**Topical Anesthetics in Children**

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**Introduction**

Needle sticks are the most common and greatest source of procedural pain in the world. From quick immunizations or glucose monitoring to venipuncture, laceration repair, dermatologic procedures, and even tattooing (and removal!), needle pain is a growing concern. Fortunately, the past decade has provided numerous solutions. This article will address the rationale for treating needle pain, the options available, and research evaluating these modalities.

While adults are also affected by needle pain, most of the research and product focus is for children. Concern for pain even in children too young to talk is not frivolous: the effects of untreated pain impact medical outcomes and are remembered by preverbal children. These effects may amplify with age: adolescents avoid medical treatment, 16% to 75% of adults surveyed refuse to donate blood, and geriatric patients refuse flu shots due to fear of needle pain. The health implications of needle phobia extend beyond the affected individuals; HIV patients continued to infect others while delaying blood tests, and needle phobic parents are less likely to immunize their children.

Research yields a distinct, age-related phobia relating to the needle procedure, suggesting untreated immunization pain is a significant contributor to needle phobia. Children now get more than 20 sticks before they are 2 years old. Despite an American Academy of Pediatrics (AAP) recommendation to use pain control "whenever possible," only 2.1 of an estimated 18 million venipunctures each year are done with pain control. Familiarity with and utilizing available methods to diminish needle pain for children can have far-reaching effects.

Available analgesic options correspond to the physiology of needle pain. Briefly, fast myelinated A-delta fibers transmit the sensation of the sharp stick. Topical anesthetics (eg, procaine, lidocaine, tetracaine) stop the transmission at the voltage-sensitive Na-positive channels, raising the action potential threshold until the impulse cannot be conducted.

Once the sharp pain impulse begins, it combines in the dorsal column in a final common pathway with continuously transmitted mechanoreceptor information: position, temperature, and vibration. Through the "gate theory," stimulating these C and A-beta fibers with cold or vibration decreases pain, as with running a burn under cold water or rubbing a bumped elbow. One adult case series described using vibrating massagers for dermatologic procedures, with a resulting decrease in or elimination of the need for topical anesthetics. A device for this purpose (Buzzy, MMJ Labs, Atlanta, Georgia) is currently under investigation in children. Although cold spray (eg, Painease, Gebauer, Cleveland, Ohio) has been widely used, research in children is equivocal.

The cortical reaction to sharp pain can be modulated through voluntary and external distraction. Children old enough to watch bubbles, blow pinwheels, or play "I Spy" games don't notice a painful procedure as much. While very effective, these methods take time and require props and trained support. The remainder of this review will discuss topical creams, lidocaine delivery devices, and cold spray.

**Topical Anesthetics Under Dressings**

**Local Anesthesia for Open Wounds**

Open lacerations permit easy absorption, rendering the hydrophilic ester issue moot. The first combinations included tetracaine and cocaine mixed with a vasoconstrictor ("adrenaline") to decrease diffusion. This mix, "TAC," was very
effective with minimal toxicity when placed directly into the wound. TAC essentially obviated the need for injection for many pediatric cuts. The use of the controlled substance cocaine, however, both increased the cost and logistical difficulty of keeping the mix available. In 1995, Ernst and colleagues[^25] demonstrated that lidocaine, epinephrine, and tetracaine (LET or LAT) were just as effective. This has become the standard of care for pediatric wound repair, either with a single application or with sequential applications.[^26]

A shred of LET-soaked cotton or LET mixed with methylcellulose is placed directly in the wound prior to cleansing and repair. The solution or gel can be held in place with an occlusive dressing, tape, or bandage, but care must be taken not to put any absorptive surface near the LET, as this will wick the medication away from the wound. The wound edges blanch when numb, usually after 20 minutes. Anesthesia lasts an average of 21 minutes after removal.[^27] LET alone gives sufficient pain control in 60% of adults,[^28] 70% to 90% of pediatric facial lacerations,[^27] and 40% to 75% of extremity wounds.[^29] In addition, use in children decreased length of stay from 108 to 77 minutes.[^30]

One study exclusively in pediatric finger lacerations found an efficacy of approximately 50%. They found no cases of digital ischemia, nor did another that left LET on for 15 minutes.[^29,31] The numbers of patients studied were 67 and 23, respectively; these small numbers are reassuring but do not establish safety. While absorption of lidocaine through mucous membranes is a theoretical concern, the use of LET for oral lacerations is more limited by loss of the pigmentation of the vermillion border from blanching.

