Topical Anesthetics Update: EMLA and Beyond

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BACKGROUND. **Topical anesthetics remain a powerful, new advance for pain relief prior to cutaneous procedures. They are frequently used by dermatologists to decrease the pain associated with laser pulses, surgical procedures, or soft tissue augmentation. EMLA is the most commonly used agent, however, several new topical anesthetic agents have been released recently that claim increased efficacy and a faster onset of action.**

OBJECTIVE. **We review and compare the efficacy of several commonly used topical anesthetics and provide a look into the future.**

CONCLUSION. **EMLA remains the most widely used topical anesthetic given its proven efficacy and safety by several clinical trials. There has been a recent release of several new topical anesthetic agents with some demonstrating efficacy after a 30-minute application time. A reservoir of anesthetic is located and stored in the upper skin layers during application, providing additional anesthetic benefit 30 minutes after removal. As the options for the practitioner continue to grow, the demand for faster onset, comparative efficacy, and safety trials will continue to be of paramount importance.**

WITH THE emergence of new laser and surgical techniques, the need for more effective topical anesthesia continues to grow. There are now several topical local anesthetics that are being used prior to various dermatologic procedures. EMLA is the most commonly used agent, however, several new topical anesthetics have been released recently that claim increased efficacy and faster onset of action. We review and compare the efficacy of several commonly used topical anesthetics and provide a look into the future.

Topical anesthetics are weak bases typically constructed of three important components: an aromatic ring, an intermediate length ester or amide linkage, and a tertiary amine. The ester anesthetics have an ester linkage, while the amide anesthetics have an amide linkage between the aromatic ring and intermediate chain. Ester-type topical anesthetics are metabolized by plasma cholinesterase and other nonspecific esterases, while amide anesthetics are primarily metabolized in the liver via microsomal enzymes. Allergic contact reactions to the ester group of anesthetics are common, while amide anesthetics, including lidocaine and prilocaine, are rare sensitizers.[1,2] The metabolite para-aminobenzoic acid (PABA) formed by ester hydrolysis is capable of causing allergic reactions in a small percentage of patients.[3] Ester-linked anesthetics are contraindicated in patients with allergies to PABA, hair dyes, and sulfonamides.

Topical anesthetics prevent the initiation and transmission of nerve impulses and provide cutaneous analgesia by targeting free nerve endings in the dermis. Topical anesthetics block nerve impulse conduction by interfering with the function of sodium channels. By inhibiting sodium flux, the threshold for nerve excitation increases until the ability to generate an action potential is lost.

The stratum corneum is the main barrier to topical anesthetic delivery.[4] The aromatic portion is primarily responsible for the lipid solubility that allows diffusion across the nerve cell membrane, determining the intrinsic potency of these agents.[5,6] Both the aromatic and amine portion determine protein-binding characteristics, which are felt to be the primary determinant of anesthesia duration.[6]

Different methods for evaluating and comparing anesthetic efficacy have included venipuncture,[7–13] pinprick testing,[14] split-thickness skin graft donation,[15–17] and laser pulses as pain stimuli. Laser-induced thermal pain stimuli are advantageous for comparing topical anesthetics by providing reproducible, quantifiable stimuli with minimal intraindividual variation.[18–20] Laser pulses also provide selective activation of nociceptors, without interference from mechanosensitive receptors.[19]

Eutectic Mixture of Local Anesthetics (EMLA)

EMLA cream is a 5% eutectic mixture of two local anesthetics, lidocaine and prilocaine. It was released in

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the United States in 1993 and is composed of 25 mg/ml of lidocaine and 25 mg/ml of prilocaine in an oil-in-water emulsion cream. A eutectic mixture is defined as a compound that melts at a lower temperature than any of its components.[21] Using a eutectic system, Fredrick Broberg discovered that equal parts of lidocaine and prilocaine produced adequate analgesia after topical application to the skin.[22] The formulation yielded an anesthetic concentration of 80% in the oil droplets. However, a low overall concentration of 5% was maintained in the vehicle, thus minimizing systemic toxicity associated with higher concentrations.[23]

EMLA is the most widely used topical agent with proven efficacy from several clinical trials.[7–19] Multiple studies have shown its usefulness in producing dermal analgesia in patients treated for molluscum contagiosum, venereal lesions, venepuncture, shave biopsies, dermabrasion for tattoo removal, and debridement of venous leg ulcers.[7–13] In addition, EMLA has provided sufficient analgesia for harvesting split-thickness skin grafts after a 90-minute application period.[15] Lahteenmaki et al.[16] in a dose-finding study demonstrated that 15 g of EMLA applied to each 100 cm^2 area with application times of 2–5 hours provided enough analgesia to perform split-thickness skin graft harvesting. More recently, Gupta and Sibbald[24] showed that either EMLA cream or patch applied for 2–3 hours provided sufficient analgesia in 87% of the subjects to perform minor skin surgical procedures such as excisional biopsy or curettage and electrosurgery.

