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REVIEW

Topical local anesthesia: focus on lidocaine–tetracaine combination

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Abstract: In recent years, the popularity of aesthetic and cosmetic procedures, often performed in outpatient settings, has strongly renewed interest in topical anesthetics. A number of different options are widely used, alone or in combination, in order to minimize the pain related to surgery. Moreover, interest in local anesthetics in the treatment of some painful degenerative conditions such as myofascial trigger point pain, shoulder impingement syndrome, or patellar tendinopathy is increasing. Numerous clinical trials have shown that lidocaine–tetracaine combination, recently approved for adults aged 18 or older, is effective and safe in managing pain. The present paper gives an overview of the recent literature regarding the efficacy and safety of lidocaine–tetracaine combination use.

Keywords: lidocaine, tetracaine, local anesthetics, efficacy, safety

Introduction

Topical anesthetics have an impressive history of efficacy and safety in medical practice. In recent years, the popularity of aesthetic and cosmetic procedures, often performed in outpatient settings, has strongly renewed interest in topical anesthetics. A number of different options are widely used, alone or in combination, in order to minimize the pain related to aesthetic and dermatologic procedures. The broad routine use of topical anesthetics is justified by the fact that they are generally easy to use, and their adverse effects are infrequent. Nevertheless, the choice from among the different formulations available in the market should take into account a number of factors such as type of surgical procedure, effectiveness profile, ease of use, application time, need for occlusion, and whether there are any side effects.[1]

Theoretically, ideal topical anesthetics should produce effective local anesthesia by penetrating the epidermis and have no systemic absorption.[2,3] The lidocaine–tetracaine (LT) combination, recently introduced in the market and available as a cream or medicated patch or peel, offers effective pain relief. Numerous clinical trials have evaluated this anesthetic combination, showing what seems to be an association with a very favorable profile compared to other topical local anesthetics thanks to the fact that it is easy to use and has mild side effects.

The aim of the paper is to give an overview on the use of LT combination with an outline of the efficacy, safety, and tolerability reported in clinical studies.

Search strategy

Articles relevant to the scope of the review were identified through a computerized search in MEDLINE or as references in relevant articles. MeSH terms "lidocaine,"

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"tetracaine," and "lidocaine/tetracaine" were used for the research. Only papers published in English were used for the review.

Overview of pharmacology of lidocaine and tetracaine, and rationale for the combination

Local anesthetics produce anesthesia by interrupting neural conduction signals at the level of sodium ion channels within neural membranes. The structure of neural fibers and the chemical properties are the main factors that primarily influence local anesthetic action.

Nerve fibers have different diameters and firing rates. A smaller diameter and higher firing rate make the neural fiber more susceptible to local anesthetics. Thus, the tiny, rapid-firing autonomic fibers are the most sensitive, followed by sensory fibers, and finally by somatic motor fibers.[4]

Like all local anesthetics, lidocaine and tetracaine have a basic structure consisting of an aromatic ring, intermediate chain, and amine group. Each of these components contributes to chemical and clinical properties of the molecule.

The lipid solubility of the molecule, thanks to the aromatic ring, strongly influences the capacity of local anesthetics to spread through the nerve sheaths. The higher the lipid solubility, the greater is the potency of the local anesthetic.

The intermediate chain makes it possible to classify local anesthetics into two groups: amides or esters.[5] Lidocaine is an amide-like anesthetic such as prilocaine, etidocaine, and bupivacaine. Tetracaine is an ester-like anesthetic like procaine and benzocaine. All local anesthetics are lipophilic and soluble in water.[6] Aside from the taxonomic aspect, the intermediate chain is the main factor influencing metabolism and elimination of local anesthetics. Lidocaine is metabolized rapidly by the hepatic microsomial enzymes to a number of metabolites, including monoethylglycinexylidide, whose pharmacological activity is similar to, but not as potent as, that of lidocaine.[7] Tetracaine is rapidly metabolized by plasmatic esterases to a number of metabolites, including para-aminobenzoic acid, with an unspecified activity.[7]

