

# Topical Anesthetics for Dermal Instrumentation: A Systematic Review of Randomized, Controlled Trials

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**Study objective:** We compare the analgesic efficacy of topical anesthetics for dermal instrumentation with conventional infiltrated local anesthesia and also compare topically available amide and ester agents with a eutectic mixture of local anesthetics (EMLA).

**Methods:** We conducted a systematic review of randomized, controlled trials. Relevant literature was identified through searches of MEDLINE, Cochrane Central Register of Controlled Trials, and the Excerpta Medica Database Drugs and Pharmacology. We limited the type of procedures to puncture of intact skin with a needle. The primary outcome was analgesic efficacy, reflected in the patient's self-report of pain intensity during dermal instrumentation. Where possible, quantitative methods were used to summarize the results.

**Results:** We identified 25 randomized controlled trials including 2,096 subjects. The results of the trials comparing the efficacy of EMLA with infiltrated local anesthetic were inconsistent. Qualitative analysis demonstrated comparable analgesic efficacy between liposome-encapsulated lidocaine and EMLA. The weighted mean difference in 100-mm visual analogue scale pain scores favored topical tetracaine over EMLA (−8.1 mm; 95% confidence interval −15.6 mm to −0.6 mm). Liposome-encapsulated tetracaine provided greater analgesia than EMLA according to the weighted mean difference in 100-mm visual analogue scale scores (−10.9 mm; 95% confidence interval −15.9 mm to −5.9 mm).

**Conclusion:** EMLA may be an effective, noninvasive means of analgesia before dermal procedures. However, we identified 3 topical anesthetics that are at least as efficacious as EMLA: tetracaine, liposome-encapsulated tetracaine, and liposome-encapsulated lidocaine. Liposomal lidocaine is commercially available in the United States and offers a more rapid onset and less expensive alternative to EMLA. [Ann Emerg Med. 2005;46:343-351.]

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## INTRODUCTION

Procedural discomfort is often undertreated and can be distressing for patients.<sup>1</sup> Analgesia is conventionally achieved through intradermal local anesthetic infiltration. However, infiltration of anesthetics per se induces discomfort, may worsen “needle anxiety” in pediatric subjects, and can distort the injection site.<sup>2</sup> Hence, topical formulations may offer significant benefits for prevention of procedural pain. The eutectic mixture of local anesthetics (EMLA) consists of prilocaine and lidocaine and was the first commercially available topical agent that provided adequate analgesic efficacy.<sup>3</sup> Accordingly, the latter is the most frequently used topical anesthetic, and its cream form provides satisfactory analgesia for numerous dermal procedures.<sup>4-7</sup> However, recent literature suggests that in addition to EMLA, there are other efficacious topical anesthetics. A review

of 5 trials limited to pediatric patients concluded that topical tetracaine is comparable to EMLA.<sup>8</sup> Moreover, liposomes have been found to be a promising vehicle for topical anesthetic delivery.<sup>9</sup> Liposomes are microscopic, spherical, phospholipid-based carriers that facilitate percutaneous drug penetration.<sup>10</sup> In vitro studies have shown that local anesthetic delivery by liposomal encapsulation provides a higher concentration of local anesthetic at peripheral sensory nerves than does conventional topical anesthesia.<sup>11</sup> Clinical trials have confirmed the potential efficacy of liposomal topical anesthetics.<sup>12</sup> Thus, a comprehensive analysis of the literature is warranted to test the hypothesis that topical anesthetics are indeed an effective, noninvasive means of procedural pain control and to confirm that there are alternative, efficacious topical anesthetics to EMLA. We performed a systematic review of randomized,

### Editor's Capsule Summary

#### *What is already known on this topic*

Dermal instrumentation (eg, laceration repair, intravenous starts) procedures are common in the emergency department, and eutectic mixture of local anesthetics (EMLA) is currently the most commonly used agent in North America to reduce pain.

#### *What question this study addressed*

The authors performed a systematic review using comprehensive search strategies, high-quality methods, and appropriate pooling to identify all randomized controlled trials involving topical anesthetics.

