Pharmacologic Approaches for Reducing Venous Access Pain in Children

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ABSTRACT

A variety of pharmacologic options are available to clinicians who want to provide effective and safe topical local anesthesia to children undergoing venous access procedures. These options can be distinguished on the basis of how they deliver active drug through the impermeable outer layer of skin, the stratum corneum, to pain receptors located in the dermis and epidermis. Three general methodologies are typically used to bypass the stratum corneum: direct injection of local anesthetics, usually via a small-gauge hypodermic syringe; passive diffusion from topical creams or gels; and active needle-free drug strategies that enhance the rate of drug passage into the dermis and epidermis. Examples of the latter mechanisms include heat-enhanced diffusion, iontophoresis, sonophoresis, laser-assisted transdermal passage, and pressurized gas delivery of powdered drug particles. Pharmacologic options in this setting can also be distinguished on the basis of the time to onset of full anesthetic effect. Several available agents induce significant local anesthesia within 1 to 3 minutes of administration, or faster, allowing easy integration into the skin preparation and subsequent venous access procedure. In combination with nonpharmacologic approaches, these agents can be used to dramatically lessen this significant source of pediatric pain. Pediatrics 2008;122:S140–S153

SIMPLE VENOUS ACCESS procedures are a significant source of pain and distress for children receiving medical care.1,2 Although guidelines from a number of national and international organizations such as the American Academy of Pediatrics, the International Association for the Study of Pain, and the American Pain Society call for multimodal management strategies for needle-stick pain,3–5 compliance with recommendations is often poor in practice.6,7 This is particularly surprising given that the hospital-accreditation process includes standards for consistent monitoring and treatment of pain8 and that venous access procedures are not only the most common cause of pain in hospitalized children but also the second most common cause of “worst pain.”10 Barriers to implementation of the guidelines are manifold and include a lack of knowledge among health care professionals regarding available pain assessment and treatment modalities in children, as well as perceived time constraints and inconvenience for administering local anesthetics.3,5

The purpose of this article is to review the growing list of local anesthetic agents used for the management of peripheral venous access procedures in children. The information is based primarily on data from published randomized clinical trials, which were identified through a variety of broad search strategies in PubMed. In addition, data from medical conferences on unpublished clinical trials were identified by personal communication and included where appropriate. For ease of reference, tables are provided to summarize important features of the trials, including design, arms, patient numbers, patient age, procedure, and outcome. Although the primary focus of the review is on pediatric venous access pain, the text and tables also describe a number of adult studies; this was deemed appropriate to ensure completeness, particularly for those agents for which adult studies comprise a significant proportion of the published literature on venous access pain. The reader is cautioned, however, to consider differences between children and adults in metabolism, pharmacokinetics, etc when reviewing these studies. It is hoped that this review, in combination with other recently published reviews,11–13 will provide clinicians with a better understanding of this evolving class of therapeutics and encourage, in turn, their more appropriate and widespread use.

THE “IDEAL” LOCAL ANESTHETIC FOR RELIEF OF VENOUS ACCESS PAIN

General properties associated with an ideal local anesthetic, as with any pharmacologic agent, include high efficacy, a good safety profile, convenient application, enduring effect, and reasonable cost. Specific properties unique to a local anesthetic for venous access pain would include a needle-free or topical administration, rapid onset of analgesia to minimize disruption and delay of needed medical procedures, minimal systemic absorption, no untoward dermal effects, and no adverse effect on the success rate of the venous access procedure. No commercially available agent is

Abbreviations

VAS—visual analog scale
IV—intravenous
LHM—lidocaine hydrochloride monohydrate

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Key Words
venipuncture, peripheral cannulation, pain, local anesthetics, analgesics, medical device, lidocaine, transdermal administrations, pediatrics

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likely to have all of these properties, but the preceding considerations nonetheless create a framework by which clinicians can compare and contrast potential options.

**DRUG-DELIVERY STRATEGIES FOR LOCAL ANESTHETICS**

Local anesthetics for venous access pain differ from one another primarily in their drug-delivery mechanisms rather than in their underlying pharmacologic modes of action. With few exceptions, most available agents have lidocaine, prilocaine, and/or tetracaine (also known as amethocaine) and produce their analgesia through similar mechanisms that involve inhibition of sodium ion channels in sensory neurons. The technologic challenge inherent in formulating a local anesthetic for venous access pain is in drug delivery, because the peripheral transducing terminals of cutaneous sensory fibers are located in the dermis and epidermis, below the outer layer of skin. This outer layer, known as the stratum corneum, consists of a thin layer of cornified nonviable keratinocytes interconnected by highly ordered lipid bilayers and has evolved to be a highly effective barrier to water-soluble substances, which typically include anesthetics.

Three general delivery methodologies have been used to bypass the stratum corneum barrier. Direct injection of local anesthetics, usually via a small-gauge hypodermic syringe, is the oldest of the methodologies. Passive diffusion from topical creams or gels comprises the second general class of methodologies. The final class uses a variety of active needle-free drug-delivery strategies to enhance the rate of drug passage through the skin and shorten the time to onset of action. Examples of the latter mechanisms include heat-enhanced diffusion, iontophoresis, sonophoresis, laser-assisted transdermal passage, or pressurized gas delivery of powdered drug particles.

Although existing delivery mechanisms for local anesthetics differ in detail, 1 of their key differentiating features is the time needed for onset of full analgesic effect. Generally, the evolution of commercial agents over the last 25 years has been associated with a parallel and progressive decrease in the time needed for pretreatment. For example, the original topical local anesthetic cream formulations required at least a 60-minute waiting period to establish full analgesic effect, whereas some current systems require 5 minutes or less. The goal of this developmental path has been to develop agents that allow for the anesthetic administration and the venous access procedure to be consolidated into 1 brief and convenient patient-provider contact to improve clinical workflow in busy settings.

