Review Article

Efficacy of Lignocaine with Buprenorphine versus Lignocaine in the Management of Postoperative Pain after Minor Oral Surgical Procedures: A Systematic Review and Meta-analysis

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Received : 05-07-20
Revised : 22-07-20
Accepted : 22-08-20
Published : 24-11-20

Abstract

We aimed to review the efficacy of lignocaine with buprenorphine versus lignocaine alone in the management of postoperative pain after minor oral surgical procedures. Randomized controlled trials evaluating the efficacy of use of lignocaine with buprenorphine versus lignocaine for intra-oral procedures were included by searching multiple databases. Outcomes assessed were onset of the time of anesthesia in seconds, duration of postoperative analgesia, postoperative pain (maximal follow-up), the number of rescue analgesics required, and adverse events. The search strategy yielded 167 publications for the title and abstract screening out of which only two trials were included for full-text screening. There was considerable heterogeneity among the included studies with regards to the outcomes assessed. The need for rescue analgesics was the only outcome that was included for meta-analyses. Forest plot showed that lignocaine with buprenorphine compared to lignocaine showed a significantly lower requirement of rescue analgesics (–0.22[–2.9,–1.55]). No trial reported any adverse effects. The results show that lignocaine with buprenorphine is effective in reducing the number of rescue analgesics required by the patient.

Keywords: *Analgesia, anesthesia, buprenorphine, lignocaine, postoperative pain, rescue analgesics*

Introduction

Pain and swelling are the most common distressing symptoms reported after extraction of wisdom teeth,[1] which arise due to the inflammatory response in relation to the surgical trauma.[2] Various methods such as modification of flap design, atraumatic osteotomy, cryotherapy postsurgery, and pharmacological agents such as steroids have been used by clinicians to reduce these early complications, thereby reducing the immediate postoperative pain (PoP) and discomfort.

One such pharmacological method has been the modification of local anesthetic (LA) agent either by using a long-acting agent or by supplementing with other agents that prolong their duration of action. Long-acting LA provides both anesthetic and analgesic effects for a prolonged period. However, they can be a source of discomfort to the patient and occasionally lead to inadvertent self-injury.[3] It is also well known that the efficacy of LA decreases in areas of inflammation.[4] Recent advances in pharmacology have led to research on supplementing the conventional LA with agents that can have prolonged postoperative analgesic effect without unduly extending the anesthetic effect and also be efficient in areas of inflammation.

Access this article online

Quick Response Code:

Website: www.jispcd.org

DOI: 10.4103/jispcd.JISPCD_316_20

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How to cite this article: Singh A, Gadicherla S, Smriti K, Pentapati KC. Lignocaine with buprenorphine versus lignocaine for postoperative pain: A systematic review and meta-analysis. J Int Soc Prevent Communit Dent 2020;10:686-91.

The use of opioids has been extensively studied in obtaining local analgesia. The evidence of opioid receptors in the peripheral nervous system paved the way for investigating the effect of opioids either alone or in combination with other LA agents.[5] Further, there have been studies that reported the efficacy of peripherally administered opioids in achieving adequate analgesia in regions with inflammation as well.[6] The response to noxious pressure by selective opioid agonists is achieved by peripheral opioid receptors that possess distinguishable pharmacological characteristics resembling those of μ, δ, and κ receptors.[7]

There have been numerous studies showing the benefit of achieving prolonged postoperative analgesia (PoA) by combining opioids with LA agents in brachial plexus blocks.[8-11] Also, studies showed that lipophilic agents, such as buprenorphine, have a long-lasting analgesic effect as compared to other agonists.[12,13]

The majority of dental procedures (endodontic treatment or tooth extraction) are performed in areas of inflammation which in turn decreases the efficacy of the conventional LA agents. The ability of opioid to act in the inflamed area has shown good postoperative analgesic effect by supplementing 1 mg morphine injection at the local dental surgical site.[14-16] Buprenorphine hydrochloride is a potent opioid that is a partial agonist of δ-opioid receptor and antagonist of κ-opioid receptor. It is analgesic, anti-hyperalgesic, and has anti-nociceptive potency which makes it more effective than morphine with minimal adverse effects.[17]

