Reducing Venipuncture and Intravenous Insertion Pain With Eutectic Mixture of Local Anesthetic

A Meta-Analysis

Susan Jane Fetzer

Background: The eutectic mixture of local anesthetics (EMLA), by producing dermal anesthesia through contact with intact skin, has become a major indication for the reduction of pain experienced during venipuncture (VE) and intravenous (IV) insertion.

Objectives: The purpose of the study was to determine the mean effect sizes and moderators of EMLA cream application in reducing VE and IV insertion pain.

Method: A meta-analysis of 20 studies was conducted to determine the magnitude of the effect of EMLA cream on VE and IV insertion pain. Effect sizes were calculated three ways: weighted, unweighted, and weighted by quality index score. Potential moderating variables of sample age, premedication, therapist control, insertion site, application duration, research design, pain scale, and funding, were investigated for their influence on EMLA's effect.

Results: EMLA cream had a large significant effect on VE pain ($d = 1.05$) with a 95% confidence interval from 0.92 to 1.34 and a large significant effect on IV insertion pain ($d = 1.04$) with a 95% confidence interval from 0.84 to 1.46. Subject age (child versus adult), type of pain scale, number of therapists, location of insertion site, premedication, funding, or study design did not appear to act as effect modifiers.

Conclusions: EMLA cream can significantly decrease VE and IV insertion pain in 85% of the population.

Key Words: local anesthesia • meta-analysis • venipuncture

The eutectic mixture of local anesthetics (EMLA), serendipitously compounded in 1980 by Swedish researchers, produces dermal anesthesia through contact with intact skin. The combination of two anesthetics, 2.5% lidocaine and 2.5% prilocaine, EMLA penetrates and blocks sensation transmission from dermal nerve fibers. Since receiving United States Food and Drug Administration approval in 1993, EMLA has been used for a variety of procedures associated with dermal discomfort.

It has been used to alleviate the pain associated with lumbar puncture, drug reservoir injections, and superficial skin surgery such as removal of condylomata, lithotripsy, and skin grafting. However, a major indication for EMLA has been to reduce the pain experienced during venipuncture (VE) and intravenous insertion (IV), especially in the pediatric population.

Anecdotal reports and literature reviews asserting the benefits of EMLA for VE and IV have appeared in a variety of nursing and medical publications (Fetzer, 1999; Gajraj, Pennant, & Watcha, 1994; Givens, Oberle, & Landers, 1993). Empirical studies have been conducted in over 15 countries; however, a quantitative summary of the research on the effect of EMLA on VE and IV pain has not been performed. If nursing is to advocate the use of EMLA, then an awareness of the magnitude of its effect, in light of healthcare cost-containment measures, is needed. Therefore, the purpose of this study was to identify and synthesize published research on the effectiveness of EMLA cream in reducing VE and IV insertion pain. A meta-analytic approach was used to answer the following questions:

1. What is the magnitude of the effect of EMLA cream on VE pain?
2. Is the effect size of EMLA cream on VE pain moderated by the following variables: study publication date, sample age, sample size, sample health status, anatomical puncture site, duration of application, method of pain measurement and research design?
3. What is the magnitude of the effect of EMLA cream on IV insertion pain?
4. Is the effect size of EMLA cream on IV insertion pain moderated by the following variables: study publication date, sample age, sample size, sample health status, premedication, anatomical puncture site, duration of application, method of pain measurement and research design?

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Method

Sample. Standard search approaches were used to retrieve the sample of published and unpublished studies for this meta-analysis. The on-line data bases searched were Medline and CINAHL, from 1980 to 2000, using the key terms EMLA, eutectic mixture local anesthetics, lidocaine and prilocaine cream, dermal anesthesia, VE pain, and IV insertion pain. Appropriate on-line journals were also searched. Citations in bibliographies of identified studies were reviewed to uncover additional references. Retrieval using the ancestry method was the most fruitful approach. Searching the Dissertation Abstracts database discovered unpublished studies. Informal contacts at a professional research conference were used to identify unpublished manuscripts. The search was limited to studies published in the English language.

Criteria for inclusion of studies in the meta-analysis were: (a) study designs used randomized clinical trials or repeated measures methods; (b) application of EMLA was the experimental intervention; (c) the control group received a placebo cream that did not include active compounds; (d) the research procedure reported puncture of the skin and underlying vein with a needle; (e) the outcome variable, pain, was measured as the subject’s report; and (f) adequate statistics or raw data were included in the results of the study to permit meta-analytic calculations.