A large number of direct interagent comparisons of topical local anesthetics have been published. Although this review cites many of these studies, it must be kept in mind that interstudy efficacy comparisons can be problematic, even between the most rigorously designed studies. Many studies, for example, have examined different populations (age groups, medical backgrounds, genders, different hospital locales [phlebotomy laboratory, emergency department, etc]), different procedures (venipuncture, peripheral venous cannulation), different treatment sites (antecubital fossa, dorsum of the hand), and different needle gauges. Moreover, the use of diverse assessment tools (self-reported, observer-reported, Wong-Baker Faces, Faces Pain Scale-Revised, Oucher, visual analog scale [VAS], Facial Affective Scale) may further confound comparisons, because even subtle variations in the format of the faces scales have been shown to influence children’s and parents’ ratings of pain. Finally, the sensation of pain is affected by age, anxiety level, and genetic traits, which may help to explain why some children rate the pain of venous access procedures so highly even when treated with a topical local anesthetic. These considerations should be borne in mind when choosing an appropriate local anesthetic to fit a specific clinical situation.

**LOCAL INFECTION**

**Injection of Local Anesthetics**

Direct intradermal injection of local anesthetic solutions, typically lidocaine, via a hypodermic syringe is the oldest method for bypassing the stratum corneum before a venous access procedure (Table 1). After lidocaine injection, onset of anesthesia is rapid, and the analgesic effect is excellent. Although pain from a local lidocaine injection has been shown to be lower than that of intravenous (IV) cannulation, direct infiltration nonetheless requires subjecting a patient to a second needle stick, with its attendant pain and distress. This may explain, in part, why this approach is not used more widely, although the pain of lidocaine injections can be mitigated by buffering the lidocaine with sodium bicarbonate and by use of smaller-gauge needles (30 gauge).

It is important to note that injection of buffered lidocaine has also been demonstrated to have no impact on the success rate of IV catheter insertion in children aged 8 to 15 years15 and in children aged <24 months.16

**Lidocaine Needle-Free Injection**

The J-Tip system (J-Tip needleless injection system [National Medical Products, Inc, Irvine, CA]) is a small, disposable, needle-free injector device that uses pressurized CO2 to infiltrate a solution of user-loaded lidocaine into subcutaneous tissue. The device contains a small syringe and a CO2 cartridge. To operate it, a lidocaine solution is loaded into the syringe and the device is placed tightly against the skin where the venous access procedure is to occur. Pressing a lever on the syringe releases the CO2 and drives a piston to eject the lidocaine solution under high pressure via a micro-orifice at the end of the device. Drug delivery occurs in a fraction of a second, and subsequent analgesia occurs within 1 to 3 minutes (see below).

Three clinical trials (2 adult and 1 pediatric) have examined the use of this device for venous access pain (Table 1). One was a randomized, partially blinded study of 360 adult surgical inpatients receiving IV cannulations on the dorsum of the hand 1 minute after administration. A significantly greater proportion of patients had “acceptable pain relief,” defined as a nu-
Lidocaine infiltration

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TABLE 1 Clinical Trials Analyzing Local Infiltration Strategies for Venous Access Pain

<table>
<thead>
<tr>
<th></th>
<th>Design</th>
<th>Arms (n)</th>
<th>Age</th>
<th>Procedure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>R, SB</td>
<td>1% lidocaine (20); LP cream (20)</td>
<td>7–12 y</td>
<td>IC</td>
<td>1% lidocaine = LP cream</td>
</tr>
<tr>
<td>19</td>
<td>R, SB</td>
<td>0.5% lidocaine (65); LP cream (49); DCTF (63); benzyl alcohol (61)</td>
<td>Adult VP</td>
<td>0.5% lidocaine &gt; LP cream; 0.5% lidocaine &gt; DCTF; 0.5% lidocaine = BA</td>
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</tr>
<tr>
<td>20</td>
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<td>Adult IC</td>
<td>Buffered lidocaine &gt; (saline = no pretreatment)</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>R, DB, P</td>
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<td>Adult IC</td>
<td>Lidocaine &gt; saline; lidocaine &gt; no treatment</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>R, CO, DB</td>
<td>1% lidocaine (101 treatments); buffered lidocaine (101 treatments)</td>
<td>6–18 y IC</td>
<td>1% lidocaine = buffered lidocaine</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>R</td>
<td>Buffered lidocaine (30); no treatment (30)</td>
<td>8–15 y IC</td>
<td>Buffered lidocaine &gt; no treatment</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>R, DB, CO, P</td>
<td>1% lidocaine (20); buffered lidocaine (20); 1% diphenhydramine (20); saline (20)</td>
<td>Adult IC</td>
<td>Duration of numbness</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>R, SB</td>
<td>Buffered lidocaine (35); liposomal lidocaine 4% (34)</td>
<td>4–17 y IC</td>
<td>Buffered lidocaine = liposomal lidocaine 4%</td>
<td></td>
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<tr>
<td>26</td>
<td>R</td>
<td>1% lidocaine (10); LP cream (45–60 min) (10); 2% lidocaine (10)</td>
<td>Adult IC</td>
<td>(1% lidocaine = 2% lidocaine iontophoresis)</td>
<td></td>
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<tr>
<td>27</td>
<td>R, DB</td>
<td>1% lidocaine (40); benzyl alcohol (40)</td>
<td>Adult IC</td>
<td>&gt; LP cream</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>R, DB, CO</td>
<td>Buffered lidocaine (74); benzyl alcohol (74); saline (74)</td>
<td>Adult IC</td>
<td>1% lidocaine &gt; (benzyl alcohol = saline)</td>
<td></td>
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<tr>
<td>29</td>
<td>R, SB, CO</td>
<td>1% lidocaine (20) vs 18-gauge cannula (20); 1% lidocaine (20) vs 20-gauge cannula (20); 1% lidocaine (20) vs 22-gauge cannula (20)</td>
<td>Adult NA</td>
<td>Injection of 1% lidocaine less painful than insertion of 18-, 20-, or 22-gauge cannula</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>R, SB, CO</td>
<td>2% lidocaine, 25-gauge needle (40); buffered 2% lidocaine, 25-gauge needle (40); 2% lidocaine, 30-gauge needle (40); buffered 2% lidocaine, 30-gauge needle (40)</td>
<td>Adult Needle prick</td>
<td>Injection pain: lidocaine 25-gauge &gt;&gt; (buffered lidocaine 25-gauge; lidocaine 30-gauge) &gt;&gt; buffered lidocaine 30-gauge; subsequent anesthesia = in all groups</td>
<td></td>
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</tbody>
</table>

> indicates greater analgesic effect; >>, more painful; =, similar analgesic effect; CO, crossover; DCTF, dichlorotetrafluoroethane; DB, double-blind; IC, IV cannulation; LP cream, lidocaine and prilocaine cream; P, placebo-controlled; R, randomized; SB, single-blind; VP, venipuncture.