Lignocaine and bupivacaine are among the most commonly used LA agents for dental surgical procedures. The addition of buprenorphine to 0.5% bupivacaine provided a 3-fold increase in PoA.[18] However, in addition to being cardiotoxic, bupivacaine itself is a long-acting LA agent, which can overlap or mimic the analgesic effect of the opioid agonist and hence, provide misleading results about the efficacy of buprenorphine.

A meta-analysis on the addition of buprenorphine to LAs for peripheral nerve blocks supported its use.[19] However, similar evidence for the intra-oral administration of buprenorphine with LA is lacking.[19] Hence, we aimed to evaluate the efficacy of the addition of buprenorphine to lignocaine in comparison to lignocaine alone for minor oral surgical procedures. Given the aim of this review, PICOS were:

- Population: Patients who required local anesthesia for minor oral surgical procedures
- Intervention: Lignocaine + Buprenorphine
- Comparison: Lignocaine
- Outcome: time of onset of anesthesia, duration of PoP, duration of PoA and number, type, and dosage of rescue analgesics (RA) at maximal follow-up
- Study design: Randomized controlled trials (RCTs)

Materials and Methods

Inclusion and exclusion criteria

The selection of studies was limited to RCTs on human subjects in need of local anesthesia for minor oral surgical procedures. The intervention under study was lignocaine with buprenorphine for local anesthesia injection compared with lignocaine. Studies of the effect of bupivacaine or any other LA agents, and studies done in other than the oral cavity were excluded.

Outcomes

Primary outcomes include the onset of anesthesia (in seconds), duration of PoA, PoP (maximal follow-up), the number of RA required, and adverse events.

Search strategy

Six electronic databases (PubMed [*n* = 8], CINAHL [*n* = 126], Scopus [*n* = 110], Embase [*n* = 13], Cochrane central [*n* = 3], and Web of Science [*n* = 10]) were searched till November 6, 2019. A combination of terms "Lignocaine" or "Lidocaine," "Buprenorphine," "dental," "oral," "teeth," or "tooth" were used [Figure 1]. No restriction on language was applied. The search strategy used for PubMed was ([Lignocaine] AND [Lignocaine AND Buprenorphine]) AND (dental OR oral OR teeth OR tooth).

We included all the RCTs that evaluated the efficacy of lignocaine compared with lignocaine + buprenorphine among humans (both men and women) aged 18 and above, with any of the primary outcomes being reported.

Data extraction and management

Two independent review authors performed the title and abstract screening and full-text screening. The third review author resolved discrepancies. Data extraction was also performed by two independent reviewers which included the author details and year of publication, age and gender of the participants and sample size, dosage and methods for the study and control groups, study design, and outcome for each study. There was no attempt to contact the authors for any additional data.

Risk of bias assessment

Two independent review authors (PKC and AS) performed the risk of bias assessment according to Cochrane guidelines.[20] Disagreements were resolved by a discussion [Figure 2].

