Double-blind evaluation of a lidocaine-prilocaine cream (EMLA) for venous cannulation pain in children

Study dates: Not available from original CSR, which predates ICH-E3 guidance
Phase of development: Therapeutic confirmatory (IIIb)
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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

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Study centre(s)

This study was conducted in 1 centre in Finland.

Publications


Objectives and criteria for evaluation

Table S1 presents the objectives and outcome variables for this study.

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Outcome variables</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>To evaluate the effect of EMLA 5% cream for alleviating venous cannulation pain.</td>
<td>Evaluation of pain by the subject and the physician at the time of cannulation using a verbal rating scale: none, slight, moderate, or severe. Evaluation of pain by the subject using a 50-mm red and white VAS: 0 mm indicated “no pain” and 50 mm “severe pain”. Evaluation of pain using a hedonic scale of facial expressions: expressions indicate ‘happy’, ‘neither happy nor sad’, ‘sad’, ‘very sad’, and ‘crying’.</td>
<td>Efficacy</td>
</tr>
<tr>
<td>To evaluate possible adverse reactions to EMLA 5% cream</td>
<td>Local reactions were evaluated by visible inspection.</td>
<td>Safety</td>
</tr>
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</table>

EMLA Eutectic mixture of local anaesthetics; VAS Visual analogue scale

Study design

This was a double-blind, placebo controlled study that evaluated the effectiveness of EMLA (eutectic mixture of local anaesthetics) 5% cream in alleviating venous cannulation pain in children. At least 60 minutes before the intravenous (IV) cannulation, a thick layer (2 g) of randomly assigned EMLA 5% cream or placebo was applied over the selected vein. The cream was covered with a thin plastic wrap (GLAD® [Union Carbide]) to form an occlusive dressing. Immediately before the insertion of the cannula, the bandage was removed, and the skin was wiped dry and inspected for any local reactions. The skin was then disinfected with 0.5% chlorhexidine in 70% alcohol. The vein was then cannulated with a Venflon® 0.8 or 1.0 mm cannula. Cannulation pain was assessed first by the anaesthesiologist and then by the subject on a verbal rating scale. Cannulation pain was then assessed by the subject visual analogue scale (VAS) and a hedonic scale.
Target subject population and sample size

Sixty male and female children, 4 to 10 years of age, who were scheduled to undergo surgery, and were without known or suspected allergy to amide local anaesthetics, were included in the trial.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Commercially available EMLA 5% cream was used in this study. This formulation consisted of lidocaine (25 mg [107 mmol/L]; prilocaine (25 mg [113 mmol/L]; Arlatone® 289 (19 mg); Carbopol® 934 (10 mg); and distilled water (up to 1 g [1 mL]). The total concentration of the active ingredients (lidocaine and prilocaine) was 50 mg/mL; Arlatone (emulsifier) and Carbopol (thickener) were used to obtain a suitable consistency. In the placebo cream, the eutectic mixture of the local anaesthetic bases was replaced by Miglyol® oil. Both formulae were visually and cosmetically identical. Investigational products were administered topically in a thick layer (2 g) over the selected vein.

Duration of treatment

Subjects received a single 1-hour application of investigational product prior to venous cannulation.

Statistical methods

The differences between EMLA and placebo groups were tested by the Mann-Whitney U-test with rank sums and variances corrected for ties when appropriate.

Subject population

A total of 60 subjects (30 in each group) were treated. For the EMLA and placebo groups, respectively, subjects had a mean age of 6.4 and 7.1 years and had a mean weight of 24.1 and 22.8 kg. A total of 15/30 subjects in the EMLA group and 8/30 subjects in the placebo group were female. The distribution according to the needle size, site of cannulation, and cream application did not differ between treatment groups. Oral premedication (diazepam 0.5 mg/kg or flunitrazepam 0.5 to 1 mg/kg up to 2.0 mg) was given to 24 subjects in the EMLA group and to 27 subjects in the placebo group. One subject in the placebo group did not undergo venous cannulation because he was anxious and uncooperative and was, therefore, withdrawn from the study.

Summary of efficacy results

Three subjects in the EMLA group were unable to cooperate in the verbal rating of pain. The differences between the EMLA and placebo groups in cannulation pain as evaluated by both the anaesthesiologist and by the subject were statistically significant (p<0.001 and p<0.05, respectively). Pain assessments were also performed using the VAS and the hedonic scale in 21 and 22 subjects in the EMLA group and 25 and 27 subjects in the placebo group, respectively. On the VAS, the mean (median) values in the EMLA and placebo groups were 12.4 (4) and 23.5 (22.5), respectively. The difference between the 2 groups was statistically
significant (p<0.05). No difference between treatment groups was observed on the hedonic scale.

Summary of safety results

Two cases of slight redness were observed in the EMLA group and 11 and 9 cases of slight paleness were observed in the EMLA and the placebo group, respectively. There was one EMLA subject with moderate paleness. All reactions were transient and considered to be clinically insignificant. One reaction lasted less than 2 hours; all other resolved within 1 hour. The reactions were not correlated with the application time.

Conclusion(s)

In conclusion, the local anaesthetic effect of EMLA 5% cream in alleviating venous cannulation pain in young children was demonstrated. The local adverse effects were minimal. EMLA 5% cream can be recommended for relieving “needle fear” in paediatric practice when painful cannulation or puncture can be anticipated. In hospital, EMLA 5% cream can be applied concomitantly with the premedication which is a practical way of overcoming the necessary 1-hour application time.