In the only published pediatric study to date that used the J-Tip system,32 children 7 to 19 years of age were randomly allocated to receive 0.25 mL of 1% buffered lidocaine via the J-Tip system (n = 57; mean time before procedure: 1.8 minutes) or 2.5 g of lidocaine and prilocaine cream (n = 59; mean time before procedure: 69 minutes) in an open-label fashion. Pain assessments of subsequent IV cannulation procedures were significantly lower in the J-Tip group, whereas success rates for line placement were similar in the 2 treatment groups. Contrary to the adult studies, administration of the J-Tip system was not associated with significant discomfort. Thus, on a VAS pain-rating scale from 0 to 10, 84% of the patients rated the administration pain a 0, and 16% rated the pain from 1 to 3. Moreover, the mean VAS pain scores for J-Tip administration were significantly lower than the mean pain scores for removing the dressing for those in the lidocaine and prilocaine cream group (P < .004). This study did not report on adverse events associated with J-Tip use or on the number of device failures.
PASSIVE DIFFUSION WITH TOPICAL CREAMS OR GELS

Lidocaine and Prilocaine Cream, 2.5%/2.5%

When mixed in a 1:1 ratio, crystals of lidocaine and prilocaine produce a “eutectic mixture” (ie, a mixture that has a lower melting point than either component alone). The lidocaine and prilocaine in the commercially available cream are each present at a concentration of 2.5%, which produces a eutectic mixture with a melting point below room temperature. Consequently, the local anesthetics exist as a liquid oil rather than as crystals and penetrate more readily into the epidermal and dermal layers. In addition to the cream formulation, a eutectic mixture of lidocaine and prilocaine is also available in a patch formulation outside of the United States.

Lidocaine and prilocaine cream, 2.5%/2.5% (EMLA cream [eutectic mixture of local anesthetics] [AstraZeneca LP, Wilmington, DE]), has been used in clinical practice for ~25 years. A large number of clinical trials in both children and adults have analyzed its analgesic effect on venipuncture35-43 and IV cannulation36,44-48 (Table 2) pain. A meta-analysis of these trials concluded that pretreatment with lidocaine and prilocaine cream provided highly significant analgesia for both venipuncture and cannulation procedures, with similar and consistent effects across both procedures.49 In total, 85% of the patients receiving lidocaine and prilocaine cream exhibited significant analgesic benefit from its application before a venous access procedure. The analgesia seems to be independent of age, location of the procedure, and IV insertion technique.49

Other studies have shown that the efficacy of lidocaine and prilocaine cream depends on dosage and application time. A randomized trial on 92 children undergoing venipuncture found that a thick layer (2.0 mL) was more effective than a thin layer (0.5 mL) in producing pain-free venipuncture.50 The minimum recommended treatment time is 60 minutes, but longer durations (>90 minutes) are known to produce greater pain relief.12 Overall, the prolonged period of time necessary for onset of full analgesic effect with lidocaine and prilocaine cream presents a practical challenge in clinical settings. Protocols have been developed to improve clinical workflow with this agent,51,52 but it is likely that the time constraint remains the single largest barrier to its broader use for venous access procedures.

Unique among the agents described in this review, lidocaine and prilocaine cream has also been studied in neonates for blood drawing and circumcision (efficacy for heel lancing has not been demonstrated).53 The recommended total dose, size of application area, and application time are lower in neonates than in older children and adults (Table 3).53

Although lidocaine and prilocaine cream is indicated for use on genital mucous membranes for superficial minor surgery and as pretreatment for infiltration anesthesia, absorption from the genital mucosa is more rapid and onset time is shorter (5–10 minutes) than after application to intact skin.53 Application of lidocaine and prilocaine cream to broken or inflamed skin could also result in higher plasma levels that could, in susceptible individuals, produce a systemic pharmacologic response.53 For similar reasons, care must be taken with small children, who may ingest the cream from under occlusive dressings or who may inadvertently contaminate their eyes.53

Lidocaine and prilocaine cream causes vasoconstriction of superficial capillaries, which leads to blanching of the skin; this vasoconstriction is greatest 1.5 hours after application.54 In rare patients, allergic and anaphylactoid reactions associated with lidocaine or prilocaine can occur and are characterized by urticaria, angioedema, bronchospasm, and shock.53 Particularly in very young infants, but also in other susceptible populations, use of lidocaine and prilocaine cream may be associated with methemoglobinemia.53

Tetracaine Gel

Tetracaine gel (Ametop Gel [Smith & Nephew, London, United Kingdom]), which is currently available in Australia, Canada, New Zealand, and the United Kingdom, consists of a 4% tetracaine base in an aqueous gel.55 When applied to skin, solid tetracaine particles, which are present as a metastable hydrate in the gel, undergo a phase change (ie, they melt) to form an oil emulsion that better penetrates the stratum corneum.55 Tetracaine gel is commonly applied with an occlusive dressing.

Three clinical trials have examined tetracaine gel compared with lidocaine and prilocaine cream or patch in the setting of pediatric venipuncture.56-59 and 4 have compared them for IV cannulation (Table 4).56-58 A critical review of these and other trials concluded that tetracaine gel produced anesthesia comparable to that of lidocaine and prilocaine cream for a wide range of cutaneous procedures, including venous access procedures.55

However, unlike the ≥60-minute application time required for lidocaine and prilocaine cream, tetracaine gel produced therapeutically equivalent analgesia in 30 to 45 minutes (application times of <30 minutes did not generally produce reliable anesthesia).55 After application, tetracaine gel has a longer duration of anesthesia (4–6 hours) than lidocaine and prilocaine cream.12 The reasons for the prolonged pharmacologic activity may be a depot effect in the stratum corneum12 and strong general affinity of tetracaine for proteins, which may prolong its inhabitancy of sodium channels on sensory neurons.53

