Reducing venipuncture and intravenous insertion pain with eutectic mixture of local anesthetic: a meta-analysis

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Authors' objectives
To assess the effectiveness of EMLA (eutectic mixture of local anaesthetics) cream on pain during venipuncture (VE) and intravenous (IV) insertion.

Searching
MEDLINE and CINAHL were searched from 1980 to 2000; the search terms were stated. Relevant online journals were searched and the reference lists in identified studies were checked. Unpublished studies were sought in Dissertation Abstracts and through contact with professionals attending a research conference. Only studies published in the English language were included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and studies using repeated measures were eligible for inclusion if they presented adequate statistics or raw data to be included in the meta-analysis.

Specific interventions included in the review
Studies that compared EMLA cream with an inert placebo cream were eligible for inclusion. Studies in which the control group received no intervention, or a non anaesthetic active cream that could alter the VE site, were excluded. The included studies applied EMLA cream for 60 to 170 minutes before VE, and from 20 to 280 minutes before IV insertion. Some of the included studies used premedication, others did not.

Participants included in the review
Studies of participants undergoing puncture of the skin and the underlying vein with a needle were eligible for inclusion. Studies of participants having skin pain inflicted using laser energy or a pinprick were excluded. The included studies were of children and adults. The studies either used a consistent VE site (either the antecubital space or the back of the hand) or varied the VE site. Studies of IV insertion consistently used the dorsum of the hand, varied the IV site, or did not report the IV site. The included studies used the same IV therapist for all VE or IV insertions, used different therapists, or did not state the number of therapists involved.

Outcomes assessed in the review
Studies that measured the participants' pain were eligible for inclusion. Studies that only reported an observer rating of pain were excluded. The included studies assessed pain using a visual analogue scale, the FACES scale and a Verbal Rating Scale.

How were decisions on the relevance of primary studies made?
The author did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The quality of the studies was assessed and scored using criteria described by Beck (see Other Publications of Related Interest): first author expertise, source of funding, sampling method, sample size, the reliability and validity of the measuring instrument, and data analysis. In addition, the following criteria were also assessed and scored: the number of therapists involved in administering the intervention (VE or IV); reports of participants having premedication; and the type of pain rating scale. These additional criteria were scored from 0 to 3. The maximum overall quality score was 26. Two reviewers assessed validity and resolved any disagreements through discussion.
Data extraction
Two reviewers extracted the data and resolved any disagreements through discussion. Inter-rater agreement was measured. Data were extracted on: age; gender; health status of the participants; whether the participants were volunteers or patients; use of premedication before the intervention; study design; quality criteria; results; year and type of publication; country where the study was conducted; and the number and qualifications of the authors. Effect sizes were estimated for each study. Where effect sizes were not reported they were calculated from the data presented (the methods were described). Studies with more than one treatment arm were treated as separate interventions.

Methods of synthesis
How were the studies combined?
The study characteristics were summarised in the text of the review. A pooled effect size with 95% confidence interval (CI) was estimated for VE and IV pain separately using a fixed-effect model. Pooled effect sizes were estimated using three different methods: unweighted, weighted by sample size, and weighted by quality score. The effect size was smallest when weighted by sample size; further meta-analyses were performed with weighting using sample size.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared statistic. The influence of the following moderator variables was investigated: study publication date; age of the participants; sample size; health status of the participants; site of VE or IV puncture; duration of EMLA application; method of pain measurement; research design; and study validity score. The fail-safe N was calculated. After finding significant statistical heterogeneity for IV insertion pain, an exploration of which studies were responsible for the heterogeneity was undertaken, two outlying studies were removed, and the meta-analysis was repeated. For IV pain, studies with different EMLA application times were compared: 60 minutes or less versus greater than 60 minutes. Potential sources of heterogeneity for studies with an EMLA application time of greater than 60 minutes were explored (using disjoint cluster analysis and other moderator variables).

Results of the review
Seven studies (9 treatment arms; 542 people) assessed VE pain: 5 RCTs and 3 repeated measures studies. Thirteen reports (612 people) assessed IV insertion pain: 10 RCTs and 3 repeated measures studies.

The overall quality scores ranged from 13 to 20 out of a possible 26. Inter-rater agreement for the data extraction ranged from 97 to 100%.

VE insertion pain.
The validity scores for the 7 studies ranged from 15 to 20. Five of the studies were funded. The sample size ranged from 18 to 140 people.

All of the studies found that EMLA cream significantly reduced VE pain. The fail-safe N was 374. The effect sizes ranged from 0.68 to 1.76; the pooled effect size was 1.05 (95% CI: 0.92, 1.34). No significant heterogeneity was detected for either significance levels (P=0.37) or effect sizes (P=0.69). The only moderator variable that influenced the results was sample size: as the sample size increased, the significance level of the results decreased (correlation, r = -0.37, P=0.01).

IV insertion pain.
The validity scores ranged from 13 to 20. Six of the studies were funded. The sample size ranged from 12 to 119 people.

Thirteen of the fourteen treatment arms found that EMLA cream significantly reduced IV pain. The fail-safe N was 994. Significant heterogeneity was detected for significance levels (P=0.0002) and for effect sizes (P<0.0001). After the removal of 2 studies with extreme effect sizes, the author reported that the remaining treatment arms were statistically homogeneous (P=0.03). The study quality score influenced the results (-0.52): as the quality increased, the effect size decreased. The effect sizes for these 10 remaining studies ranged from 0.62 to 2.13; the pooled effect size was 1.04 (95% CI: 0.84, 1.46). The moderator variables did not appear to influence the results.
Studies with an EMLA application duration of 60 minutes or less had an effect size of 1.07 with no significant heterogeneity. Results for the 6 studies with an EMLA application time of greater than 60 minutes were statistically heterogeneous (P=0.004). Further exploration of potential sources of heterogeneity did not reveal the source of this difference.

**Authors' conclusions**
EMLA cream significantly reduces VE and IV insertion pain in around 85% of people.

**CRD commentary**
The review question was clear in terms of the study design, intervention, participants and outcomes. Several relevant sources were searched, the search terms were stated, and attempts were made to locate unpublished studies. Limiting the included studies to those in English may have resulted in other relevant studies being omitted. Two reviewers assessed validity and extracted the data, which reduces the potential for bias and errors. However, the methods used to select the studies were not described; hence, the adequacy of the method used cannot be judged.

Validity was assessed using, in part, validated criteria. Some relevant information on some of the included studies was presented, and the study characteristics were adequately summarised in the text. After testing for statistical heterogeneity, the data were combined in a meta-analysis and the influence of various moderating variables was investigated. However, the author interpreted a P-value of 0.03 as showing statistical homogeneity; the generally accepted level for statistical heterogeneity is a P-value of less than 0.10. This resulted in one meta-analysis being declared homogeneous when convention would classify it as heterogeneous. When the author detected statistical heterogeneity, an exploration of the studies responsible for the heterogeneity was undertaken. These studies were removed from the subsequent meta-analysis, but no potential reasons for these outlying studies were put forward. The evidence presented appears to support the author's conclusions.

**Implications of the review for practice and research**
Practice: The author stated that the use of EMLA cream to reduce VE and IV insertion pain is recommended. It was also stated that in view of the potential costs, health care providers should identify patients at risk of increased pain and its side-effects. In particular, EMLA cream should be used in patients with a history of vasovagal reaction to needles and those, especially children, who require repeated VE or IV insertions.

Research: The author stated that further studies are required to assess the effect of EMLA cream application for less than 30 minutes before VE and IV insertion.

**Bibliographic details**

**PubMedID**
11984382

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.