EMLA can also provide cutaneous analgesia for various laser procedures. Many studies have shown that EMLA is effective in reducing or eliminating pain associated with pulsed dye laser treatments after a 60-minute application period.[25,26] Ashinoff and Geronemus[27] demonstrated that EMLA is a safe and effective topical anesthetic for use in the treatment of port-wine stains with the pulsed dye laser. The use of EMLA did not interfere with the clinical efficacy of the pulsed dye laser, despite the fact that local vasoconstriction occurred in cutaneous blood vessels.[27] EMLA has also been shown to provide effective anesthesia after a 60-minute application period (Figures 1–3)[20] to laser-induced pain stimuli produced by the Q-switched Nd:YAG laser.

EMLA has produced dermal analgesia after application under an occlusive dressing for 60 minutes and inadequate analgesia after application for only 30 minutes.[28–30] Increased dermal analgesia is seen with up to 2 hours of occlusion.[31] Dermal analgesia has been shown to continue and even increase for 15–60 minutes after its removal.[18,20,28] This is likely due to a reservoir of anesthetic that accumulates in the stratum corneum during occlusion.[18,28] After the anesthetic is removed, the diffusion continues from the stratum corneum to the sensory nerves located in the dermis. Arendt-Nielsen and Bjerring,[18] based on their study, recommend application of EMLA cream under occlusion 1 hour prior to laser treatment followed by removal on the way to the hospital.

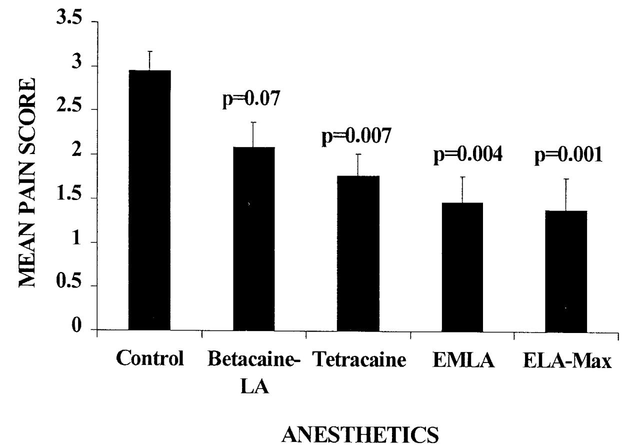


Figure 1. Mean pain scores after application of topical anesthetics for 60 minutes. *P*-values represent comparisons of each anesthetic with the control. ELA-max was statistically superior to tetracaine and betacaine-LA at 60 minutes, while EMLA was statistically superior to betacaine-LA at 60 minutes.[20]

The required application period of EMLA may vary depending on the location of treatment. EMLA has been shown to be effective on the face and thighs after as little as 25 minutes.[32] On mucosal surfaces, analgesia can be obtained in as little as 5–15 minutes given the lack of a stratum corneum.[33] In fact, the blood levels of lidocaine after application to mucosal surfaces have been shown to approach levels obtained after parenteral adminstration.[34] Therefore caution must be exercised when using topical anesthetics on mucosal surfaces. EMLA is less effective on the palms and soles despite long application periods due to the greatly thickened stratum corneum.

Adverse effects experienced with EMLA are generally transient and localized. Blanching and redness are

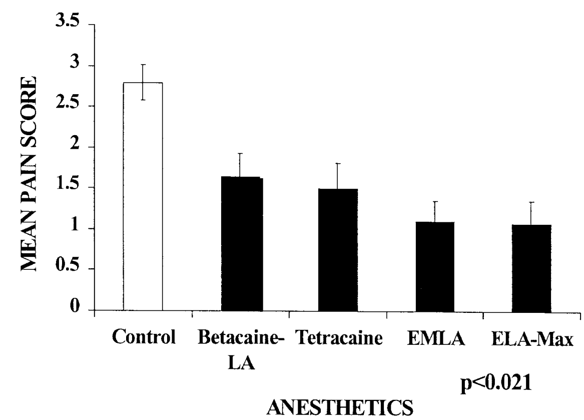


Figure 2. Mean pain scores 30 minutes after removal of the topical anesthetics. All anesthetics were superior to the control.[20]