Overall, tetracaine gel has a favorable safety profile.55 No significant systemic adverse events were reported from pediatric trials. Transient erythema was the most commonly reported local skin reaction, followed by edema and pruritus.55 Some rare case reports of more-serious local skin reactions, including severe redness, pruritus, erythema, wheal, and rash, have been documented, but these events were generally self-limiting. Severe overexposure can lead to a “bruise-like” discoloration.51 Contrary to the vasoconstriction associated with lidocaine and prilocaine cream, tetracaine causes vasodilation in response to the initial transient local erythema, which may facilitate vascular access.12
<table>
<thead>
<tr>
<th>Design</th>
<th>Arms (n)</th>
<th>Age</th>
<th>Procedure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref 35</td>
<td>R, CO, DB, P</td>
<td>LP cream (140 applications), placebo cream (80 applications)</td>
<td>Adult</td>
<td>VP</td>
</tr>
<tr>
<td>Ref 36</td>
<td>R, DB, P</td>
<td>LP cream (128), placebo cream (130)</td>
<td>5–18 y</td>
<td>IC, VP</td>
</tr>
<tr>
<td>Ref 37</td>
<td>R, DB, P</td>
<td>LP cream (23), placebo cream (26)</td>
<td>8–17 y</td>
<td>VP</td>
</tr>
<tr>
<td>Ref 38</td>
<td>R, DB, P</td>
<td>LP cream (9), placebo cream (9)</td>
<td>6–12 y</td>
<td>VP</td>
</tr>
<tr>
<td>Ref 39</td>
<td>R, CO, DB, P</td>
<td>LP cream (8), placebo cream (8)</td>
<td>6–15 y</td>
<td>IC</td>
</tr>
<tr>
<td>Ref 40</td>
<td>R, CO, DB, P</td>
<td>LP cream (48), placebo cream (48)</td>
<td>5–12 y</td>
<td>VP</td>
</tr>
<tr>
<td>Ref 41</td>
<td>R, CO, DB, P</td>
<td>LP cream (90), placebo cream (90) (stratified according to skin type, application time [60–120 min], and gender)</td>
<td>Adult</td>
<td>VP</td>
</tr>
<tr>
<td>Ref 42</td>
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<td>LP cream (20), placebo cream (20)</td>
<td>3–13 y</td>
<td>VP</td>
</tr>
<tr>
<td>Ref 43</td>
<td>R, DB, P</td>
<td>LP cream (30), placebo cream (30)</td>
<td>5–11 y</td>
<td>VP</td>
</tr>
<tr>
<td>Ref 44</td>
<td>R, DB, P</td>
<td>LP cream (75), placebo cream (75) (stratified according to application time [30, 45, or 60 min])</td>
<td>Adult</td>
<td>IC</td>
</tr>
<tr>
<td>Ref 45</td>
<td>R, DB, P</td>
<td>LP cream (30), placebo cream (30)</td>
<td>4–10 y</td>
<td>IC</td>
</tr>
<tr>
<td>Ref 46</td>
<td>R, DB, P</td>
<td>LP cream (49), placebo cream (49) (stratified according to procedure [presurgical oxycodone and scopolamine injection; IV catheterization])</td>
<td>4–15 y</td>
<td>IC</td>
</tr>
<tr>
<td>Ref 47</td>
<td>R, DB, P</td>
<td>LP cream (59), placebo cream (60) (stratified according to application time [20–45 or 45–60])</td>
<td>16–68 y</td>
<td>IC</td>
</tr>
<tr>
<td>Ref 48</td>
<td>R, DB, P</td>
<td>LP cream patch (24), placebo patch (26)</td>
<td>Adult</td>
<td>IC</td>
</tr>
<tr>
<td>Ref 18</td>
<td>R, SB</td>
<td>LP cream (20), 1% lidocaine (20)</td>
<td>7–12 y</td>
<td>IC</td>
</tr>
<tr>
<td>Ref 19</td>
<td>R, SB</td>
<td>LP cream (49), DCTF (63), 0.5% lidocaine (65), benzyl alcohol (61)</td>
<td>Adult</td>
<td>VP</td>
</tr>
<tr>
<td>Ref 32</td>
<td>R</td>
<td>LP cream (59), 1% lidocaine via J-tip (57)</td>
<td>7–19 y</td>
<td>IC</td>
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<td>Ref 50</td>
<td>R, SB</td>
<td>LP cream (thick layer 2.0 mL, n = 47); LP cream (thin layer 0.5 mL, n = 45)</td>
<td>1.5–13 y</td>
<td>IC</td>
</tr>
<tr>
<td>Ref 51</td>
<td>R</td>
<td>LP cream (parent application [21]; LP cream (clinician application [20]) (stratified according to age)</td>
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<td>IC</td>
</tr>
<tr>
<td>Ref 110</td>
<td>R, DB</td>
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<td>3 mo–10 y</td>
<td>VP</td>
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<td>1–14 y</td>
<td>VP</td>
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<td>1–15 y</td>
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<tr>
<td>Ref 113</td>
<td>R, SB</td>
<td>LP cream (60); tetracaine cream (60)</td>
<td>1–15 y</td>
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<td>5–16 y</td>
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<td>Ref 58</td>
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<td>LP cream (40-min application) (55); tetracaine cream (55)</td>
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<td>Ref 17</td>
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<tr>
<td>Ref 65</td>
<td>R, CO, DB</td>
<td>LP cream (60); liposomal lidocaine 4% (60) (stratified according to treatment time [30 or 60 min] and ± occlusion)</td>
<td>5–17 y</td>
<td>VP</td>
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<td>Ref 66</td>
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<td>LP cream (30); liposomal lidocaine 4% (30)</td>
<td>8–17 y</td>
<td>IC</td>
</tr>
<tr>
<td>Ref 69</td>
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<td>LP cream, 20 min (39); LP cream, 60 min (37) (stratified according to ± preheating and application site)</td>
<td>Adult</td>
<td>IC</td>
</tr>
<tr>
<td>Ref 73</td>
<td>R, CO</td>
<td>LP cream (82); lidocaine/tetracaine patch (82) (stratified according to treatment time [10, 20, 30, or 60 min])</td>
<td>Adult</td>
<td>IC, VP</td>
</tr>
</tbody>
</table>
Liposomal Lidocaine 4%