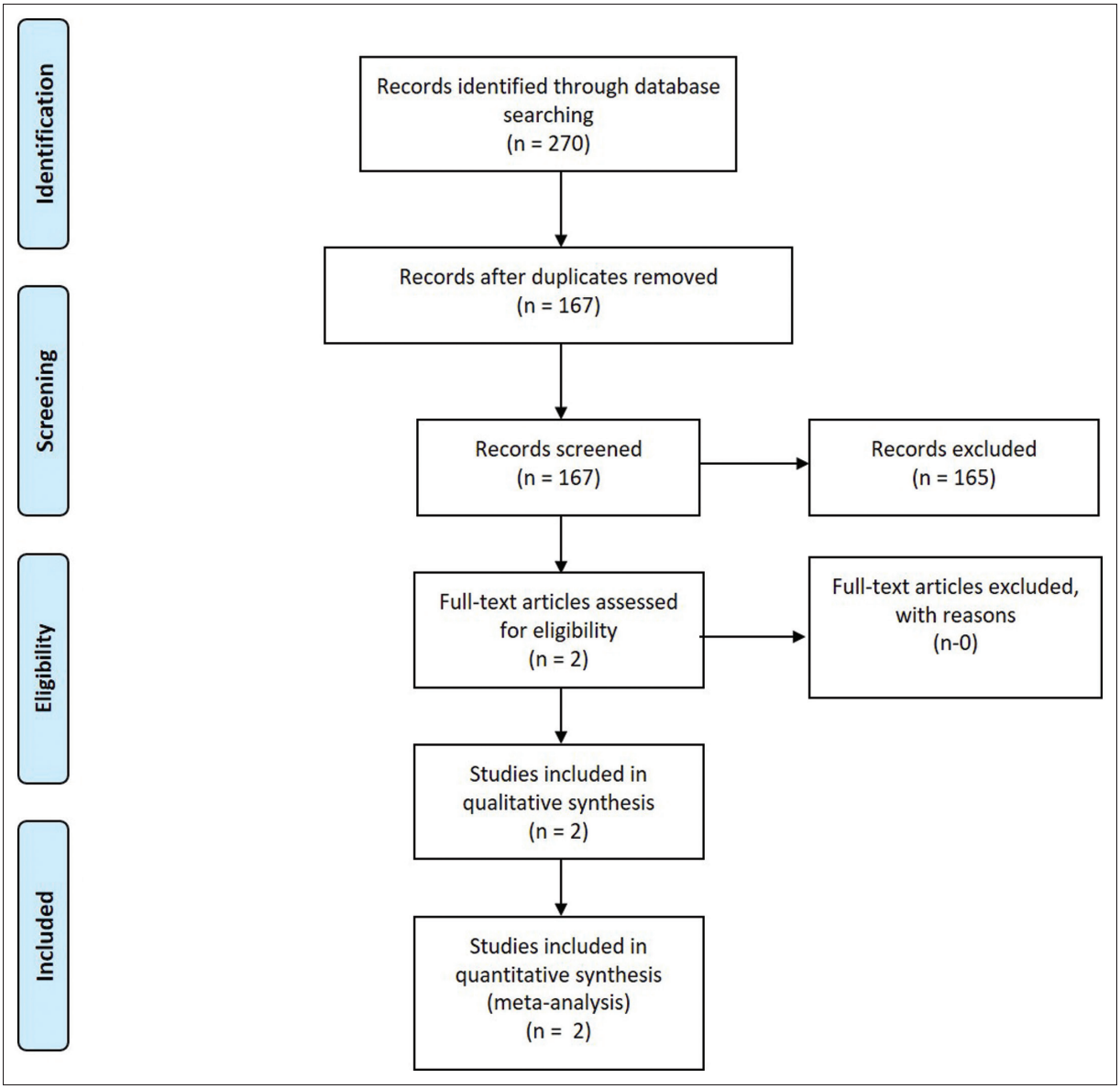

Figure 1: Detailing of the included studies for systematic review and meta-analysis as per PRISMA guidelines

Statistical analyses

Data analysis was performed using non-Cochrane mode in RevMan 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Heterogeneity was assessed using the I^2 statistic and χ^2 test. If I^2 is more than 50%, we used the random-effects model. Publication bias was not assessed owing to the less number of publications. We used the mean difference for continuous data and inverse variance, random effect model, to generate the forest plot.

Results

Six electronic databases (PubMed [n = 8], CINAHL [n = 126], Scopus [n = 110], Embase [n = 13], Cochrane [n = 3], and Web of Science [n = 10]) yielded a total of 167 publications after removing duplicates (n = 103) for title and abstract screening. Only two studies were included for the full-text screening [Figure 1].

