased pain scores. In comparison, many studies in the orthopedic surgery literature report no significant difference in pain scores and opioid consumption (25-27). A few studies have even reported an increase in opioid consumption following total knee arthroplasty in the liposomal bupivacaine group compared to the standard of care (28,29). The reason for these paradoxical findings remains unclear. A possible explanation for increased opioid consumption in patients that received liposomal bupivacaine postoperatively can be seen in a report by Surdam *et al.* In this study, subjects received either a femoral nerve block or periarticular injection of liposomal bupivacaine for total knee arthroplasty. They found that on postoperative day 0 the femoral nerve block group required significantly fewer opioids, but on postoperative day 1 the liposomal bupivacaine group required significantly fewer opioids. This finding is likely due to the bimodal release profile of liposomal bupivacaine (30).

Regarding the promising findings following OMS procedures as compared to the mixed findings of other medical specialties, it could be a matter of anatomy. The head and neck are highly vascularized areas, and data suggests that the median time to peak bupivacaine plasma concentrations following administration of liposomal bupivacaine occurs earlier in surgical areas that are highly vascularized (31). It is also possible that the bimodal release profile lends itself more to the scope of procedures performed by oral and maxillofacial surgeons. For instance, pain following third molar surgery typically diminishes quickly in the postoperative period and most patients experience peak pain levels within 2 postoperative days (32). Given that liposomal bupivacaine has been shown to have an initial bupivacaine peak within 1 hour after administration, and a second peak about 12 to 36 hours later, this would provide pain relief during periods when more severe pain is typical (31).

There are many surgical procedures within the scope of OMS that cause moderate to severe pain (33). Temporomandibular joint surgery, maxillofacial trauma surgery, and the treatment of severe odontogenic and non-odontogenic head and neck infections all may lead to acute postoperative pain and are commonly treated with opioids in the postoperative period. To date, there are no studies evaluating the efficacy of liposomal bupivacaine for postoperative pain management and opioid dose limitation following these OMS procedures. Maxillofacial trauma

Table 2 Included studies assessing the use of liposomal bupivacaine in various oral and maxillofacial surgery procedures

Study name	Authors	Date of publication	Study type	Subjects (n)	Intervention	Primary outcome	Results
Liposomal bupivacaine used in third molar impaction surgery: innovate study	Lieblach and Danesi	2017	Phase 3 randomized, double-blind, placebo-controlled, parallel-group study	89	Experimental arm (n=59): 10 mL/133 mg of liposomal bupivacaine (4 mL maxilla; 6 mL mandible) post extraction of all 4 wisdom teeth Control arm (n=30): placebo (10 mL of normal saline—same injection pattern as experimental arm	Area under the curve of numeric rating scale pain severity scores through 48 hours	Statistically significant difference in least-squares mean for area under the curve of numeric rating scale pain severity scores through 48 hours (P=0.23) No difference in postsurgical opioid consumption between groups (P=0.93)
A retrospective cross-section study of the effect of liposomal bupivacaine on postoperative opioid prescribing after third molar extraction	Lieblach, Misiek, Olczak, *et al.*	2021	Retrospective cross-sectional study	600	Experimental arm (n=300): 10 mL/133 mg of liposomal bupivacaine (4 mL maxilla; 6 mL mandible) post extraction of all 4 wisdom teeth Control arm (n=300): no liposomal bupivacaine	Total prescribed opioids in morphine milligram equivalents	Study group was prescribed significantly fewer total opioids (P≤0.001) Study group had a significantly lower opioid prescription refill rate (P=0.28)
A multimodal analgesic protocol may reduce opioid use after third molar surgery: a pilot study	Magraw, Pham, Neal, *et al.*	2018	Retrospective pilot study	24	Experimental arm (n=24): 10 mL/133 mg of liposomal bupivacaine (2 mL maxilla; 8 mL mandible) post extraction of all 4 wisdom teeth Control arm: none	Number of opioid doses available from filled prescriptions postsurgery	10 of 24 (41.6%) subjects filled zero prescriptions postsurgery 8 of 24 (33.3%) subjects filled one prescription postsurgery
A prospective, randomized, open-label study comparing an opioid-sparing postsurgical pain management protocol with and without liposomal bupivacaine for full-arch implant surgery	Iero, Mulherin, Jensen, *et al.*	2021	Prospective, randomized, open-label study	69	Experimental arm (n=34): 20 mL/266 mg of liposomal bupivacaine injected local around implants Control arm (n=35): no liposomal bupivacaine	Pain level as rated by visual analogue scale (0–10)	Study group had significantly less cumulative pain than control at all time points (P≤0.0083) No difference between groups in use of rescue opioid medication (P≥0.05)
Does liposomal bupivacaine injection decrease postoperative opioid usage following bimaxillary surgery?	Gulko, Carr, Neal, *et al.*	2021	Retrospective cohort analysis	19	Experimental arm (n=10): 20 mL/266 mg of liposomal bupivacaine injected at all 4 surgical sites Control (n=9): no liposomal bupivacaine	Immediate post-operative morphine milligram equivalents consumed	Significant difference in post-operative morphine milligram equivalents between the two groups (P=0.243)