Liposomes are biocompatible nonimmunogenic vesicles consisting of concentric lipid bilayers (phospholipids and cholesterol) that enclose an aqueous compartment.63 By encapsulating a drug in liposomes, at least 2 important properties are imparted. First, because the surrounding bilayer protects it from in vivo degradation enzymes, the therapeutic effects of the encapsulated drug may be significantly extended. Second, because lipid bilayers can fuse with other bilayers either indiscriminately or in a targeted fashion, liposomes may also provide a unique delivery mechanism for the encapsulated drug. First released in Canada under the brand name Maxilene, a liposomal version of lidocaine 4% (LMX4 topical anesthetic cream [Ferndale Laboratories, Inc, Ferndale, MI]; previously known as ELA-Max) is available over-the-counter in the United States. Liposomal lidocaine 4% is available with or without an occlusive dressing.64

A number of clinical trials have demonstrated the analgesic efficacy of liposomal lidocaine 4% in pediatric patients undergoing venipuncture and IV cannulation (Table 4). Three of the trials found that a 30-minute application of liposomal lidocaine 4%, with or without occlusion, provided the same analgesic effect as a 60-minute application of lidocaine and prilocaine cream with occlusion.17,65,66 A fourth study demonstrated superiority of liposomal lidocaine 4% to a placebo cream.67 Moreover, the latter study showed that the mean total nursing time for IV cannulation was significantly shorter and the procedure success rate was higher for subjects in the liposomal lidocaine 4% group compared with those in the placebo group. Finally, a randomized open-label trial that compared liposomal lidocaine 4% and buffered lidocaine showed similar analgesic effects for the 2 agents during cannulation procedures in children.65

Overall, the safety profile of liposomal lidocaine 4% in the preceding pediatric trials was favorable. In a crossover-design trial in children that examined safety in most detail, there were no serious adverse events in either treatment group, and only 1 treatment with liposomal lidocaine 4% resulted in a potentially treatment-related adverse event: redness and itching at the application site, which was mild in nature and resolved spontaneously (2 mild events were reported after lidocaine and prilocaine cream treatment).64 In >84% of the treatments, no local skin reactions were observed. Of those skin reactions that were documented, pallor occurred at the highest frequency after treatment with liposomal lidocaine 4% but was not significantly different from lidocaine and prilocaine cream.65 A second randomized, double-blind study found that local skin reactions after liposomal lidocaine 4% treatment occurred at a rate of ~25%, which was similar to the rate in the lidocaine and prilocaine cream comparator arm.67 Liposomal lidocaine 4% has not been investigated in great detail in children <2 years of age.12

NEEDLE-FREE STRATEGIES TO ACCELERATE LOCAL ANESTHETIC ONSET

Lidocaine and Tetracaine Topical Patch, 70 mg/70 mg

Penetration of local anesthetics through the stratum corneum is accelerated by heat.68–70 The lidocaine/tetracaine topical patch (Synera [Endo Pharmaceuticals Inc, Chadds Ford, PA]) consists of a thin layer of 70-mg lidocaine and 70-mg tetracaine, an integrated heating component that generates a mild warming, and an adhesive to fix the patch to the skin.71 When removed from its airtight pouch, the heating component in the patch is activated by oxygen to produce a controlled level of heating (maximum skin temperature ≤ 40°C).71

The majority of published studies have examined the use of the lidocaine/tetracaine patch in minor dermatologic procedures, but 1 placebo-controlled double-blind study examined its efficacy during pediatric venous access procedures (Table 5).72 In this study, children aged 3 to 17 years who were undergoing venipuncture or peripheral cannulation as part of their standard medical care were randomly assigned to receive the lidocaine/tetracaine or placebo patches. All patients were treated

---

**TABLE 2** Continued

<table>
<thead>
<tr>
<th>Design</th>
<th>Arms (n)</th>
<th>Age</th>
<th>Procedure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref 26</td>
<td>R</td>
<td>LP cream (45–60 min) (10); 1% lidocaine (10); 2% lidocaine iontophoresis (10)</td>
<td>Adult</td>
<td>IC</td>
</tr>
<tr>
<td>Ref 78</td>
<td>R, CO</td>
<td>LP cream (22); 2% lidocaine iontophoresis (22)</td>
<td>7–16 y</td>
<td>IC</td>
</tr>
<tr>
<td>Ref 79</td>
<td>R, CO, DB</td>
<td>LP cream (20); 4% lidocaine iontophoresis (20)</td>
<td>Adult</td>
<td>IC</td>
</tr>
<tr>
<td>Ref 80</td>
<td>R</td>
<td>LP cream (50); 2% lidocaine iontophoresis (50)</td>
<td>5–21 y</td>
<td>IC, VP</td>
</tr>
</tbody>
</table>

> indicates greater analgesic effect; =, similar analgesic effect; CO, crossover; DB, double-blind; IC, IV cannulation; LP cream, lidocaine and prilocaine cream; O, open; P, placebo-controlled; R, randomized; SB, single-blind; VP, venipuncture.

**TABLE 3** Lidocaine and Prilocaine Cream Maximum Recommended Dose, Application Area, and Application Time According to Age and Weight

<table>
<thead>
<tr>
<th>Age and Body Weight</th>
<th>Maximum Total Dose, g</th>
<th>Maximum Application Area, cm²</th>
<th>Maximum Application Time, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 up to 3 mo or &lt;5 kg</td>
<td>1</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>3 up to 12 mo and &gt;5 kg</td>
<td>2</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>1 to 6 y and &gt;10 kg</td>
<td>10</td>
<td>100</td>
<td>4</td>
</tr>
<tr>
<td>7 to 12 y and &gt;20 kg</td>
<td>20</td>
<td>200</td>
<td>4</td>
</tr>
</tbody>
</table>

If a patient >3 months old does not meet the minimum weight requirement, the maximum total dose of lidocaine and prilocaine cream should be restricted to that which corresponds to the patient’s weight. These are broad guidelines for avoiding systemic toxicity in applying lidocaine and prilocaine cream to patients with normal intact skin and with normal renal and hepatic function. For more individualized calculation of how much lidocaine and prilocaine may be absorbed, physicians can use the following estimates of lidocaine and prilocaine absorption for children and adults: the estimated mean (± SD) absorption of lidocaine is 0.045 (± 0.016) mg/cm²/hour, the estimated mean (± SD) absorption of prilocaine is 0.077 (± 0.036) mg/cm²/hour.
for 20 minutes. The children who received the active patch experienced significantly less pain during the subsequent venous access procedures than those who received the placebo patch, as measured by an Oucher pain-assessment scale. In total, 59% of the children in the lidocaine/tetracaine patch group reported no pain (Oucher score = 0), compared with 20% of the children in the placebo patch group (P < .001).