The recipe is somewhat complicated: lidocaine 20% 100 mL (20 g lidocaine powder, 100 mL normal saline); racemic epinephrine 2.25% 50 mL; tetracaine 2% 125 mL; sodium metabisulfate 315.4 mg; 225 mL sterile water -- yielding a total of 500 mL of LET. This will keep for 3 weeks at room temperature or 5 months refrigerated.

Local Anesthesia for Intact Skin

The 3 most common anesthetic formulations that absorb through intact skin are **EMLA** (AstraZeneca, Wilmington, Delaware), **LMX-4** (Eloquest Healthcare, Ferndale, Michigan), and tetracaine (eg, Ametop gel, Smith & Nephew, Hull, United Kingdom; Synera, Endo Pharmaceuticals, Chadds Ford, Pennsylvania).

**EMLA.** One of the first and most studied topical creams is a eutectic mixture of local anesthetics, a prilocaine 2.5% and lidocaine 2.5% cream. When applied for a minimum of 45 to 60 minutes, extensive evidence supports reduction of pain from IV catheter insertion.[^32-37] In contrast to the other topicals, **EMLA** can be left on up to 4 hours, and its duration of action continues an hour after removal.[^32] In addition, depth of anesthesia increases up to 6 mm during prolonged application.[^38]

The perception that **EMLA**'s vasoconstriction[^39,40] necessitates multiple needle sticks is one barrier to use. Vasoconstriction has been described with all creams and placebos: one adult study found maximal constriction at 1.5 hours, although **EMLA** subsequently increased vein diameter to 148% of baseline at 6 hours.[^41] With regard to ease of venipuncture, smaller studies in children have shown either no difference[^42] or improved procedure ease with **EMLA** in outpatient or anesthesia settings.[^34,43] One abstract found that **EMLA** use resulted in successful cannulation for 53 of 65 children (82%) vs 58 of 89 (65%) venipuncture attempts in untreated skin. Venipuncture success was improved the longer **EMLA** was applied, up to 92% when left on for 2-3 hours.[^44]

**EMLA** has been found to be safe[^45] and effective for neonatal circumcisions, even warranting its own Cochrane review.[^4,46] While conclusively demonstrated to decrease the pain of lumbar punctures (LP) in older children,[^47] **EMLA** is the only topical anesthetic studied shown to decrease pain in newborn LPs. Kaur and colleagues[^48] showed decreased pain when compared with placebo, using physiologic parameters and a videotaped coded behavioral scale. **EMLA** decreases immunization pain, with no change in antibody response.[^49,50] For open wounds, **EMLA**'s efficacy is 40% compared with 74% for LET.[^51]

Methemoglobinemia is rare side effect more likely in preterm infants lacking the enzyme to reduce it.[^52] Current recommendations limit **EMLA** to infants of at least 37 weeks gestational age. A purpuric rash of presumed toxic origins
has been described in 1% to 2% of users, particularly in atopic patients.\textsuperscript{53,54} The cost of \textit{EMLA} is approximately US$7 for the tube and occlusive dressing.

**LMX-4.** \textit{LMX-4} (previously called \textit{ELA-Max}) is a liposomal delivery system that allows a 4% lidocaine preparation to be rapidly absorbed by the skin.\textsuperscript{55} It has effect in 20-30 minutes and works as well as \textit{EMLA} for venipuncture pain.\textsuperscript{56,57} The rapid absorption also results in a rapid dissipation of the drug, with diminishing anesthesia approximately 40-60 minutes after application, although this has not been formally reported.

Taddio and colleagues\textsuperscript{58} evaluated procedural success and pain relief in a pediatric emergency department using \textit{LMX-4} for venipuncture. They demonstrated improved cannulation success on the first attempt (74\% vs 55\%, \(P = .03\)) when compared with placebo. In addition, they noted a decreased mean total procedural duration of 6.7 vs 8.5 minutes (\(P = .04\)) and significantly lower pain scores.