There was a substantial variation in the outcomes that were evaluated in the included studies. Chhabra *et al.*[21] evaluated the depth of anesthesia, PoP, and analgesia. However, the exact assessment time interval was not explicitly mentioned. Kumar *et al.*[22] systematically evaluated PoP assessment at 2, 4, 6, 12, 24, 36, 48, and 72 h. Also, patients daily rating of discomfort was recorded. Both studies used the VAS scale. RA was the only outcome that was evaluated in both studies. The need for rescue analgesic was self-reported by the patient and reported as the average number of analgesics consumed during the 3-day postoperative period in both the studies. Also, diclofenac (50 mg) was prescribed in both the studies. Forest plot showed

that Buprenorphine with lignocaine compared to lignocaine showed a significantly lower requirement of RA (–0.22[–2.9, –1.55]). None of the included studies reported any adverse effects [Figure 3].

In both the studies, randomization was done by a person not involved with the research and both patient and investigators were blinded for the intervention. However, there was no mention of number operators involved in the administration of the intervention in both the studies.

Discussion

We conducted this systematic review to evaluate the efficacy of the addition of buprenorphine to lignocaine for the management of PoP after minor oral surgical procedures. Overall, two studies with 140 subjects were included for meta-analysis. Overall, the risk of bias was low for Chhabra *et al.*[21] and while it is unclear for the study done by Kumar *et al.*[22] Chhabra *et al.*[21] evaluated the patients undergoing third molar extraction and evaluated intraoperative and postoperative parameters (onset of anesthesia, depth of anesthesia, duration of anesthesia, duration of PoA, the severity of PoP, and number of RA taken). Subjects were randomized into three groups such as Inferior alveolar nerve block (IANB) with 2% lignocaine and 1:80,000 adrenaline, IANB with 0.01 mg buprenorphine/ml of 2% lignocaine with 1:80,000 adrenaline and IANB with 2% lignocaine and 1:80,000 adrenaline with 0.03 mg IM buprenorphine. Kumar *et al.*[22] evaluated the patients undergoing various types of intra-oral minor surgical procedures such as third molar surgeries, alveoloplasties, and cyst enucleation. They did not specify the type of nerve block/infiltration administered. The patients were assessed for only two parameters (PoP and the number of RA). Also, a direct comparison was made between two groups of patients, one group being administered anesthesia with 2% lignocaine with 1:80,000 adrenaline and the other group being administered anesthesia with 0.01 mg buprenorphine per ml of 2% lignocaine with 1:80,000 adrenaline.

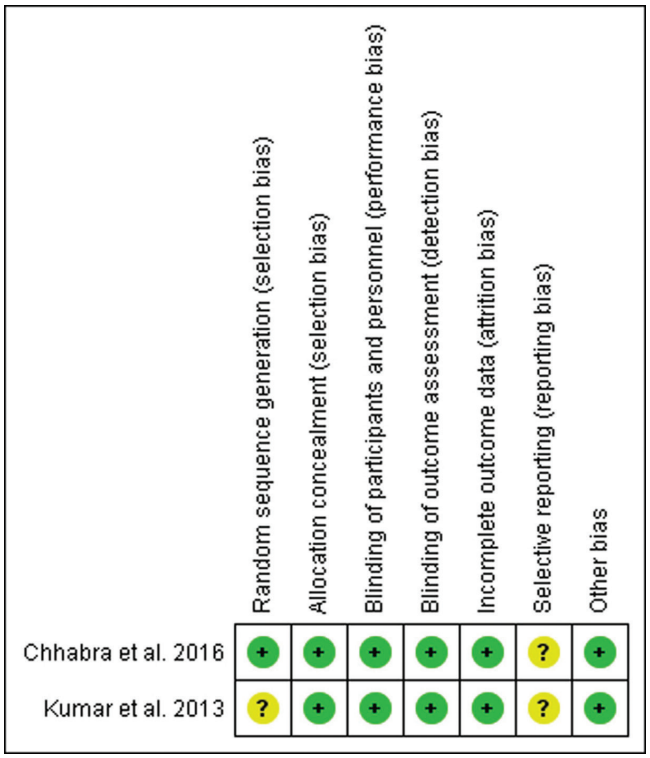

Figure 2: Risk of bias summary: review authors' judgments about each risk of bias item for each included study