In another randomized crossover study of adults receiving a venous access procedure at the antecubital fossa, pretreatment with the lidocaine/tetracaine patch for 10, 20, and 30 minutes provided significantly more pain relief than lidocaine and prilocaine cream applied for the same times.73 After 60 minutes, the analgesic effects provided by the lidocaine/tetracaine patch and lidocaine and prilocaine cream were indistinguishable.

In the published pediatric trial, “very slight” and “well-defined” erythema were slightly higher for children in the lidocaine/tetracaine patch group (51%) than for those in the placebo patch group (43%) (P = .21).72 No cases of edema or blanching were observed in the active group. The most common local reactions listed on the Synera package insert are erythema (71%), blanching (12%), and edema (12%).71 The lidocaine/tetracaine patch is not recommended for use on mucous membranes, on areas with a compromised skin barrier, or on broken or inflamed skin.71

**Lidocaine Iontophoresis**

Iontophoresis is the process whereby an ionic form of a drug is accelerated into subcutaneous regions of the skin or through a mucosal surface under the influence of a low-voltage direct electrical current. The quantity and distribution of delivered drug depends on the ion charge, molecular weight, intensity of the electric current, concentration of the drug, contact surface area of the delivery electrode, and duration of current.74 In lidocaine iontophoresis, a solution of the anesthetic is typically present in the cathode (positive electrode) and migrates through the stratum corneum down an electrical gradient. An anode (negative electrode) connected at a distant site is required to complete the electrical circuit. Electric current is supplied via a reusable external controller.

Numby Stuff (Iomed, Inc, Salt Lake City, UT), 1 of the earliest lidocaine iontophoresis systems, has been examined in a number of clinical trials in children and adults undergoing venipuncture or peripheral cannulation (Table 5).75–77 These studies demonstrated that a 10- to 15-minute treatment with Numby Stuff provided significantly more pain relief than iontophoresis of placebo (saline). The efficacy of the device has also been compared with lidocaine and prilocaine cream and lidocaine infiltration.26 In most of these studies, a 10- to 15-minute treatment with Numby Stuff provided similar or better analgesia than either a 60-minute application of lidocaine and prilocaine cream or lidocaine infiltration in randomized open-label trials.78–80 One study found that lidocaine and prilocaine cream was superior to lidocaine iontophoresis.26

However, there has been some concern regarding the tolerability of lidocaine iontophoresis when using the Numby Stuff system. Intolerable tingling, itching, burning sensation, and discomfort have been documented in trials,74,76 and 23% of the children in 1 study required a temporary reduction in the initial current.77 Some evidence indicates that these adverse effects, which are related to iontophoretic current, can be mitigated by...
<table>
<thead>
<tr>
<th>Ref</th>
<th>Design</th>
<th>Arms (n)</th>
<th>Age</th>
<th>Procedure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref 72</td>
<td>R, DB, P</td>
<td>Lidocaine/tetracaine patch (43); placebo patch (21)</td>
<td>3–17 y</td>
<td>IC, VP</td>
<td>Lidocaine/tetracaine patch &gt; placebo patch</td>
</tr>
<tr>
<td>Ref 73</td>
<td>R, CO</td>
<td>Lidocaine/tetracaine patch (82); LP cream (82) (stratified according to treatment time: T [10, 20, 30, or 60 min])</td>
<td>Adult</td>
<td>IC</td>
<td>Lidocaine/tetracaine patch &gt; LP cream (10, 20, 30 min); LP cream = lidocaine/tetracaine patch (60 min)</td>
</tr>
</tbody>
</table>

**Lidocaine iontophoresis with TactSite topical system**

| Ref 75 | R, DB, P | 2% lidocaine iontophoresis (22); saline iontophoresis (25) | 7–18 y | IC | 2% lidocaine iontophoresis > saline iontophoresis |
| Ref 76 | R, DB, P | 2% lidocaine iontophoresis (40); saline iontophoresis (19) | 6–17 y | VP | 2% lidocaine iontophoresis > saline iontophoresis |
| Ref 77 | R, DB, P | 2% lidocaine iontophoresis (22); saline iontophoresis (20) | 7–18 y | IC | 2% lidocaine iontophoresis > saline iontophoresis |

**Epitute EasyTouch followed by lidocaine**

| Ref 80 | R | 2% lidocaine iontophoresis (50); LP cream (50) | 5–21 y | IC, VP | 2% lidocaine iontophoresis > LP cream |

**Lidocaine iontophoresis with LidoSite topical system**

| Ref 82 | R, DB, P | 1% lidocaine iontophoresis (137); placebo (139) | Adult | IC, VP | 1% lidocaine iontophoresis > placebo |
| Ref 83 | R, DB, P | 1% lidocaine iontophoresis (136); placebo (136) | 5–17 y | IC, VP | 1% lidocaine iontophoresis > placebo |

**SonoPrep followed by liposomal lidocaine 4%**

| Ref 88 | R, DB, P | Laser treatment + liposomal lidocaine 4% (160); laser treatment + placebo cream (160) | Adult | Needle stick | Laser treatment + liposomal lidocaine 4% > laser treatment + placebo cream |
| Ref 89 | R, CO, DB, P | Laser treatment + liposomal lidocaine 4% (160); liposomal lidocaine 4% (160) | Adult | Needle stick | Laser treatment + liposomal lidocaine 4% > liposomal lidocaine 4% |