While \textit{LMX-4} has not been explicitly studied for pain of infant LP, one study found doubled LP success rates for residents when \textit{LMX-4} was used compared with no pain control (odds ratio = 2.2, 95\% confidence interval = 1.04-4.6).\textsuperscript{59} When studied for office-based meatotomy, \textit{LMX-4} for 30 minutes was equivalent to \textit{EMLA} for 45 minutes.\textsuperscript{20}

\textit{LMX-4} does not carry the risk of methemoglobinemia and is over the counter, diminishing the barrier of requiring a physician's order. Cost is similar, $6-7 per 1- to 2-g application. If a medical-grade occlusive dressing is not available, both \textit{EMLA} and \textit{LMX-4} can be occluded with Glad \textit{Press-n-Seal}. The product is not sterile, but over unbroken skin this is not an issue. It does not contain latex and has the added benefit of painless removal.

**Tetracaine Products.** Tetracaine gel, formerly known as amethocaine, is available alone and compounded with lidocaine. The 4\% formulation works in 30-45 minutes and has a duration of action of 4-6 hours. It has a similar efficacy to \textit{EMLA}.\textsuperscript{60-62} In a randomized, blinded, crossover study, Bishai and colleagues\textsuperscript{63} compared the two for \textit{Port-a-Cath} access and found tetracaine worked as well in 30 minutes as \textit{EMLA} did in 60.

In addition to venous access efficacy, tetracaine has also been studied for immunizations. It reduced pain significantly for measles-mumps-rubella vaccine, with no decrease in antibody response.\textsuperscript{62}

\textbf{Synera (Formerly S-Caine Patch).} Tetracaine and lidocaine mixed 7\%/7\% in a self-contained patch have been studied for venipuncture. The currently available product, \textit{Synera}, is designed to look like a child's bandage and is recommended for children aged 3 years and older. \textit{Synera} contains a heating element that, when activated, enhances absorption, allowing for rapid anesthesia and some degree of vasodilation. A recent adult study found that 73\% of adults reported "adequate analgesia" compared with 31\% with placebo.\textsuperscript{64} Cost is approximately $12 per patch. The mixture was tested as the \textit{S-Caine Patch} without the heating element prior to being licensed to Endo Pharmaceuticals and showed good results in children for venipuncture.\textsuperscript{65}

\textbf{Other Absorbable Topicals.} A mixture of lidocaine, tetracaine, and phenylephrine (tetralidophen) was compared with injected lidocaine for mucous membrane repairs but was not as effective.\textsuperscript{66} Capsaicin ointment 15\%, (\textit{Myolaxin}, Geno, Mumbai) performed favorably against \textit{EMLA} when applied for 60 minutes.\textsuperscript{67} While described as less expensive, it is not currently available in the United States and does not offer the timing benefits of other products.

**Devices to Enhance Topical Lidocaine Absorption**

Iontophoresis uses a low-voltage electrical current to drive the positively charged end of lidocaine through the epidermis.\textsuperscript{68} As the current flows to the negative reservoir, drug in the positive reservoir is carried into the skin. The current flow is noxious to some children, but those who tolerate the device find pain control equivalent and may prefer it. Galinkin and colleagues\textsuperscript{69} found in a crossover trial that 11 of 22 children preferred iontophoresis, 5 (including 2 who did not tolerate iontophoresis) preferred \textit{EMLA}, and 6 children did not care.

Cost of the method includes the delivery device (ActivaTek [Salt Lake City, Utah], $290; Iomed [Salt Lake City, Utah],...
$695), and each individual-use lidocaine reservoir packet (from $5 to $14; eg, lomed $64/6). Time of application is at a minimum 10 minutes with newer delivery systems, such as LidoSite (Vyteris, Inc., Fair Lawn, New Jersey).