Numerous VE and IV studies were identified but excluded for several reasons. Studies were excluded if (a) EMLA was compared to another anesthetic treatment (i.e., tetracaine, amethocaine, lidocaine, nitrous oxide, ethyl chloride), (b) dermal pain was produced by laser energy or pinprick, (c) the control group received no placebo (were not blinded to the treatment), (d) the control group received a nonanesthetic active compound (i.e., nitroglycerin) that could alter the VE site, or (e) an observer ranked the subject’s pain or behavior. Twenty-two reports were identified from the literature search that met the inclusion criteria. One study did not provide adequate statistics or raw data for meta-analytic study. When necessary test statistics were not provided, available raw data was used to reconstruct the appropriate test. Several studies failed to report test statistics or raw data, in these cases conservative estimates of study outcomes were made from the provided p values (Lipsey & Wilson, 2001). The researcher on the basis of interest and clinical relevance selected the levels of each moderator variable. Therefore, a fixed effects model was used as no attempt was made to generalize to the population of moderator variable levels (Tabachnick & Fidell, 1989).

Data analysis. Advanced BASIC Meta-Analysis software (Mullen, 1989) was used to compute effect sizes for each study. A quality index for each study was calculated based on the criteria used by Beck (1995): first author expertise, funding, sampling method, sample size, instrument reliability and validity, and data analysis. Additional quality indicators pertinent to the topic were number of therapists involved in administering the intervention (VE or IV), report of subject premedication, and type of pain rating scale. These additional indicators were scored from 0–3. The highest quality score achievable was 26; the lowest possible score was 6. The range of scores on the quality index for the 19 studies was 13 to 20.

Venipuncture pain. Seven reports, published between 1985 and 1999, composed the corpus of studies to determine the magnitude of the effect of EMLA cream on VE pain. Two studies were conducted in the United States, two in Canada, two in Sweden, and one in France. Five of the studies were funded and two were not funded. The sample sizes for the studies ranged from 18 to 140 subjects with a total sample size of 542 for the meta-analysis. Three studies used repeated measures designs while four used randomized control trials. Subjects had not been premedicated in any of the studies. Five studies used a consistent VE site, either the antecubital space or hand, while two studies varied the VE site. Only two studies used the same therapist for VE. The remaining five VE studies did not report the number of therapists or used several therapists. The size of the needle was controlled in only one study. Mean EMLA application times ranged from 60 minutes to 170 minutes.
The Visual Analog Scale (VAS) measured the dependent variable in five VE studies; the FACES scale and a Verbal Rating Scale (VRS) were also used in two studies. The quality scores for the seven studies ranged from 15 to 20. One report (Reindeau, Bennett, Black-Nolley, Fan & Scavone, 1999) described three trials in which application time was the independent variable. As the trials used independent samples and provided separate statistics, three hypothesis tests were entered into the meta-analysis from this report (Lipsey & Wilson, 2001).

**Fail-safe number.** All of the VE studies reported a significant positive effect of EMLA cream on VE pain. Because published research is biased toward positive findings (Wolf, 1986), the fail-safe number or the minimum number of unpublished studies reporting null findings that would be required to overturn the meta-analysis was computed. The fail-safe number was 374, which exceeds the reasonable tolerance level of 55, (5k+10, where k = number of hypothesis included in the meta-analysis) (Rosenthal, 1991). Therefore, it is extremely unlikely that data from missed studies would invalidate the conclusions of the meta-analysis.

**Tests of homogeneity.** A meta-analysis assumes that each study provides an effect size for a sample that is representative of the population effect size. Studies that are homogeneous are more likely to be testing the same hypothesis. Homogeneity tests were conducted to identify any outliers among the studies. Tests for significance levels ($\chi^2(8) = 8.70, p = .37$) and for effect sizes ($\chi^2(8) = 5.57, p = .69$) were both nonsignificant indicating the differences in study outcomes can be attributed to sampling error alone and not study characteristics.

**Research question 1.** Statistical data for the hypothesis tests included in the analysis are found in Table 1. Effect sizes were computed three different ways: unweighted, weighted by sample size, and weighted by quality score. The effect size was smallest when weighted by sample size. All subsequent data analysis was based on weighted analysis using sample size (Lipsey & Wilson, 2001).

When using $d$ as an indicator of effect size, $d = .2$ is considered small, $d = .5$ is a medium effect size, and $d = .8$ is a large effect size (Cohen, 1988). The study by Vivien et al. (1996) yielded a medium effect size ($d = .68$). The remaining effect sizes ranged from .82 to 1.76. The mean effect, weighted by sample size, was $d = 1.05$, indicating the application of EMLA cream had a strong positive effect on reducing VE pain. A 95% confidence interval (CI 95%) was constructed around the mean effect size ($d$) to assist in determining the clinical significance of the EMLA effect. The CI 95% ranged from .92 to 1.34.