The amine group influences water solubility of the local anesthetic. It can exist in a tertiary lipid-soluble form (three bonds) or in a quaternary water-soluble form. The onset of anesthesia is directly related to the amount of local anesthetic in the tertiary lipid-soluble form. Conversion from quaternary water-soluble to tertiary lipid-soluble form is influenced primarily by physiologic tissue pH (7.4), according to the Handerson–Hasselbach equation: log (tertiary form/quaternary form) = pKa – pH, where pKa is the ionization constant for local anesthetics. Local anesthetics have a pKa greater than 7.4 and this favors the quaternary water-soluble form at the physiologic pH of 7.4. In the presence of inflammation tissue, pH tends to decrease and this further favors the quaternary water-soluble form.

The rationale for the LT combination is largely due to the pharmacokinetics of the two components. The anesthesia produced by lidocaine is faster, more intense, longer lasting, and more extensive than that produced by an equal concentration of procaine. Lidocaine is an alternative choice for those who are sensitive to ester-type local anesthetics.[8] Tetracaine, a long-acting amino-ester, is more lipophilic than lidocaine, concentrating in the stratum corneum of the epidermis, where it slowly diffuses. Its duration is thus prolonged and systemic uptake is limited.[9] As a result, LT combination produces rapid and durable topical anesthesia. LT combination is available in the market as a 7%/7% self-occluding dermatologic cream or as a 7%/7% cutaneous patch. This allows choosing the best solution on the basis of the kind of procedure and the area to be anesthetized.

Efficacy

In literature, there are many studies that have evaluated the efficacy of LT combination.

Bryan and Alster[10] first proposed using LT combination for cutaneous laser surgery comparing it to placebo in 60 patients undergoing laser surgery. The three protocols of this blinded, randomized trial had different anesthetic application times: in the first of these protocols, 30 subjects were randomized to receive either placebo or LT cream for 60 minutes. In the second and third protocols, subjects (n=15 each) were randomized to receive placebo or LT cream for 20 or for 30 minutes. Clinical effectiveness was evaluated by the subjects, the investigators performing the laser surgery, and an independent observer. The authors found that subjects who received the active drug had less pain compared to those who received the placebo. Only 9% of those receiving the active drug reported inadequate pain relief compared to 66% in the placebo group. Similarly, the investigators rated 75% of the LT cream subjects with no pain and 25% of the placebo group.

In another study, Wallace et al investigated the LT combination with the aim of determining the depth and duration of anesthesia.[11] The authors therefore conducted a randomized, double-blind, placebo-controlled, 2-period crossover study in 24 healthy subjects. Randomization was either to period 1= the heated LT patch and then period 2= placebo patch, or vice versa. Patches were applied for 30

minutes to the volar aspect of the forearm. Pain and sensory depths were measured at baseline and again at 30, 60, 90, and 150 minutes after patch application. Duration of anesthesia was measured at 40, 70, 110, and 130 minutes after patch application by evaluating thermal and mechanical sensation. The author found that pain and sensory depths with the LT patch were greater than those with placebo ($P<0.001$) at all postdose time points. The active patch achieved a maximum mean pain depth at 8.22 mm; anesthesia lasted at least 100 minutes after the patch had been removed. Cool and warm sensations and hot pain thresholds were increased compared with placebo ($P<0.001$). The author concluded that the LT patch provided favorable depth and duration of anesthesia without significant sensory loss for superficial venous access and minor dermatological procedures after a 30-minute application.