Both the studies used similar dose and composition for administering local anesthesia (0.01 mg buprenorphine per ml of 2% lignocaine with 1:80,000 adrenaline), but there were variations in the type of anesthesia and procedures that were performed after administration of local anesthesia, which can have a substantial impact on PoA. Such variability could have contributed to the heterogeneity among the included studies.

Previous studies supported the addition of buprenorphine to long-acting LA agents such as bupivacaine for effective management of PoA as compared to bupivacaine alone.[9,13,18] However, we did not include long-acting agents such as bupivacaine in our study because of the possible chances of bupivacaine masking the postoperative analgesic effects of buprenorphine with lignocaine. Also, the long-acting agents have their risk of trauma to the oral tissues.

Buprenorphine is a semi-synthetic compound that is classified as a mixed agonist-antagonist opioid. Buprenorphine, being highly lipophilic, more potent than morphine and has a substantially long-acting

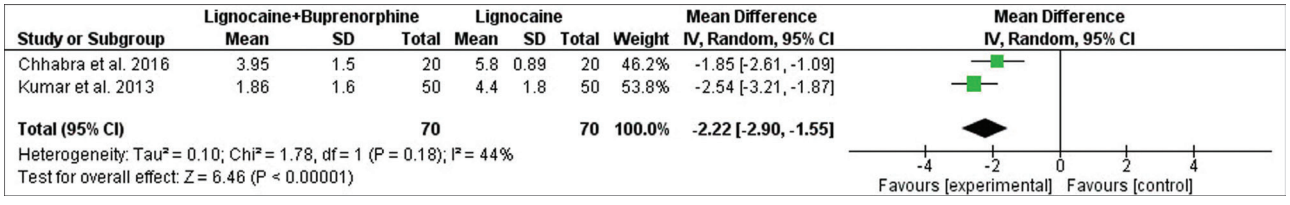

Figure 3: Forest plot for the outcome need for rescue analgesics

with less potential adverse effects.[18,23-25] There were no adverse effects reported among the included studies.

It has been established that the peripheral administration of opioids is much more effective in providing stronger and longer pain relief at much lower doses and without any central side-effects such as respiratory depression, GI disturbances, etc. This has been supported by various reports done in the field of orthopedics.[13,26,27]

The two unique properties of buprenorphine which make it suitable for use in minor oral surgical procedures are its ability to dissociate at a slower rate from opioid receptors, thereby prolonging the duration of analgesia[18,28] and the ability to act in the area of inflammation due to upregulation of opioid μ receptors from dorsal root ganglion and change in pH levels which further activates the opioid receptors by increasing G protein coupling and cAMP levels.[29,30]

The results of this systematic review support the addition of buprenorphine to lignocaine in reducing PoP through an indirect patient-reported outcome (reduced number of RA at 72-h postoperative period). Both the studies prescribed Diclofenac (50 mg) as the rescue analgesic for the participants.

The limitations of this review were that the number of studies included was too less to carry out any meta-analysis for other outcomes to prove the efficacy of the addition of buprenorphine to lignocaine. Also, the number of operators involved in the administration of intervention was not mentioned in both the studies.

The addition of buprenorphine to 2% lignocaine with 1:80,000 adrenaline can be useful to reduce the need for postoperative RA by the patient. Further, well-documented RCTs are needed including outcomes such as the onset of the time of anesthesia, duration of PoA, and PoP (maximal follow-up).

Acknowledgement

Nil.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Authors contributions

Not applicable.

Ethical policy and institutional review board statement

Not applicable.

Patient declaration of consent

Not applicable.

Data availability statement

Not applicable.

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