**Research question 2.** The lack of significance established by the homogeneity analyses predicted that none of the moderator variables, study publication date, sample age, sample size, sample health status, anatomical puncture site, duration of application, method of pain measurement, or research design, influenced the effect size of EMLA cream on VE pain. Of the tested moderators only the sample size was related to the significance levels of the hypotheses tests ($r = -.37, p = .01$). This correlation indicates that as sample size increases, the significance level becomes smaller.

**Intravenous insertion pain.** Thirteen reports, published between 1982 and 1998, were identified that studied the effect of EMLA cream on IV insertion pain. Research conducted by Lander et al. (1996), used in the VE meta-analysis, also contained data evaluating EMLA cream on IV insertion pain. Five studies were conducted in Sweden; two studies each were conducted in the United States, Canada, and Finland. England and Thailand each reported a single study. Forty-six percent ($n = 6$) of the studies were funded. The sample sizes for the studies ranged from 12 to 119 subjects. Three studies used

<table>
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<th>Z</th>
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<th>r</th>
<th>r²</th>
<th>D</th>
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</table>

*Represents single study with independent samples.

Note. EMLA, eutectic mixture of local anesthetics.
repeated measures designs while the remaining ten reported randomized control trials. All of the subjects had been premedicated in three studies, two studies reported that some subjects had been premedicated. Nine studies consistently used the dorsum of the hand for the IV site. Two studies varied the IV sites, and two studies did not report the IV site. Six studies used the same IV therapist for all insertions. There was a wide range of EMLA application times from 20 to 280 minutes. The Visual Analog Scale (VAS) measured the dependent variable in seven studies, the FACES scale and a Visual Rating Scale were used to measure the dependent variable in the remaining six studies. One report (Ehrenstrom-Reiz, Reiz, & Stockman, 1983) described two trials in which application time was the independent variable. As the two trials used independent samples and provided separate statistics, two hypothesis tests were entered into the meta-analysis from this report (Lipsey & Wilson, 2001).

**Fail-safe number.** Thirteen of the fourteen hypotheses reported a significant positive effect on IV pain with EMLA cream, Yamamoto and Boychuk (1998) reported no significant effect. Because published research is biased toward positive findings (Wolf, 1986), the fail-safe number or the minimum number of unpublished studies reporting null findings that would be required to overturn the meta-analysis was computed. The fail-safe number was 944, which exceeds the reasonable tolerance level of 80, (5k + 10, where k = number of hypothesis included in the meta-analysis) (Rosenthal, 1991). Therefore, it is extremely unlikely that data from missed studies would invalidate the conclusions of the meta-analysis.

**Tests of homogeneity.** The homogeneity test for significance levels ($\chi^2$ (13) = 38.78, $p = .0002$) indicated that the hypotheses may have been sampled from different populations of study outcomes (Mullen, 1989). Disjoint cluster analysis revealed that results from Ehrenstrom-Reiz and Reiz (1982) and Yamamoto and Boychuk (1998) differed significantly from the remaining hypotheses. When these hypotheses were dropped from the analysis, the homogeneity test for significance levels ($\chi^2$ (11) = 15.70, $p = .1526$) indicated that the remaining twelve hypotheses were not significantly different from one another.

The effect size homogeneity test for the twelve hypotheses revealed a significant heterogeneity ($\chi^2$ (11) = 44.29, $p = .0707E-07$). Beck (1996) recommends that outliers be removed one at a time until a nonsignificant homogeneity statistic is reached. After two studies were removed (Evers, Van Dardel, Juhlin, Ohlesen, & Vinnars, 1985; Manner et al., 1987) the remaining hypotheses were combined for effect size analysis ($\chi^2$ (9) = 18.09, $p = .03$).

**Research Question 3.** Statistical data for the ten hypotheses tests included in the analysis are found in Table 2. Effect sizes were computed three different ways: unweighted, weighted by sample size and weighted by quality score. The effect sizes were smallest when weighted by sample size. The quality scores ranged from 13–20. Focused comparison of effect sizes by quality score detected a significant difference (z = 2.59, $p = .004$) and a correlation between effect size and quality score of $r = -.52$. These data indicate that effect size decreased with a stronger research design.

Three hypotheses yielded a medium effect size ($d = .62, .70, .72$). The remaining effect sizes ranged from .84 to 2.13. The mean effect, weighted by sample size, $d = 1.04$, indicated that the application of EMLA cream had a strong positive effect on reducing IV insertion pain. A 95% confidence interval (CI 95%) was constructed around the mean effect size ($d$) to assist in determining the clinical significance of the EMLA effect. The CI 95% ranged from .84 to 1.46.