Recently, Ruetzler et al proposed the use of a topical anesthetic patch containing 70 mg each of lidocaine and tetracaine as an alternative topical anesthetic to subcutaneous injection of local anesthetic for arterial catheterization.[12] This prospective, double-blind clinical trial included 90 patients undergoing elective major cardiac surgery who were randomly assigned to receive one of the following: either an LT patch, followed by subcutaneous injection 0.5 mL of normal saline solution, or a placebo patch with subsequent subcutaneous injection of 0.5 mL of lidocaine 1%. The primary outcome, measured using 100 mm-long visual analog scale (VAS), was pain during arterial catheterization. VAS scores during arterial puncture were comparable in both groups and LT 7%/7% patch was noninferior to subcutaneous lidocaine. Pain scores at the time of subcutaneous injection were significantly lower in patients assigned to the LT patch than to lidocaine ($P=0.001$). The authors' conclusion was that both the LT patch and subcutaneous injection of lidocaine were comparable in providing pain control during arterial catheter insertion.

Interestingly, in a recent study, Rauck et al tested the usefulness of LT combination for treatment of pain associated with myofascial trigger points in 17 patients.[13] In this open-label, single-center outpatient pilot study, patients with ≥1 month history of pain associated with myofascial trigger points applied one patch to each myofascial trigger point for 4 hours twice daily for 2 weeks, followed by a 2-week, treatment-free period. At baseline, mean ± standard deviation average pain intensity was 6.3±1.56, which decreased to 4.5±2.31 (33%) (N =20) at the end of treatment. In all, 40% of patients had a clinically significant (≥30%) decrease and 25% had a substantial (≥50%) decrease. In 35% of patients (N=20), pain interference with lifestyle decreased by ≥50%, with an improvement of worst trigger point sensitivity in 45% of them. Average pain intensity was 5.0±2.04 2 weeks after stopping treatment; treatment benefit was maintained in eight patients (40%). The author concluded that the heated LT patch has potential utility as a noninvasive pharmacologic approach for managing myofascial trigger point pain.

Similarly, in a recent prospective, single-center pilot study, Gammaitoni et al tested the self-heated LT patch in 13 patients with patellar tendinopathy confirmed by physical examination, with pain of ≥14 days' duration and baseline average pain scores ≥4 (on a 0–10 scale), to determine whether the self-heated LT patch might relieve pain and improve function.[14] In the authors' opinion, the pain of patellar tendinopathy might be mediated by neuronal glutamate and sodium channels. Lidocaine and tetracaine might be effective by blocking both of these channels. Patients applied a self-heated LT patch to the affected knee twice a day for 2–4 hours each time for 14 days. Variations from baseline to day 14 in terms of average pain intensity and interference (Victorian Institute of Sport Assessment) scores were assessed. The authors found that the average pain scores decreased from a baseline of 5.5±1.3 to 3.8±2.5 on day 14. Similarly, the Victorian Institute of Sport Assessment scores improved going from 45.2±14.4 at baseline to 54.3±24.5 on day 14. A clinically important reduction in pain score (≥30%) was demonstrated by 54% of patients. The authors concluded that the results of their pilot study suggested that patellar tendinopathy may benefit from topical treatment that targets neuronal sodium and glutamate channels.

In a 2-week pilot study in 2013, Radnovich and Marriott investigated the effects of heated LT patch in reducing pain in 18 adult patients with shoulder impingement syndrome-associated pain.[15] In the authors' opinion, participation in an appropriate physical therapy program is possible only if fear of pain is eliminated. Patients were treated with the heated LT (70/70 mg) patch placed over the site of shoulder tenderness each morning and evening for a period of 2 to 4 hours. Average and worst pain during the previous 24 hours and shoulder range of motion were assessed at baseline and on day 14. According to the authors, the mean average pain score at baseline in the per-protocol population was 5.5±1.1 (range 4 to 8); average and worst pain scores decreased by 2.4±2.0 and 3.7±2.7 points, respectively. Two-thirds of the patients achieved a clinically meaningful (≥30%) reduction in average pain score, and half of the patients achieved a ≥50% reduction in average pain score. Shoulder internal rotation increased by 29.7°±21.8° and abduction increased

by 40.0°±44.2°. The authors' conclusion was that patients treated with the heated LT patch for 14 days achieved clinically meaningful improvement in pain intensity and range of motion.