#### *What this study adds to our knowledge*

In 10 trials involving 955 patients, there were inconsistencies in results when EMLA was compared to infiltrated local anesthetics. Topical tetracaine was more effective than EMLA, and liposome-encapsulated tetracaine also provided greater analgesia than EMLA.

#### *How this might change clinical practice*

Judged on analgesic efficacy alone, topical tetracaine and liposome-encapsulated tetracaine are both more effective than EMLA.

Topical anesthesia	Eutectic mixture of local anesthetics
Topical anesthesia	Ela-max
Topical anesthetic(s)	S-caine
Topical anaesthetic(s)	Liposomal anesthetic
Dermal anesthesia	Liposomal lidocaine
Dermal anaesthesia	Liposomal tetracaine
Topical amethocaine	Liposome-encapsulated lidocaine
Topical benzocaine	Liposome-encapsulated tetracaine
Topical bupivacaine	Liposome-encapsulated anesthetic
Topical butamben	Anesthetic gel
Topical dibucaine	Anesthetic jelly
Topical etidocaine	Anesthetic spray
Topical lidocaine	Anesthetic lotion
Topical lignocaine	Anesthetic ointment
Topical mepivacaine	Anesthetic cream
Topical pramoxine	Anesthetic balm
Topical prilocaine	Anesthetic patch
Topical tetracaine	Dermal patch
EMLA	

**Figure 1.** "Text words" used in literature search strategy.

controlled trials using an explicit methodology to select, appraise, and consolidate the literature to minimize bias in our conclusions.<sup>13</sup> Our primary objectives were to compare the analgesic efficacy of each topical anesthetic with conventional infiltrated local anesthesia and compare the efficacy of each topically available amide or ester local anesthetic with EMLA.

## MATERIALS AND METHODS

To identify the relevant literature, 2 authors searched the following electronic databases: MEDLINE (1966 through August 2003), the Cochrane Central Register of Controlled Trials (through August 2003), and Excerpta Medica Database Drugs and Pharmacology (1980 through November 2003). A Medical Subject Headings subject heading for "topical anesthesia" was not found, so a search strategy was accomplished using the "text words" listed in Figure 1. No language limitations were applied to the search strategy. Furthermore, the references of the procured articles were reviewed to locate additional relevant papers that may have been overlooked in our search of electronic databases. No attempts were made to obtain unpublished studies. Two authors independently examined the retrieved articles to select studies that met the inclusion criteria below. In the event of disagreement, a third reviewer was consulted, and consensus was reached.

Only randomized, controlled trials were included. The randomized, controlled trial is the most appropriate method of study design, especially in the setting of analgesia, because suggestibility, patient and clinician expectations, and the

placebo effect are potentially significant sources of bias.<sup>14</sup> Randomized controlled, crossover trials were included in the review. Data from review articles, case reports, abstracts, posters, or letters to the editor were not considered. Adult and pediatric patients of either sex were included. Recognizing that the lower age limit at which children can credibly quantify pain intensity is controversial, we chose the threshold of 3 years of age to identify as many studies as possible. Furthermore, at least 1 study has suggested that children this young can provide accurate ratings of acute pain intensity.<sup>15</sup> Only trials that evaluated the efficacy of topical anesthesia for dermal-related procedures were included. To minimize the variability of nociceptive stimuli in the studies we analyzed, we limited the type of procedures to puncture of the intact dermal surface with a needle. We included superficial procedures (eg, intravenous cannulation or venipuncture) and deep instrumentation that involved needle penetration into subcutaneous tissue (eg, arterial cannulation or insertion of spinal needle). More invasive procedures that involved incising the dermis or harvesting skin grafts were excluded. Dermal stimuli that did not involve penetration of the skin (eg, pinprick sensory testing, epilation, or laser-induced pain) were not included. Trials that evaluated injection pain, including dermal infiltration of steroid or local anesthetic, were excluded. Studies involving application of anesthetics to nonintact skin, including lacerated open wounds or dermal ulcerations, were eliminated. Papers investigating topical anesthesia of mucous membranes were not considered for this review. Forms of topical anesthetic administration acceptable for the present review included liquid solution, gel, cream, ointment, lotion, jelly, balm, dermal patch, and aerosol spray. Studies that assessed transdermal iontophoretic anesthetic administration were excluded. Also, studies comparing topical

One point was assigned for each “yes” answer to each of the questions:  
 Was the study randomized?  
 Was the study double blinded?  
 Was there a description of withdrawals and dropouts?