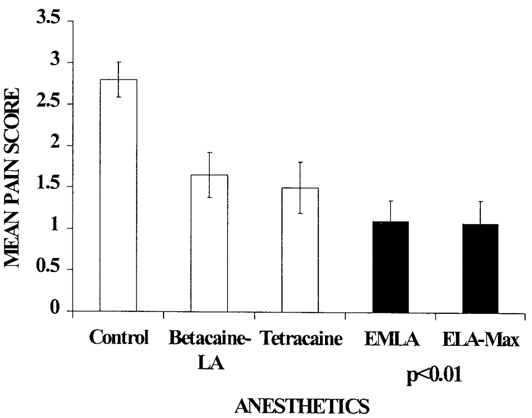


Figure 3. ELA-max and EMLA were superior to tetracaine and betacaine-LA 30 minutes after the 60-minute application period.[20]

commonly observed in the area of application and is thought to be due to peripheral vasoconstriction. The vasoconstriction is maximal after 1.5 hours and is followed by vasodilation after 2–3 hours.[35] Other effects include pruritus, burning, and purpura.

Contact hypersensitivity is exceedingly rare but has been reported in a few cases. Both lidocaine and prilocaine belong to the amide group of anesthetics. Allergic reactions are rarely encountered in this group, unlike the ester group of anesthetics (eg, procaine, benzocaine).[2,36,37] Cross-reactivity among amide class anesthetics has been documented. However, recent case reports of contact sensitivity specifically to EMLA cream have clearly shown that the offending agent is indeed prilocaine alone, with patch test failing to implicate lidocaine.

The development of methemoglobinemia is the most important systemic concern regarding the use of EMLA cream, a known complication of prilocaine. The development of methemoglobinemia involves the oxidation of iron from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state. This renders the hemoglobin molecule unable to transport oxygen. Cyanosis is evident when as little as 10% methemoglobin is present. At levels of 35% breathlessness occurs and toxicity occurs at levels in excess of 80%. Methemoglobinemia has been reported in a 3-month-old infant who was also taking trimethoprim-sulfamethoxazole and became cyanotic after 5 g of EMLA was applied for an extended period of 5 hours.[38] The use of EMLA for pain relief in neonatal circumcision is becoming more prevalent. The neonate, and especially premature infants, may be vulnerable to this complication due to immaturity of the methemoglobinemia reductase pathway. Other people at risk are those with glucose-6-phosphate deficiency. Caution should be exercised with EMLA in patients with congenital methemoglobinemia or in patients less than 12 months of age and who are concomitantly receiving a medication known to exacerbate methemoglobinemia.[39]

Despite these warnings, the development of methemoglobinemia with the use of EMLA is rare. Taddio et al.[40] found no increase in methemoglobin or adverse effects in 38 neonates who had 1 g of EMLA cream applied 60–80 minutes prior to circumcision. In a study of 22 infants, EMLA was applied for 4 hours and plasma methemoglobin levels were measured up to 8 hours after the last application. The highest reported level of methemoglobin was 2%, well below toxic or clinically significant levels.[41] Current guidelines recommend that in children weighing less than 10 kg, application should be limited to 2 g and applied to an area smaller than 100 cm^2. In children weighing 10–20 kg the maximum dose is 10 g and should not be applied to an area larger than 100 cm^2 (Table 1).

Although most adverse effects noted with the use of EMLA are localized and transient, care must be taken when EMLA cream is used near the eyes. Sodium hydroxide is a component of the vehicle that imparts a pH of 9 to the product. This level of alkalinity is necessary to allow for proper penetration of the anesthetic. It is also sufficient to cause chemical eye injury in the form of corneal abrasions and ulcerations. Several cases have been reported where eye injury occurred in association with the use EMLA near the eye.[42–44]