The following year, Radnovich et al tested the heated LT patch in a prospective, randomized, open-label clinical trial in order to evaluate its efficacy in reducing shoulder impingement syndrome pain.[16] The 60 adult patients with shoulder impingement syndrome pain enrolled in the study were randomized to receive either treatment with the heated LT patch or a single subacromial injection of 10 mg of triamcinolone acetonide. Patients in the heated LT patch group applied a single heated LT patch to the shoulder for 4 hours twice daily, with a 12-hour interval between treatments during the first 14 days and could continue to use the patch on an as-needed basis during the second 14-day period. At baseline and at days 14, 28, and 42, patients rated their pain and pain interference with specific activities by a VAS score (0–10). The authors found that the average pain scores declined from 6.0±1.6 at baseline to 3.5±2.4 at day 42 in the heated LT patch group (n=29, $P<0.001$) and from 5.6±1.2 to 3.2±2.6 in the injection group (n=31, $P<0.001$). Similar improvements were seen in each group for worst pain, pain interference with general activity, work, sleep, and range of motion. The authors concluded that the efficacy of short-term, noninvasive treatment with the heated LT patch was similar to that of subacromial corticosteroid injections for the treatment of pain associated with shoulder impingement syndrome.

In 2014, Gahalaut et al compared the anesthetic potential of 2.5% lidocaine and 2.5% prilocaine topical cream with 7% lidocaine and 7% tetracaine combination cream when applied under occlusion for 30 minutes for radioablative dermatosurgery.[17] Forty subjects of achrocordons were enrolled in this split-side randomized trial. The authors found that pain severity experienced by subjects in terms of VAS score was significantly less for LT combination cream than for the lidocaine–prilocaine combination. They concluded that LT combination was effective when applied for a short time (30-minute intervals) in achieving local anesthesia to perform various dermatological procedures.

Recently, Bourne et al studied prospectively the anesthetic effect provided by an LT patch in comparison with that of injectable lidocaine during incision and drainage of skin abscesses.[18] Twenty adult patients with a skin abscess needing incision and drainage were randomized to one of two groups: one received LT patch and injectable normal saline for anesthesia, the other a placebo patch and injectable 1% lidocaine. The authors found that preprocedure pain scores were similar in the two groups. Pain scores during incision and drainage and postprocedure in the two groups were compared. The pain experienced by patients receiving injectable lidocaine (50.1±5.9 mm; 95% confidence interval 45.2–55.1) and those receiving the transdermal LT patch (60.1±11.0 mm; 95% confidence interval =55.2–68.1, $P=0.04$) was similar. The power to detect a difference of 20 mm at $P\leq0.05$ was 80%. Although this was statistically significant, it was not clinically significant. There was also no statistical difference between the two groups in the postprocedure pain scores ($P=0.65$). The authors concluded that both a local injection of lidocaine and the LT patch provided clinically similar analgesia during incision and drainage of skin abscesses. Pain at presentation and after the procedure was similar in both groups. Despite this, in the authors' opinion, emergency physicians should continue to use a local injected anesthetic for incision and drainage of skin abscesses until a less painful alternative is identified.

In two studies, Alster et al evaluated anesthetic efficacy of lidocaine 70 mg/g and tetracaine 70 mg/g in laser-assisted hair removal.[19] Studies A (Phase II) and B (Phase III) were randomized, double-blind, placebo-controlled and paired; applications of LT peel and placebo were concurrent. In Study A, 60 subjects were randomized to groups of 30, 45, or 60 minutes, while in Study B, 50 subjects had 30-minute applications. Efficacy evaluations were achieved by VAS, subject's/investigators impression of anesthetic adequacy, and investigators' pain ratings. VAS scores were significantly lower ($P<0.05$) for LT peel: mean scores were 26.7 for LT peel versus 44.3 for placebo (Study A total population, similar between application times) and 23 versus 31.7 (Study B), respectively. The authors concluded that a 30-minute LT peel application was effective and well tolerated in providing anesthesia for laser-assisted hair removal.