Two additional points were potentially awarded:  
 One if the method to determine randomization was described and appropriate (ie, computer-generated or table of random numbers)  
 One if the method of double blinding was described and appropriate (must report that the placebo and active drug were used and indistinguishable)

Two additional points were potentially deducted:  
 One if the method to determine randomization was described and inappropriate (ie, patients were allocated alternatively or according to birthday/hospital number)  
 One if the method of double blinding was described and inappropriate (ie, comparison of topical versus infiltration without identical placebo dummy)

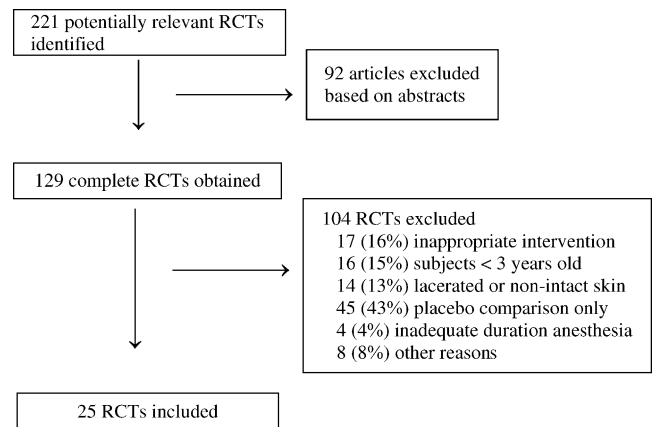
**Figure 2.** Grading system to assess methodological quality of each trial. A maximum of 5 points were awarded as described above.

anesthetics only with placebo were not included. Only trials that used the topical anesthetic for an appropriately long duration were included. The EMLA package insert recommends applying the cream at least 1 hour before the procedure. However, EMLA has been found to provide efficacious analgesia after 45 minutes before dermal needle puncture.<sup>16</sup> Therefore, we excluded randomized, controlled trials<sup>17-20</sup> that applied the topical anesthetic for shorter than 45 minutes.

One reviewer read and completed a standard data extraction sheet for each article that met the inclusion criteria. A second reviewer independently assessed each article and verified the accuracy of the extracted data. If the study presented results in bar graph format,<sup>21-23</sup> 2 reviewers independently extracted numeric data through measurement of the graphs with a ruler, and these results were averaged. In 2 papers,<sup>22,23</sup> SDs were calculated from individual pain scores. In 1 article,<sup>23</sup> the SD was calculated from the 95% confidence interval (CI). In 3 studies,<sup>22,24,25</sup> EMLA was applied for various durations. We included data only from subject groups in which EMLA was administered for a mean duration of at least 45 minutes.

### Outcome Measures

The primary outcome was analgesic efficacy, reflected in the patient’s self-report of pain intensity during needle puncture of the skin. Acceptable tools to quantify pain intensity included the visual analogue scale, numeric pain rating, verbal rating, faces scale, or other validated descriptors of pain intensity. We did not include surrogate pain scores provided by the physician, parent, or other observers, because poor concordance has been demonstrated between patients’ and practitioners’ assessments of procedure-related pain.<sup>26</sup>



**Figure 3.** Identification of included randomized controlled trials. RCT, Randomized controlled trials.

Two reviewers independently assessed the methodological quality of each study. The grading system was adopted from that of the Oxford Group as described by Jadad et al<sup>27</sup> and is shown in Figure 2. Quality scores for each individual trial are reported in the Table.