**Lidocaine injection system**

| Ref 90 | R, CO, DB, P | Laser treatment + liposomal lidocaine 4% (20); laser treatment + placebo cream (20) | Adult | IC, VP | Laser treatment + liposomal lidocaine 4% > laser treatment + placebo cream |
| Ref 91 | R, DB, P | Sonophoresis + liposomal lidocaine 4% (38); sonophoresis + placebo cream (39) | 8–18 y | IC | Sonophoresis + liposomal lidocaine 4% > Sonophoresis + placebo cream |
| Ref 92 | R | Sonophoresis + liposomal lidocaine 4% (45); no treatment (49) | Adult | IC | Sonophoresis + liposomal lidocaine 4% > no treatment |
| Ref 93 | R | Sonophoresis + liposomal lidocaine 4% (29); liposomal lidocaine 4% cream (31) | 3–7 y | VP | Sonophoresis + liposomal lidocaine 4% = liposomal lidocaine 4% cream |

**Liposomal lidocaine 4%**

| Ref 95 | R, DB, P | Active (predecessor system; 0.25 mg/20 bar; n = 48); active (predecessor system; 0.5 mg/20 bar; n = 48); sham placebo (49) | 3–18 y | VP | Active, 0.5 mg/20 bar > (active, 0.25 mg/20 bar = sham placebo) |
| Ref 96 | R, CO, DB, P | Active (predecessor system; n = 272); sham placebo (272) (stratified according to lidocaine weight/pressure: 0.25 mg/20 bar, 0.5 mg/20 bar, 0.5 mg/40 bar) and postadministration time (1, 3, 5, 10, 15, 20, 30, or 60 min) | Adult | VP | Active > sham placebo (optimal configuration: 0.5 mg lidocaine/20 bar pressure; maximal efficacy: 1–5 min after administration) |
| Ref 97 | R, DB, P | Active (predecessor system; n = 152); sham placebo (153) (stratified according to age group) | 3–18 y | VP | Active > sham placebo (3–7 and 13–18 y, P < .05; 8–12 y, P = .073) |
using a lower iontophoretic dose.\textsuperscript{81} Burns, which have been reported to occur at incidences of 1 per 15 000 to 20 000 treatments,\textsuperscript{82} can be caused by faulty electrode design, placement of electrodes over skin defects or other areas of low resistance, excessive current levels or iontophoretic dose, or the build-up of HCl or NaOH under the anode and cathode, respectively.\textsuperscript{13} Erythema, paresthesia, and urticaria secondary to mast-cell activation has also been observed under the lidocaine electrode.\textsuperscript{13}

The lidocaine/epinephrine topical iontophoresis system (LidoSite Topical System [B. Braun Medical, Inc, Franksonton, Australia], which is no longer readily available in the United States for human use, is a single-pulse erbium/yttrium-aluminum-garnet (Er/YAG) laser device (2940-nm wavelength) that can be used before a venous access procedure to painlessly ablate a patch of stratum corneum 6 mm in diameter.\textsuperscript{86} This system has been shown to be effective in reducing pain associated with needle sticks (a quick insertion and removal of a 27-28-gauge hypodermic needle)\textsuperscript{85} and intramuscular needle insertions\textsuperscript{86} in healthy adults (Table 5). For needle sticks, laser pretreatment plus liposomal lidocaine 4% (5 minutes) reduced pain by 62% compared with laser pretreatment plus placebo cream; laser pretreatment plus liposomal lidocaine 4% reduced pain by 61% compared with a 5-minute application of liposomal lidocaine 4% with no laser ablation.\textsuperscript{85} For intramuscular needle insertions, there was a 51.3% reduction in pain score when using laser ablation and a 5-minute application of liposomal lidocaine 4% with no laser ablation.\textsuperscript{85} Another randomized, double-blind, crossover study of adults compared the efficacy and adverse-event profile for laser-assisted delivery of topical anesthetic before venipuncture using 2 output energies (2.0 and 3.5 J/cm\textsuperscript{2}).\textsuperscript{87} Mean VAS pain scores were not statistically different (P = .57) between the low-energy (mean = 6.7) and high-energy (mean = 8.1) lasers.

Mild pain, itching, and erythema of the skin may be apparent at the ablation site after treatment and are typically resolved within 2 weeks.\textsuperscript{88} A small percentage of patients treated with dermatologic lasers are known to experience temporary hyperpigmentation or hypopigmentation at the treatment site; this will typically resolve within a period of weeks to months.\textsuperscript{88}
Ultrasound-Assisted Local Anesthetic Delivery

Low-frequency ultrasound produces gaseous cavities in a liquid medium, a process known as acoustic cavitation. When produced, these cavities collapse and release energy in the form of shock waves or microjets; these, in turn, can disrupt lipid bilayers in the stratum corneum to accelerate transdermal passage of drugs. The SonoPrep ultrasonic skin-permeation device (Echo Therapeutics, Franklin, MA) applies this technology at the site of an impending venous access procedure. As with laser-assisted delivery strategies, sonophoretic treatment is used in conjunction with local anesthetic creams.

Two clinical trials examined the pain of IV cannulation procedures after pretreatment with sonophoresis using SonoPrep (maximum application time of 90 seconds), followed by a 5-minute application of local anesthetic cream (Table 5). One of these studies, a non-blinded randomized trial in adults admitted to the emergency department, examined the efficacy of liposomal lidocaine 4% after sonophoresis compared with no treatment. The second, a randomized, placebo-controlled, and double-blinded trial conducted in a pediatric emergency department, also used liposomal lidocaine 4% cream. In both trials, statistically significant analgesia was observed with active topical anesthetic cream after sonophoresis, relative to no treatment or treatment with placebo cream. Most participants in the preceding trials exhibited no observable effect from sonophoretic treatment or only minor redness that resolved within 24 hours. In the pediatric trial, 13% to 16% of the children felt that the sonophoretic treatment was uncomfortable, very uncomfortable, or hurt. The area affected by the ultrasonic skin permeation system measures ~1 cm², but the device can be used multiple times to provide coverage over a broader area.

One recently published randomized open trial examined the utility of sonophoresis for treating venipuncture pain in children aged 3 to 7 years. Twenty-nine patients received sonophoretic treatment followed by a 5-minute application of liposomal lidocaine 4%, and 31 children received a 30-minute application of liposomal lidocaine 4% treatment alone. Patient self-assessments of the subsequent pain of venipuncture were similar in the 2 treatment groups, demonstrating that ultrasound pretreatment accelerated the onset time of anesthesia by liposomal lidocaine 4%. Skin effects immediately after ultrasound were limited to minor redness in 9 of 29 patients.