Safety and tolerability

Currently, there are no guidelines for the use and safety of compound mixtures of local anesthetics. Despite the fact that local anesthetics are considered safe and well tolerated, systemic toxicity has been reported by different authors when they are used either with simple topical application or under occlusion.[20–23] Systemic effects may include dizziness, seizures, respiratory distress, loss of consciousness, or cardiac arrest.

LT combination is reported to have a safe profile with mild side effects when used according to recommendations.[2,3,5,6,21] Transient cutaneous erythema and edema and skin discoloration are the most common side effects. No cases of

methemoglobinemia have been reported.[1] All patients with history of sensitivity to local anesthetics should avoid LT combination use.

In 2008, Ogden et al's randomized study in 36 adult volunteers evaluated the pharmacokinetic profile of lidocaine and tetracaine after a single application of the LT peel.[24] The LT peel was applied to a 50, 100, or 200 cm^2 area of the anterior surface of the left or right thigh of volunteers for 30, 60, or 90 minutes. Venous blood samples were collected at 0, 30, 60, 90, 120, 150, 180, 210, 300, and 420 minutes after the initial application of the LT peel. The authors found that plasma concentrations of lidocaine and tetracaine were below the limits of quantification for the assay (100 and 5 ng/mL, respectively) at all time points. A single application of the LT peel was well tolerated; no study subject reported an adverse event. Ogden et al concluded that a single application of LT peel to up to 200 cm^2 of anterior thigh in adults for up to 90 minutes did not produce systemic levels of lidocaine and tetracaine that were clinically significant at any time point measured up to 420 minutes after the initial application.

In 2013, Rauck et al reported erythema as the most common adverse event following LT combination application.[13]

In their 2014 Phase III study to assess the efficacy and safety of LT 7%/7% cream versus placebo cream, Cohen and Gold reported no related adverse events with LT combination. There was, however, one related adverse event of erythema with placebo cream.[25]

These studies suggest that LT combination seems to have a safe profile and be well tolerated as most subjects reported no major adverse effects.

Patient satisfaction

Two recent studies addressed the specific issue of patient satisfaction while testing the anesthetic efficacy of LT combination.

In their Phase II–III studies regarding the efficacy of LT combination versus placebo in achieving local anesthesia for laser-assisted hair removal, Alster et al specifically addressed the issue of patient satisfaction.[19] For both studies, subjects' ratings favored LT peel ($P<0.05$ vs placebo).

In their 2014 Phase III study, Cohen and Gold reported that a significant percentage of subjects declared that they achieved adequate pain relief with LT combination and that they would use it again.[25]

In 2013, Rauck et al investigated the satisfaction of patients affected by myofascial trigger points treated with LT combination.[13] The authors reported that 75% of patients enrolled in the study were either satisfied or very satisfied with treatment. Two weeks after stopping treatment, average pain intensity was 5.0±2.04; treatment benefit was maintained in eight patients (40%).

Conclusion

As the number and type of outpatient surgical procedures continue to grow, and as many minor inpatient surgical procedures involve some pain and discomfort, physicians are faced daily with pain management. They therefore need to adequately manage different anesthetic options. A number of local anesthetics, used alone or in combination, have been proposed in clinical practice. Numerous clinical trials have shown that LT combination, recently approved for adults aged 18 or older, is effective and safe in managing pain. Interestingly, LT combination has been successfully tested for the treatment of some painful syndromes such as myofascial trigger point pain, patellar tendinopathy, and shoulder impingement syndrome pain. Thus, it may represent a noninvasive treatment of these painful conditions and may help to limit pain killer prescriptions. Given its topical formulation, LT combination eliminates the use of needles, thereby reducing patient discomfort and anxiety. LT combination, when used according to recommendation of the US Food and Drug Administration, shows a high tolerability and a safe profile, with no major side effects compared to other topical anesthetics.

Nevertheless, as most of the randomized controlled trials reported compared LT combination versus placebo, further studies comparing LT combination versus standard treatment should be conducted in the future.

Disclosure

The authors report no conflicts of interest in this work.

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