### Primary Data Analysis

Calculations were computed with Review Manager 4.2.3 software, which was downloaded from the Cochrane Collaboration Web site (available at <http://www.cochrane.org>). A  $\chi^2$  test was performed to test for heterogeneity. Data were then pooled using a random-effects statistical model. We used mean pain scores and SDs to calculate the weighted mean difference, as well as 95% CIs. If the outcomes reported in the studies of the same agent were not statistically combinable, a qualitative analysis was performed.

### RESULTS

The initial electronic database search, completed in November 2003, yielded 221 references that were at least potentially relevant controlled trials. Independent review of the abstracts and titles of these identified 129 potentially relevant randomized, controlled trials. Each of the 129 studies were obtained in full and reviewed for inclusion. Independent assessment of the articles resulted in 25 studies being included in this systematic review. The reasons for exclusion are described in Figure 3. Furthermore, several potentially relevant studies were obtained from bibliographic searching of the included articles; however, none of these met inclusion for this review.

The 25 randomized, controlled trials included in the present systematic review enrolled a total of 2,096 subjects and evaluated 6 topical anesthetics. A detailed summary of each trial, including methodologic quality scores, is provided in the Table. The literature investigating EMLA is summarized below, followed by analysis of various forms of topical lidocaine and topical tetracaine-based agents.

The literature comparing EMLA cream (AstraZeneca, Wilmington, DE) with intradermal local anesthetic infiltration

**Table.** Summary of randomized, double-blinded, placebo-controlled trials comparing topical anesthetics with infiltrated intradermal local anesthesia and EMLA.

Topical Anesthetic Application/Study	Quality Score	Study Size (Age Range)	Dosage/Duration	Intervention	Measurement of Pain Intensity	Conclusion
<b>Various Forms of EMLA</b>						
<b>EMLA 5% cream versus infiltrated local anesthesia, for superficial instrumentation</b>						
Patterson et al <sup>28</sup>	3	114 Adult (NR)	2.5 g, 60–240 min	Venipuncture	VAS	Infiltration >EMLA a. EMLA = infiltration b. EMLA >infiltration
Watson et al <sup>31</sup>	3	26 (19–70 y)	NR, 60 min	Cannulation AV fistula (a. arterial site b. venous site)	VAS	
Fry et al <sup>32</sup>	2	42 (19–79 years)	NR, 60 min	PICC line insertion	VAS	Infiltration >EMLA
Soliman et al <sup>30</sup>	2	42 (7–12 years)	2.5 g, 60 min	IV cannulation	VAS	EMLA = infiltration
Miller et al <sup>29</sup>	1	20 (>18 y)	2.5 g, 45–60 min	IV cannulation	VAS	Infiltration >EMLA
<b>EMLA 5% cream versus infiltrated local anesthesia, for deep instrumentation</b>						
Elson and Paech <sup>35</sup>	4	51 (26–53 y)	2.5 g, 90 min	Insertion of epidural needle	VAS	Infiltration >EMLA
Sharma et al <sup>24</sup>	3	41 Adult females (NR)	2.5 g, 45–75 min	Insertion of spinal needle	VAS	EMLA >infiltration
Smith et al <sup>23</sup>	3	20 (22–69 y)	5.0 g, 60 min	Radial artery cannulation	VAS	EMLA >infiltration
Giner et al <sup>34</sup>	2	101 Adults (NR)	1.0 g, 60 min	Arterial puncture	VAS	Infiltration >EMLA
Joly et al <sup>33</sup>	0	538 (44–72 y)	NR, 120 min	Radial artery cannulation	VPS	EMLA >infiltration
<b>EMLA patch versus infiltrated local anesthesia</b>						
Koscielniak et al <sup>36</sup>	3	169 (18–89 y)	1.0 g, 45 min	Insertion of spinal needle	VAS	EMLA >infiltration
<b>EMLA patch versus EMLA 5% cream</b>						
Nilsson et al <sup>37</sup>	2	60 (5–15 y)	1.0 g, 60–180 min vs. 2.5 g, 60–180 min	Venipuncture	Oucher Scale	Cream = patch
Chang et al <sup>40</sup>	1	178 (3–10 y)	1.0 g, 60 min vs. 2.5 g, 60 min	IV cannulation	VPS	Cream = patch
Robieux et al <sup>38,*</sup>	1	160 (5–18 y)	1.0 g, 60–120 min vs. 1.0 g, 60–120 min	IV cannulation	VAS	Cream = patch
Calamandrei et al <sup>39,*</sup>	1	24 (3–16 y)	1.0 g, 60–120 min vs. 1.0 g, 60–120 min	Lumbar puncture	VAS, Faces Scale	Cream = patch
<b>Various Forms of Topical Lidocaine</b>						
<b>Lidocaine 5% ointment versus EMLA 5% cream</b>						
Lander et al <sup>41</sup>	2	7 Adults (NR)	5.0 g, 60 min vs. 5.0 g, 60 min	IV cannulation	VAS	EMLA >lidocaine
<b>Liposome encapsulated lidocaine 4% cream versus EMLA 5% cream</b>						
Eichenfield et al <sup>25</sup>	4	90 (5–17 y)	2.5 g, 30–60 min vs. 2.5 g, 60 min	Venipuncture	VAS	EMLA = lidocaine
Kleiber et al <sup>42</sup>	3	30 (7–14 y)	2.5 g, 30 min vs. 2.5 g, 60 min	IV cannulation	Oucher Scale	EMLA = lidocaine