**Research Question 4.** As the tests for homogeneity of the 10 hypotheses were not significant, the moderator variables (premedication, control of IV therapist, insertion site, study design, type of pain scale, and funding) did not appear to influence the effect of EMLA cream on IV insertion pain. However, as there is considerable clinical controversy related to the minimum optimal application time for EMLA cream, diffuse comparisons were used to compare EMLA application less than and greater than 60 minutes. A minimum of 60 minutes has been suggested in the literature and in clinical guidelines. The combined weighted effect size of the two hypotheses reporting EMLA duration less than 60 minutes was 1.07, with diffuse comparison not significant. The six hypotheses that applied EMLA for 60 minutes or more provided heterogeneous in effect sizes ($\chi^2$ (5) = 16.22, $p = .004$). Disjoint cluster analysis revealed two groups. Data from Manuskela and Korpela (1986) and Cooper, Gerrish, Hardwick, and Kay (1987) had a mean effect size $d = 1.95$, while the Hallen and Uppfeldt (1982), Lurngnateetape and Tritrakarn (1994), Lander et al., (1996) and Vaghadia, Al-Ahdal, and Nevin (1997) hypotheses had a mean effect size of $d = .75$. Additional analysis of substantive and methodological moderator variables failed to identify the source of the difference.

**Discussion**

This meta-analysis indicates that EMLA cream has a large effect on VE pain and a large effect on IV insertion pain. Examination of the mean weighted effect sizes between VE and IV ($d = 1.05, d = 1.04$) indicates that the effect of EMLA is consistent across both procedures. Patients who receive EMLA cream report a lower pain experience than those who do not receive EMLA cream by at least one standard deviation. Confidence intervals for VE and IV insertion effect size reveal a significant and large mean effect of
EMLA cream on the population. Cohen (1988) transforms the effect size into a more meaningful value Meaningful valve to determine the percentage of scores in the control group that differs from the EMLA group. Meaningful valve transformation of $d$ revealed that 85% of the pain scores in the control group would be higher than the pain scores of a group in which EMLA cream had been applied prior to VE or IV insertion.

The findings showed no moderating effect of age, indicating that both children and adults undergoing VE or IV insertion can obtain a large benefit from EMLA application. The findings also showed no moderating effect of EMLA application duration; however, it is noted that the Yamamoto and Boychuck (1998) study was not included in the meta-analysis because of its heterogeneity. These researchers intentionally investigated a short application time, 20 minutes, on IV insertion pain. The shortest time reported in the hypotheses included in this meta-analysis was 30 minutes (Maddi, Horrow, Mark, Concepcion, & Murray, 1990). For those hypotheses ($n = 6$) in which the EMLA contact exceeded the minimum recommended application time of 60 minutes, there was a heterogeneous effect size. The inability of the researchers to carefully control application time may have contributed to this finding. Studies have reported that EMLA continues to increase in effectiveness even after removal. Further study using tight controls are indicated to investigate the effects of EMLA cream application of less than 30 minutes on VE or IV insertion pain.

It was anticipated that a premedicated subject would report less benefit from EMLA cream than nonpremedicated subjects. However, there was no statistical difference in effect size between the two groups. Intravenous insertion technique, as reflected by the IV therapist or insertion site, also does not appear to influence effect size. This may come as a surprise to many healthcare providers who pride themselves on their skill in minimizing IV pain. In addition it appears to dispel the notion that the dorsum of hand is more or less painful than other areas. However, caution is needed when interpreting the findings of VE and IV pain moderators as the number of hypotheses per moderator level was limited.

When the researcher’s funding source has a vested interest in the study outcome, readers can develop an index of suspicion about the validity of the findings. In the case of this meta-analysis, funding by the manufacturer of EMLA (Astra, Inc.) did not appear to significantly impact the findings.

In view of the findings of this meta-analysis, the use of EMLA cream to reduce VE and IV insertion pain is recommended. Unfortunately, in healthcare systems that have scarce or rationed resources, the cost of one application of EMLA may be prohibitive. However, healthcare providers should identify patients at high risk for VE or IV insertion pain and its side effects. Research indicates that over 15% of patients under 40 years old will experience vasodepressor syncope during IV insertion in an ambulatory setting (Pavlin, Links, Rapp, & Nessley, 1993). Patients with a history of vasovagal reaction to needles should be prepared with EMLA cream. Patients, particularly children, who will be requiring repeated VE or IV insertion for chronic conditions might also be good candidates for EMLA cream.

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**References**


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**Table 2. Meta-Analysis Statistics of EMLA Effect on IV Insertion Pain ($N = 10; \Sigma n = 612$)**

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*Represents single study with independent samples.

Note. EMLA, eutectic mixture of local anesthetics.
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*Studies included in meta-analysis.*