ELA-Max

ELA-max contains 4% or 5% (ELA-max5) lidocaine in a liposomal delivery system (Table 1) that uses multilamellar vesicles containing several lipid bilayers dispersed in an aqueous medium. ELA-max5 is marketed for temporary relief of anorectal pain, however, there is no medical reason why it cannot be used as a skin anesthetic. Liposomes facilitate the penetration of anesthetic into the skin, carrying the encapsulated drug into the dermis and providing sustained release.[45] Liposomes as drug carriers also protect the anesthetic from metabolic degradation, allowing prolonged duration of action.[46] Prior studies have shown the benefit of liposomal encapsulation in the delivery of topical anesthetics. As assessed by the pinprick method, liposomally encapsulated tetracaine (0.5%) has been shown to be more effective than tetracaine in an inert base in producing significant skin anesthesia.[47] Bucalo et al.[14] found that after an application time of 30 minutes, 5% liposomal lidocaine preparations provided a longer duration of anesthesia than lidocaine preparations in nonliposomal vehicles. The 5% liposomal lidocaine was also shown to be superior to a control in producing effective anesthesia to laser-induced pain stimuli after a 30-minute application period under occlusion.[48] Additional variables such as shorter application times and occlusion versus nonocclusion are currently being evaluated.

petrolatum base. Betacaine-LA is not approved by the U.S. Food and Drug Administration (FDA) and must be obtained from the manufacturer (Table 1).

There have been anecdotal reports of betacaine-LA providing more effective and rapid topical anesthesia as compared with EMLA without requiring occlusion. The recommended application time by the manufacturer is 30–45 minutes. The only prospective, controlled study of betacaine-LA was performed with occlusion and demonstrated only a borderline superiority to the control ($P = .07$) after 60 minutes of application (Figure 1).[20] Thirty minutes after removal, betacaine-LA was found to be significantly better than the control (Figure 2).[20] EMLA and ELA-max were statistically superior to betacaine-LA at both time intervals. More clinical trials are needed to determine the comparative efficacy and safety profile, as well as the role of occlusion.

Tetracaine

Amethocaine 4.0% gel, which contains 4% tetracaine, is marketed in Europe as providing more rapid and perhaps a longer duration of cutaneous anesthesia than EMLA. In a double-blind study of 29 patients using 4% amethocaine and EMLA for 1 hour prior to pulsed dye laser treatment of port-wine stains, amethocaine was significantly better than EMLA by visual analog and verbal rating scores in reducing pain caused by the laser treatment.[52] Amethocaine gel has also been shown to be safe and effective in alleviating the pain of venous cannulation in children[53] and adults.[54]

Adverse events reported with amethocaine are similar to those reported with EMLA and include local erythema, pruritus, and edema.[55] Plasma concentrations of amethocaine were measured by Mazumdar et al.[56] after topical application of amethocaine cream 2 g (5% w/w) to the dorsum of the right hand of 10 adult volunteers. The cream was applied for 4 hours and plasma was assayed for amethocaine and its metabolite *p*-n-butylaminobenzoic acid. There was no amethocaine detected in the plasma of seven volunteers, while plasma concentrations of amethocaine up to 0.20 mg/L were observed in three volunteers. There were no significant side effects and the absence of clinical toxicity in the 10 healthy volunteers was concluded to be a reflection of slow absorption and tissue hydrolysis of amethocaine after topical dermal application.[56]

Tetracaine gel is a recently introduced compounded, proprietary anesthetic containing 4% tetracaine in a lecithin-gel base. It is a long-acting ester anesthetic with a recommended application time of 30 minutes under an occlusive dressing. Tetracaine gel is not approved by the FDA and must be obtained from the manufacturer (Table 1). The only prospective, controlled study of tetracaine demonstrated a superiority to the control in minimizing pain after 60 minutes of occlusion, as well as at 30 minutes after removal[20] (Figures 1 and 2). More clinical trials are needed to determine the comparative efficacy and safety profile of tetracaine gel (Table 1).

Topicaine

Topicaine is 4% lidocaine in a gel microemulsion drug delivery system. It was released in 1997 for use prior to electrolysis and is gaining popularity as a topical anesthetic prior to laser hair removal. The recommended application time by the manufacturer is 30–60 minutes ~~under an occlusive dressing.~~ Topicaine is FDA approved for the temporary relief of pain and itching on normal intact skin and may be obtained without a prescription. The manufacturer is currently evaluating the systemic absorption of lidocaine after topicaine application. The maximum area of application should not exceed 600 cm^2 in adults and 100 cm^2 in children (Table 1). Localized adverse events have been mild and transient, including erythema, blanching, and edema.[57]

Topicaine demonstrated a very rapid onset with a long duration of cutaneous anesthesia in a prospective, randomized, double-blind, controlled study investigating the efficacy of EMLA, ELA-max5, and topicaine using a 30-minute application time.[48] Equal amounts of the above topical anesthetics as well as a control were randomly applied to eight test sites under occlusion on the volar forearms of 24 adult volunteers. The degree of anesthesia to pulses emitted with a Q-switched Nd:YAG laser at 1064 nm was measured. Similar testing was performed 15 and 30 minutes after removal of the anesthetics, with patients' responses being recorded on an ordinal scale of 0 (no pain) to 4 (maximal pain). Maximal pain for each subject was determined by testing untreated volar arm skin with a laser stimulus, which was used as an internal control. Under the parameters of this study, effective anesthesia to laser-induced pain stimuli was demonstrated with topicaine and ELA-max5 after only a 30-minute application period as compared to the control ($P = .002$). The highest level of anesthetic efficacy was obtained with topicaine and EMLA 30 minutes after their removal.