Table (continued).

Topical Anesthetic Application/Study	Quality Score	Study Size (Age Range)	Dosage/Duration	Intervention	Measurement of Pain Intensity	Conclusion
<b>Various forms of topical tetracaine (amethocaine)</b>						
<b>Tetracaine (amethocaine) 4% gel versus infiltrated local anesthesia</b>						
Olday et al <sup>43</sup>	4	100 (>18 y)	NR, 60 min	Radial artery cannulation	VAS	Tetracaine = infiltration
<b>Tetracaine (amethocaine) 4% gel or 5% cream versus EMLA 5% cream</b>						
Speirs et al <sup>21,*</sup>	4	20 (22–53 y)	1.0 g, 45 min vs. 2.5 g, 45 min	IV cannulation	VAS, VPS	Tetracaine gel = EMLA
Browne et al <sup>44,*</sup>	3	32 (20–46 y)	1.5 g, 60 min vs. 2.5 g, 60 min	IV cannulation	VAS	Tetracaine gel >EMLA
Romsing et al <sup>45</sup>	3	60 (3–15 y)	1.0 g, 45 min vs. 2.0 g, 60 min	IV cannulation	PCT	Tetracaine gel >EMLA
Molodecka et al <sup>22,*</sup>	3	91 (18–82 y)	1.0 g, 30–60 min vs. 2.5 g, 60 min	IV cannulation	VAS, VPS	Tetracaine cream >EMLA
<b>Liposomal encapsulated tetracaine 5% cream (LET) versus EMLA 5% cream</b>						
Hung et al <sup>47,*</sup>	3	40 (>18 y)	0.5 ml, 60 min vs. 0.5 ml, 60 min	IV cannulation	VAS	LET >EMLA
Fisher et al <sup>46,*</sup>	2	40 (22–64 y)	NR, 60 min vs. NR, 60 min	Insertion 22-gauge needle	VAS	EMLA = LET

NR, Not reported in study; IV, intravenous; AV, arteriovenous; PICC, peripherally inserted catheter center; VAS, visual analogue pain scale (0–100 mm); VPS, verbal pain scale (0–10); PCT, poker chip tool pain scale; >, statistically significant result favoring first group (pain scores significantly lower in first group); =, no significant difference in pain scores between groups.