Table 2 (*continued*)

Table 2 (*continued*)

Study name	Authors	Date of publication	Study type	Subjects (n)	Intervention	Primary outcome	Results
Retrospective cohort-based comparison of intraoperative liposomal bupivacaine versus bupivacaine for donor site iliac crest analgesia during alveolar bone grafting	Patel, Jablonka, Rustad, *et al.*	2019	Retrospective cohort study	38	Experimental arm (n=17): local infiltration of liposomal bupivacaine at hip site postsurgery dose weighted for pediatrics (4.4 mL average dose) Control arm (n=21): 0.25% bupivacaine-soaked gel foam placed in hip site dose weighted for pediatrics (9.3 mL average dose)	Mean postoperative pain scores in first 24 hours	Significant difference in mean postoperative pain scores between groups in first 24 hours (P=0.01) Significant difference in morphine milligram equivalents consumed between groups (P=0.002)
The association of liposomal bupivacaine on opioid consumption in the pediatric alveolar cleft population	Crowley, Mclean, Gabriel, *et al.*	2020	Retrospective cohort analysis	44	Experimental arm (n=25): 1.3% liposomal bupivacaine as local infiltration at cleft site dose weight for pediatrics Control (n=19): no liposomal bupivacaine	Immediate post-operative morphine milligram equivalents consumed	Significant difference in post-operative morphine milligram equivalents between the two groups (P=0.0006)
Extended-release liposomal bupivacaine injection (Exparel) for early postoperative pain control following pharyngoplasty	Day, Nair, Griner, *et al.*	2018	Retrospective cohort study	60	Experimental arm (n=30): 20 mL/266 mg of liposomal bupivacaine as palatal and posterior pharyngeal submucosal field blocks Control arm (n=30): no liposomal bupivacaine	Face, legs, activity, cry, consolability pain scale scores	Significant difference between the two groups in pain scale scores (P=0.0006) Study group had significantly shorter length of stay (P=0.0002)
Extended-release liposomal bupivacaine injection (Exparel) for early postoperative pain control following palatoplasty	Day, Nair, Sargent, *et al.*	2018	Retrospective patient series	27	Experimental arm (n=27): 20 mL/266 mg of liposomal bupivacaine as greater palatal and submucosal field blocks Control arm: none	Face, legs, activity, cry, consolability pain scale scores	Average pain score was 2.4±2.2/10 in the post-anesthesia care unit and 3.8±1.8/10 while inpatient

surgery is of particular importance given a recent finding by Morgan *et al*. They reported an average inpatient perioperative MME of 967.6 for patients treated surgically for isolated facial fractures (34). Future studies investigating the use of liposomal bupivacaine following these procedures would certainly be beneficial to both the patient and the surgeon.

The cost related to liposomal bupivacaine has been studied in the orthopedic surgery literature with mixed results. Hyland *et al*. found that patients who received liposomal bupivacaine following total knee arthroplasty had significantly higher medication charges with no significant difference in postoperative physical therapy sessions or length of hospital stay compared to the standard of care. They also determined that liposomal bupivacaine does not provide a significant cost benefit compared with the standard of care (26). Contrary to these findings, Little *et al*. reported that patients who received liposomal bupivacaine following various plastic surgery procedures had decreased length and cost of hospital stay compared to patients that did not receive liposomal bupivacaine (35). To date, there have been no studies investigating the financial impact of liposomal bupivacaine following inpatient OMS procedures. In the outpatient setting, liposomal bupivacaine is approved for separate reimbursement in ambulatory surgery centers, however, cost remains a draw-back to the private practice oral and maxillofacial surgeon. It is important to note that the estimated total economic burden of prescription opioid misuse in the United States is $78.5 billion a year, including the costs of healthcare, lost productivity, addiction treatment, and criminal justice involvement (36). With this perspective, liposomal bupivacaine appears to be well worth the cost.

Conclusions

Liposomal bupivacaine may be a promising tool to adequately manage postoperative pain and limit opioid doses following OMS procedures. Current studies show favorable results, however, further studies investigating the effectiveness of liposomal bupivacaine following common oral and maxillofacial surgical procedures such as maxillofacial trauma surgery, orthognathic surgery, and temporomandibular joint surgery are needed.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://joma.amegroups.com/article/view/10.21037/joma-21-22/rc

Peer Review File: Available at https://joma.amegroups.com/article/view/10.21037/joma-21-22/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://joma.amegroups.com/article/view/10.21037/joma-21-22/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/joma-21-22
Cite this article as: Neal TW, Hammad Y, Schlieve T. Liposomal bupivacaine: a literature review of applications in oral and maxillofacial surgery. J Oral Maxillofac Anesth 2022;1:3.