The delivery system is indicated for children over the age of 5 years and is contraindicated in children with pacemakers. It should not be used over broken skin or through mucous membranes, palms, or soles, where the conduction is either enhanced or impeded, respectively. In a placebo-controlled study of 500 subjects with a more rapid device, 1 subject experienced a partial-thickness burn.[70]

Intradermal Lidocaine Delivery

Even the few minutes needed to apply creams or run current are a barrier to their use. While the following methods are by definition not topical, they should be considered as alternative modalities for venipuncture when time is the reason not to use pain control.

One rapidly effective and well tolerated pain relief method is simply to inject buffered lidocaine using a 30-gauge needle prior to venipuncture.[71] Luhmann and colleagues[71] found no difference in pain comparing this method with LMX-4 for pediatric cannulation using 22-gauge needles. Patterson and colleagues[72] included unbuffered lidocaine in a comparison with cold spray, EMLA, and injected benzyl alcohol and found the former to be cheapest and most effective, though more painful upon application because it was unbuffered. Use of this method is inexpensive, depending on bundled hospital charges for the extra needle, syringe, and buffered lidocaine.

A newer product, the J-Tip (National Medical Products, Irvine, California), puts lidocaine under the skin via a jet of compressed carbon dioxide. Early studies found the delivery method less painful than a 25-gauge needle but found the numbing to be less effective.[34] Subsequent venipuncture investigations in children have had better results, with better pain relief from J-Tip use than EMLA. Of note, 81% found J-Tip lidocaine administration painless compared with 64% who felt pain with removal of EMLA’s occlusive dressing.[73] The price for the single-use disposable unit is $2 to $4.

Several products enhance absorption of LMX-4, decreasing time until efficacy. One product, Sonoprep (Sontra Medical Corporation, Franklin, Massachusetts), improved pain control vs placebo by pretreating with ultrasound for 15 seconds, then applying LMX-4 for 5 minutes.[74] A low-power erbium:YAG laser (Epiture Easytouch, Norwood Abbey, Frankston, Victoria, Australia) was tested with 10 seconds of laser vs sham laser prior to 5-minute LMX-4 application. The $2500 laser significantly reduced pain of cannulation in the 47 children randomized to the laser group.[75]

Finally, a disposable product approved for children in 2007 uses compressed air to puff lidocaine through the skin in a 1-cm area.[76] The devices, which will be marketed as Zingo (Anesiva, South San Francisco, California), will cost between $12 and $15 per use. As with the other devices, if the prepared area is not subsequently used, the cost recurs in a newly chosen site.

Cold Spray

The idea of cold for pain is as old as the ice pack. Applying cold spray (Painease) directly to the penetration site has been used in hospitals for needle sticks, but placebo-controlled, randomized trials have produced varying results. Whereas Mawhorter and colleagues[77] found cold spray effective for adult immunizations, others found increased distress in small children[22] and adults prior to venipuncture.[72] The cold also causes veins to shrink, making inserting an intravenous cannula difficult.[22] Results with cold spray for pediatric immunization have been mixed,[21] most likely because the spray is subfreezing and can injure children’s more delicate tissues (LL Cohen, personal communication, 2007). Cold spray is appealing because it costs pennies per application and can be used at another site instantly if the intended location for venipuncture needs to change. Painease was removed from the market in 2006 due to the discovery of mold in the cans, but Gebauer reports on its Web site that the product should be back on the market in early 2008.
In sum, needle pain is important and has broad and lasting effects, but it can be relieved.

Comparison of Options for Venipuncture

<table>
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<tr>
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<th>EMLA</th>
<th>LMX-4</th>
<th>Synera</th>
<th>Cold Spray</th>
<th>Iontophoresis</th>
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<th>J-Tip</th>
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<tr>
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<td>20-30</td>
<td>20</td>
<td>1</td>
<td>5-10</td>
<td>1</td>
<td>1</td>
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<tr>
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<td>1 hour</td>
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<tr>
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<td>Burns&lt;12 years</td>
<td>Noxious to some users</td>
<td>Extra needle preparation</td>
<td>Waste of disposable unit</td>
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<tr>
<td>Cost</td>
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<td>$5-7</td>
<td>$12</td>
<td>$0.25</td>
<td>$10 + unit</td>
<td>&lt; $2</td>
<td>$3</td>
</tr>
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SQ = subcutaneous

Table 1. Comparison of Options for Venipuncture

References


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