\*Included in meta-analysis.

consisted of 10 randomized, controlled trials.<sup>23,24,28–35</sup> We separately compared the efficacy of the 2 anesthetics according to depth of needle insertion. Five trials performed superficial procedures, including venipuncture,<sup>28</sup> intravenous cannulation,<sup>29,30</sup> arteriovenous fistula cannulation,<sup>31</sup> and peripherally inserted central catheter line insertion.<sup>32</sup>

The results were inconsistent because 3 trials found infiltrated local anesthetic to be significantly more efficacious than EMLA,<sup>28,29,32</sup> and the remaining 2 randomized, controlled trials<sup>30,31</sup> concluded that EMLA provided comparable or greater analgesia. Five other studies involved deep dermal instrumentation, including radial artery cannulation,<sup>23,33</sup> arterial puncture,<sup>30</sup> and insertion of a spinal needle<sup>24</sup> or epidural needle.<sup>34</sup> The conclusions of the trials in this subgroup were also variable. Three authors found EMLA to be more efficacious than infiltrated local anesthesia,<sup>23,24,33</sup> whereas 2 trials showed the opposite result.<sup>34,35</sup> There is significant heterogeneity between the trials ( $\chi^2$  test;  $P < .00001$ ). Therefore, we did not statistically combine the pain scores.

One randomized, controlled trial<sup>36</sup> reported that the EMLA patch (AstraZeneca) provided significantly greater analgesia

than lidocaine infiltration for insertion of a 25-gauge spinal needle in 169 adult patients. The pain induced by the needle puncture was assessed with a 100-mm visual analogue scale.

The literature comparing the EMLA cream and EMLA patch consisted of 4 trials.<sup>37–40</sup> Each of these studies concluded that the analgesic efficacies of the 2 topical forms of EMLA did not differ. The results of 2 randomized, controlled trials could be statistically combined,<sup>38,39</sup> and no difference was found in mean 100-mm visual analogue scale pain scores (weighted mean difference  $-0.7$  mm; 95% CI  $-5.5$  mm to  $4.0$  mm). Two randomized, controlled trials could not be included in the quantitative analysis, because pain intensity was measured with the Oucher pain scale<sup>37</sup> and verbal pain description.<sup>40</sup>

Only a single randomized, controlled trial was identified and met our inclusion criteria that evaluated lidocaine ointment (Xylocaine 5% ointment; AstraZeneca). The study by Lander et al<sup>41</sup> found lidocaine 5% ointment to be significantly less efficacious than EMLA for intravenous cannulation in adults.

Two studies<sup>25,42</sup> showed comparable efficacy between liposomal lidocaine 4% cream (LMX-4, previously ELA-Max; Ferndale Laboratories, Ferndale, MI) and EMLA cream.



Kleiber et al<sup>42</sup> found equivalent analgesia between EMLA cream administered for 60 minutes and liposomal lidocaine applied for only 30 minutes. In the trial, 30 pediatric subjects who were undergoing intravenous cannulation used the Oucher scale to quantify procedural discomfort.

Another article<sup>25</sup> demonstrated similar findings for venipuncture in 90 children. Again, there was no significant difference in the analgesia provided by liposomal 4% lidocaine for 30 minutes compared to an EMLA for 60 minutes. Furthermore, the study compared different application times of liposomal lidocaine. There was no difference in analgesia provided by topical liposomal 4% lidocaine applied for 30 minutes or 60 minutes. Both studies concluded that liposome-encapsulated lidocaine is preferable to EMLA because of the shorter required application time. However, the randomized, controlled trials could not be statistically pooled because 2 pain scales (visual analogue scale, Oucher) were used.

Olday et al<sup>43</sup> compared a 60-minute application of topical 4% tetracaine gel (Ametop; Smith and Nephew, London, UK) with infiltrated local anesthetic. The study involved 100 adults undergoing radial artery puncture and found comparable efficacy between the 2 forms of anesthesia. Four other randomized, controlled trials compared either tetracaine 4% gel<sup>21,44,45</sup> or tetracaine 5% cream<sup>22</sup> with EMLA cream. The procedure in each trial was intravenous cannulation. Speirs et al<sup>21</sup> found topical tetracaine to provide greater analgesia than EMLA, but the difference in visual analogue scale scores was not statistically significant. The remaining 3 trials<sup>22,44,45</sup> concluded that topical tetracaine provides significantly greater anesthesia than EMLA.

