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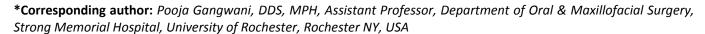
Research Reports in Oral and Maxillofacial Surgery

REVIEW ARTICLE

Evolving Role of Liposomal Bupivacaine in Managing Post- Surgical Analgesia in Oral Surgery

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Abstract

According to the report from Department of Health and Human Services, dental caries is the most common chronic condition in childhood. But the prevalence of tooth decay is high in the adult population as well. Ultimately, untreated non-restorable decayed teeth require oral surgery. Additionally, surgical removal of impacted third molars (wisdom teeth) is a routinely performed procedure on a younger patient population. Approximately, 5 million people undergo extraction of third molars annually in the United States. Post-operative pain is common sequelae of oral surgery and limits function, thereby affecting the quality of life. Therefore, control of post-surgical pain is an essential component of patient management after oral surgery. The intensity of pain after surgery is usually moderate to severe and lasts for at least 3 days post-operatively. Local anesthetics are vital to post-operative multi-modal pain regimen. But due to its limited duration of action, prescription medications including opioids have been heavily relied upon.

According to the study conducted by the University of Michigan, Institute of Social Research, the use of opioids before high school graduation is linked with an increased risk of future opioid use by 33%. Considering, adverse effects of opioids and current opioid crisis, a need to use long acting local anesthetics prevails. One such example is, a single dose administration of liposomal bupivacaine (LB), the drug that is released over a period of 72 to 96 hours after its infiltration at the surgical site. The aim of this paper is to review the current literature on the use of LB after oral surgery, its formulation, and safety profile, and discuss future directions.

Pain

According to the Statistical Brief on Dental Procedures published by the U.S. Department of Health & Human Services in 2009, approximately 17 million peo-

ple underwent oral surgery procedures [1]. Extraction of impacted wisdom teeth is a common procedure performed by Oral and Maxillofacial Surgeons. Pain and inflammation are frequently experienced post-operatively after the extraction of mandibular wisdom teeth, especially if they are impacted (unable to fully erupt in the oral cavity). International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Majority of patients after surgery experience moderate to severe pain during their first few days of post-operative recovery [2,3]. Increased difficulty and longer duration of surgery are typically associated with more post-surgical pain, swelling and limited mouth opening [3]. Consequently, interfering with oral functions, daily activities, social interaction and sleep [4]. Furthermore, there is an increased risk for development of chronic pain with under-treatment of acute post-surgical pain [5]. Therefore, pain management is of utmost importance for Oral and Maxillofacial Surgeons.

Anesthesia and Analgesia

Local anesthetics are a main stay of multimodal post-surgical pain regimen. They are safe and very effective in controlling acute pain but their duration of action is relatively short, which routinely leads to the use of pain medications including non-steroidal anti-inflammatory drugs (NSAIDS) and opioids [6,7]. Adverse effects of opioids include nausea, vomiting, constipation, urinary retention, pruritus, respiratory depression, dependency, drug abuse, addiction and diversion [8,9].



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Thus, it is medically necessary to extend the duration of local anesthesia. Liposomal bupivacaine (LB) uses a drug delivery system, which allows for slow release of active component bupivacaine, over 3 to 4 days after the infiltration at the surgical site.

Literature Review

In a phase 3, randomized, double-blind, placebo-controlled, parallel-group trail conducted by Lieblich, et al. 150 patients (n = 99 LB, n = 51 placebo) undergoing bilateral third molar extractions (at least 1 impacted mandibular molar) were included. This study demonstrated notable improvement in pain scores in the LB group (LB 133 mg/10 ml), but due to extensive protocol violations additional studies are required to determine its effectiveness [10].

In another prospective, randomized, open-label study, conducted by lero, et al. 69 patients (n = 34 LB, n = 35 placebo) undergoing full-arch implant surgery were included. The authors concluded that LB 266 mg for full-arch implant placement significantly reduces post-surgical pain and clinically relevant decline in opioid consumption [11]. In both of the above mentioned studies, the adverse effects were comparable between the LB and placebo groups [10,11].

Formulation

Liposomal Bupivacaine is made of multivesicular liposomes, which is comprised of phospholipid bilayer with an aqueous core, using DepoFoam technology. This formulation of bupivacaine provides increased stability and extended drug release [12]. Liposomal formulation requires an optimal drug-to-phospholipid ratio (D/PL). For example, formulations with a low D/PL require administration of a large lipid load to obtain the desired analgesic effect, making it unsuitable for clinical use [13]. Therefore, it is critical to achieve a high D/PL in the formulation of liposomal bupivacaine. Remote loading technique and large aqueous space in the structure of multivesicular liposomes are two ways of achieving favorable D/PL [13].

Liposomal Bupivacaine is available as 266 mg/20 mL (13.3 mg/mL) and 133 mg/10 mL (13.3 mg/mL) single-dose vial, to be administered by infiltration only [14]. Simultaneous administration of non-bupivacaine based local anesthetics, such as lidocaine, can cause an immediate release of bupivacaine from the liposomal formulation. Hence, it is recommended to wait at least 20 minutes or more, if liposomal bupivacaine needs to be administered after the injection of non-bupivacaine based local anesthetics [14].

Safety

The available clinical trial safety data on liposomal bupivacaine has revealed its tolerability and safety profile. Based on 10 randomized, multi-center, double-blind, clinical trials in various surgical models, the most common adverse effects of liposomal bupivacaine local infiltration at the surgical site, include nausea, vomiting and constipation [15]. The surgical models comprised of hernia repair, hemorrhoidectomy, breast augmentation, bunionectomy, and total knee arthroplasty [15]. In the study conducted by Lieblich, et al. the patients didn't experience any signs and symptoms of systemic toxicity, in-spite of receiving 133 mg of liposomal bupivacaine infiltration at the surgical site [10].

Future Directions

Prospective randomized clinical studies are necessary to confirm the success of using liposomal bupivacaine in the surgical setting. The use of liposomal bupivacaine in patients requiring reconstructive surgery secondary to facial trauma and orthognathic surgery due to jaw deformities should be researched as well.

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