(Lidocaine Hydrochloride Monohydrate) Powder Intradermal Injection System

(Lidocaine hydrochloride monohydrate [LHM]) powder intradermal injection system (Zingo [Anesiva, Inc, South San Francisco, CA]) is a ready-to-use, sterile, single-use, disposable, needle-free system that delivers LHM powder (nominal particle size of 40 μm) into the dermis. To do so, the system is sealed against the skin at the site of the impending needle insertion, and the start button is depressed. This releases pressurized medical-grade helium from an enclosed microcylinder, which in turn causes a cassette containing 0.5 mg of lidocaine powder to rupture. The gas then accelerates the released lidocaine particles to velocities that are sufficient to penetrate the epidermis and produce local analgesia. Onset of action for venous access procedures is within 1 to 3 minutes, and the duration of analgesic effect is ~10 minutes.

The significant analgesic effects of the LHM powder intradermal injection system have been demonstrated in pediatric populations undergoing venipuncture (Table 5). In 1 randomized double-blind study, 307 children aged 3 to 18 years were randomly assigned to receive a predecessor system similar to the currently approved device or matching sham placebo at the back of the hand 2 to 3 minutes before venipuncture. Subjects who received the active system exhibited mean pain reductions (effect sizes) of 33% to 46% relative to sham placebo.

In addition, 2 large-scale randomized trials (n = 579 and 535) examined the effect of the LHM powder intradermal injection system (the currently available product) compared with sham placebo in children aged 3 to 18 years who required venipuncture or peripheral IV cannulation as part of their clinical care (Table 5). Treatment was administered at the antecubital fossa or dorsum of the hand, as medically warranted, 1 to 3 minutes before venous access. In each trial, the mean Wong-Baker Faces scores were significantly lower for children in the active-system group than for those in the sham placebo group. Parental assessments of their children’s pain were also significantly lower for those in the active-system group. Finally, the venipuncture and cannulation procedures were conducted successfully on the first attempt in >95% of the patients in both treatment groups (active system versus sham placebo, P = not significant), indicating that the needle-free system did not impede procedural success.

In a combined analysis of the preceding 2 trials, delivery of lidocaine to pediatric patients via the needle-free system was well tolerated by self-assessed ratings of device administration “comfort.” Moreover, rates for non–treatment-related adverse events were the same in the active and placebo groups, and the rates of treatment-related adverse events were similarly low in the active-system group (16 of 561 [2.9%]) and the sham placebo group (14 of 553 [2.5%]). Most events were considered mild to moderate in severity, and all resolved without sequelae. Nearly all of the treatment-related adverse events were localized to the application site, consistent with a previous pharmacokinetic study of 38 healthy adults that showed no detectable systemic lidocaine levels after treatment. The frequency and severity of skin-site abnormalities were greater in the active-system group, likely because the LHM powder intradermal injection system accelerates lidocaine particles into the epidermis, particularly for erythema (very slight to well defined, 62% for active system versus 38.2% for sham placebo) and petechiae (52.8% for active system versus 7.6% for sham placebo). However, most skin reactions were minor, short-lived, and self-limited.
Vapocoolant Sprays

Unlike the other local anesthetic options described in this review, vapocoolant sprays do not rely on a chemical anesthetic. Rather, they function by rapidly cooling the skin, which slows initiation and conduction of impulses in cutaneous sensory nerves and increases their refractoriness. Composed of volatile liquid refrigerants, vapocoolant sprays are applied to the skin at the site of the impending venous access procedure, and their rapid evaporation produces a short-lived (<1-minute) analgesic effect (see below). Because the effect is so transient, it may be more convenient in the clinic to use 2 providers, 1 to administer the spray, the other to carry out the venous access procedure itself. Alternatively, these agents can be applied via spray-saturated cotton balls.

Studies of vapocoolant sprays for prevention of venous access pain have reported mixed results. Two randomized trials in pediatric populations revealed that a vapocoolant spray consisting of ethyl chloride was no more effective in preventing IV cannulation pain than either isopropyl alcohol control spray or no treatment, whereas a third randomized trial in children showed that ethyl chloride spray was as effective as tetracaine cream in preventing procedural pain (Table 5). Despite the apparent inconsistent benefits for venous access pain, these agents have been shown to be effective for immunization pain. Thus, a vapocoolant spray (Fluori-Methane [Gebauer Company, Cleveland, OH; subsequently replaced by the manufacturer with Pain Ease topical aerosol skin refrigerant]) provided significantly more analgesia than cold saline spray in adults and, when combined with distraction, provided significantly more analgesia than distraction alone in children (the analgesic effect was similar to lidocaine and prilocaine cream plus distraction). The reasons underlying the observed variability between needle-stick procedures remain unclear but may reflect the transient nature of the anesthetic effect produced by vapocoolant sprays. Specifically, the short-lived nature of the anesthetic effect may be of less importance during vaccination procedures, which can be accomplished more easily within the time frame of the induced anesthesia.

Use of vapocoolant sprays containing ethyl chloride has been shown to be associated with some rare cases of allergic contact dermatitis, and prolonged spraying can cause hypopigmentation and atrophic scarring, especially in patients with poor circulation. Most vapocoolant sprays contain chemicals that are eye irritants; consequently, care must be taken to avoid the eyes during application. Using a spray-saturated cotton ball may lessen the chance of eye contamination. In general, vapocoolant sprays are not advised on damaged skin and should be kept away from mucous membranes, although the Pain Ease spray has been formulated such that it can be applied to intact mucous membranes (but not genital membranes).

CONCLUSIONS

There are a variety of effective topical needle-free and needle-requiring options for delivering local anesthetics for reducing pain from venous access procedures in children. When head-to-head comparator trials have been performed, efficacy was generally similar between active agents. However, the extent and quality of pediatric clinical trial data, the number of steps required for treatment, the safety profile, and time to analgesia onset differ between the options. These factors should be considered when determining the treatment strategy that is most appropriate in a particular clinical setting. Given the available therapeutics, adherence to needle-stick pain guidelines and other quality standards is both feasible and, with the availability of newer faster-acting systems, increasingly more practical.

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William T. Zempsky
Pediatrics 2008;122;S140
DOI: 10.1542/peds.2008-1055g

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