The results of 3 randomized, controlled trials<sup>21,22,44</sup> were statistically pooled. One trial<sup>45</sup> was not included in the quantitative analysis, because discomfort was measured with the poker chip tool. A difference was found in the mean visual analogue scale pain scores, favoring topical tetracaine over EMLA (weighted mean difference  $-8.1$  mm; 95% CI  $-15.6$  mm to  $-0.6$  mm). Furthermore, Molodecka et al<sup>22</sup> included a comparison of the efficacy of tetracaine 5% cream applied for 30 and 60 minutes. Although the mean visual analogue scale scores were higher in the former group, the results were not statistically different.

Two trials,<sup>46,47</sup> each including 40 adults, compared liposome-encapsulated tetracaine 5% cream with EMLA. Dermal instrumentation in both articles was superficial, consisting of intravenous cannulation<sup>47</sup> or insertion of a 22-gauge needle.<sup>46</sup> In both studies EMLA and liposomal tetracaine were administered for 60 minutes. Although Fisher et al<sup>46</sup> found liposome-encapsulated tetracaine to be more efficacious than EMLA, the difference in mean visual analogue scale scores was not significant. However, Hung et al<sup>47</sup> concluded that liposome-encapsulated tetracaine is significantly more efficacious than EMLA.

The results of the 2 trials were statistically consolidated, and the pooled mean visual analogue scale (100 mm) scores favor liposome-encapsulated tetracaine over EMLA (weighted mean difference  $-10.9$  mm; 95% CI  $-15.9$  mm to  $-5.9$  mm).

## DISCUSSION

The present systematic review addressed 2 principal questions concerning topical anesthesia for dermal instrumentation. First, where possible we compared the efficacy of each topical anesthetic with infiltrated intradermal local anesthesia. Ten randomized, controlled trials<sup>23,24,28-35</sup> compared EMLA with infiltrated local anesthesia. The studies were not statistically combined because of significant heterogeneity. The results of the trials are inconsistent because approximately half of the trials favor EMLA, whereas the remainder of the studies find infiltrated local anesthetic to be more efficacious. Thus, we are unable to make a definitive conclusion, and additional high-quality clinical trials comparing the 2 forms of anesthesia are needed. Despite these inconclusive findings, EMLA is advantageous because it is significantly less painful to apply than infiltration of local anesthetics. Moreover, according to a single study, there is no difference in analgesic efficacy between topical tetracaine and infiltrated local anesthesia. No randomized, controlled trials were identified that compared conventional infiltrated anesthetics with topically applied lidocaine, liposomal lidocaine, or liposomal tetracaine.

Second, we compared the efficacy of each topically available amide and ester anesthetic with EMLA. We identified 3 topical anesthetics that are at least as efficacious as EMLA: tetracaine, liposome-encapsulated tetracaine, and liposome-encapsulated lidocaine. Topical tetracaine provides greater analgesia than EMLA according to the pooled 100-mm visual analogue scale scores (weighted mean difference  $-8.1$  mm). However, previous research has shown that the minimum clinically detectable difference in 100-mm visual analogue scale pain scores is between 9 mm and 13 mm for adults<sup>48,49</sup> and 10 mm for pediatric patients.<sup>50</sup> Therefore, we conclude that the difference in analgesia provided by EMLA and topical tetracaine before dermal puncture does not reach the threshold of clinical detectability. Notably, our review demonstrates the efficacy of liposomal preparations of local anesthetics. Based on qualitative synthesis, we found comparable dermal analgesia between EMLA and 4% liposomal lidocaine. In fact, meta-analysis of 100-mm visual analogue scale pain scores favored liposome-encapsulated tetracaine over EMLA, although the difference may not be clinically detectable (weighted mean difference  $-10.9$  mm). Although the minimum onset time of each topical anesthetic cannot be precisely determined from the included trials, we were able to evaluate the efficacy of each agent after different durations of dermal administration. Liposomal lidocaine provides efficacious topical analgesia after only 30 minutes,<sup>25,42</sup> and no further increase in efficacy was reported from extending the application to 60 minutes.<sup>25</sup> Therefore, liposomal lidocaine has a more rapid onset than EMLA. A single randomized, controlled trial<sup>22</sup> compared application of tetracaine 5% cream for 30 or 60 minutes. Although analgesia was greater after 1 hour, the results were not statistically or clinically different. Further investigation of the onset of topical tetracaine is warranted. The randomized,