S-Caine Patch

The S-caine local anesthetic patch is a new drug delivery system that utilizes controlled heating to reportedly enhance the rate of anesthetic delivery into the dermis. The patch contains a 1:1 eutectic mixture of lidocaine base and tetracaine base with a disposable, oxygen-activated heating element. The heating ele-

NOTE: ESBA LABORATORIES does not recommend occlusion of TOPICAINE

ment generates a controlled level of heating (39–41°C) over a period of 2 hours.

Clinical studies have demonstrated that a 30-minute administration of the S-caine patch is efficacious in relieving the pain associated with shave biopsies and venipuncture. In a double-blind, placebo-controlled clinical trial the S-caine patch provided sufficient anesthesia for a shave biopsy in 72% of the active group compared to 16% of the placebo group ($P < .001$) (Rodriguez D and Stewart D, unpublished data). In a randomized, double-blind, placebo-controlled study in pediatric patients, the active S-caine patch was significantly better than placebo in providing cutaneous anesthesia for venipuncture after a 30-minute application period ($P < .001$). Close to 80% of the patients receiving the active patch reported "no pain" associated with the vascular access procedure compared to 40% with placebo (Eichenfield L, et al., unpublished data).

S-Caine Local Anesthetic Peel

The S-caine local anesthetic peel contains a similar formulation to a 1:1 eutectic mixture of lidocaine base and tetracaine base (Table 1). The peel is a cream which, as it dries, becomes a flexible membrane that is easily removed (Figure 4). These unique features of the drug reduce application time, ease the delivery of anesthetic to contoured regions of the body, and eliminate the need for application under occlusion.

A randomized, double-blind, placebo-controlled trial with the S-caine peel for local anesthesia prior to pulsed dye laser treatment on the face was recently completed. The results indicated that a 60-minute application of S-caine peel was better than placebo ($P < .001$) in providing local anesthesia prior to pulsed dye laser treatment of various vascular lesions (port-wine stain, telangiectasia, hemangioma) on the face of adult patients (Alster T and Rist T, unpublished data). The S-caine peel is currently in FDA phase III clinical trials and is being studied for local anesthesia prior to laser and surgical procedures.

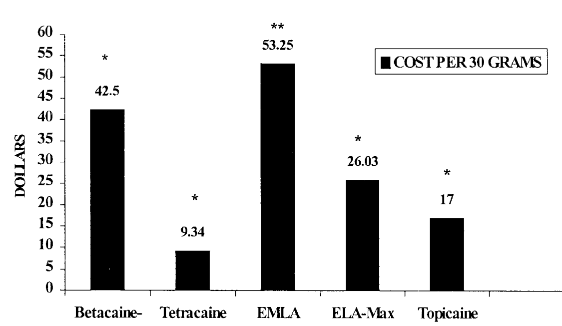
Cost Comparison

A cost comparison revealed that ELA-max and topicaine are substantially less expensive than EMLA (Figure 5). A 30 g tube of EMLA at the New York University Medical Center outpatient pharmacy is $53.25, while the same amount of ELA-max or ELA-max5 costs $26.03 through the distributor for the manufacturer. Topicaine may be purchased from the manufacturer for $17. A physician can obtain all of the topical anesthetics compared here at the manufacturer's cost except for EMLA.

Figure 4. A,B) S-caine peel.

Conclusion

Topical anesthetics remain a powerful, new advancement for minimizing pain during cutaneous procedures. While several new topical anesthetic agents have been released recently that claim increased efficacy and faster



*Can be obtained at manufacturer's cost.
** NYU pharmacy cost.

Figure 5. Cost comparison.[20]

onset, EMLA remains the most widely used topical anesthetic given its proven efficacy and safety by several clinical trials. As the options for the practitioner continue to grow, the need for studies comparing onset of action, efficacy, and safety continues to be of paramount importance.

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