controlled trials included in this article recommended dermal application of liposome encapsulated tetracaine for at least 1 hour.<sup>46,47</sup>

In the United States, the January 2004 average wholesale price of a 30-g tube of EMLA cream (AstraZeneca) was \$51.20, whereas a 30-g tube of liposomal lidocaine 4% (LMX-4, previously ELA-Max; Ferndale Laboratories) was \$42.62. Therefore, a small cost savings would be realized from using the latter topical anesthetic, assuming a 1:1 substitution from the clinical trials (Table). At the present time, liposomal tetracaine is approved only in Canada and Europe, and therefore no US cost information is available.

Our findings extend 2 previous qualitative reviews that evaluated the efficacy of topical anesthetics for dermal procedures. A narrative summary<sup>12</sup> of 5 trials compared EMLA with liposome-encapsulated lidocaine (ELA-Max) and reported comparable efficacy between the 2 agents. Similarly, the author concluded the latter was clinically superior to EMLA because of its more rapid onset of only 30 minutes. Taddio et al<sup>8</sup> reviewed 8 trials that compared EMLA and topical tetracaine in children. That paper found tetracaine to provide equivalent or greater analgesia than EMLA. However, one of the trials assessed in that review was not randomized. Several of the studies involved children as young as 1 year, in whom pain assessment is a challenge.<sup>15</sup>

Moreover, 4 of the included trials used estimates provided by the parent or health care practitioner to quantify the subject's discomfort, an approach that has been shown to be inaccurate.<sup>26</sup> Our study used an explicit method to select, appraise, and consolidate the literature to minimize bias in our conclusions.

Our findings are consistent with previous reviews, and we provide additional evidence that tetracaine and liposomal lidocaine are effective topical analgesics.

Despite our efforts to prepare a systematic review that minimizes bias, there are possible sources of error. Publication bias, the tendency for studies with positive results to be accepted by journals and those with negative findings to be rejected, may distort the literature. Assuming that the majority of any potentially unpublished trials show no difference between EMLA and the compared topical anesthetic (negative results), then we may have overestimated the efficacy of alternatives to EMLA. Although our literature search strategy was comprehensive, we did not address the issue of publication bias by attempting to acquire unpublished trials from individual authors or manufacturers. Also, the validity of a systematic review is strengthened when the compared trials are homogeneous. Accordingly, to ensure a similar nociceptive stimulus, we limited instrumentation to needle puncture of intact skin. Therefore, our findings may not be generalizable to procedures or instrumentation that is more invasive or less invasive than dermal puncture. Furthermore, there was variability in the caliber and depth of needle insertion in the compared trials. For example, insertion of a 17-gauge epidural needle to an approximate depth of 5 mm would likely produce greater pain than dermal puncture with a 20-gauge venous cannula. However, we attempted to

account for this heterogeneity by separately evaluating topical anesthesia for superficial and deep instrumentation. Another limitation is that some of the comparisons were confined to a relatively small number of studies.

Also, although the review used quantitative analysis to strengthen the conclusions, many groups of trials could not be statistically pooled.

In summary, EMLA may be an effective, noninvasive means of analgesia before dermal puncture. However, we identified 3 other topical anesthetics that are at least as efficacious as EMLA: tetracaine, liposome-encapsulated tetracaine, and liposome-encapsulated lidocaine. Liposomal lidocaine is commercially available in the United States and offers a more rapid onset and less expensive alternative to EMLA.

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