Clinical trial on the effectiveness of the application of lidocaine and prilocaine cream (EMLA) prior to lumbar puncture versus placebo to reduce pain in adults

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KEYWORDS
Lumbar puncture; Lidocaine; Local anaesthetics

Abstract
Introduction: Several studies provide evidence on the effectiveness of the application of EMLA cream in reducing pain in lumbar puncture in infants. However, as there are very few studies in adults, it is quite scarce, it cannot be determined that its use is also effective in adults. Objective: To determine if the application of the EMLA anaesthetic cream reduces the pain compared to the application of placebo when performing lumbar punctures in an adult population.
Material and method: A clinical trial was conducted with 22 patients using lidocaine-procaine cream (EMLA) versus placebo (moisturising cream). Eleven subjects were assigned to each group, randomising the first patient and alternatingly distributing the others into both groups. Results: The median in level of pain of both groups 60 min before puncture, was 1 with an interquartile range of 2, according to a visual analogue scale (VAS). In both cases there was mild pain (less than 4). During puncture, both groups reported moderate pain (EMLA: 6.54 ± 2 vs. Placebo: 5.46 ± 2.09) p = 0.464. One hour after the technique, both groups had a median in level of pain of 1, with an interquartile range of 2, p = 0.317. No significant within or between group differences were detected in the level of pain or other variables, such as systolic blood pressure and heart rate, 1 hour before and during puncture.

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Introduction

Lumbar puncture, is a technique that consists of the insertion of a needle into the spinal cord for therapeutic ends (meningitis, subarachnoid haemorrhage, etc.) or the administration of drugs, especially analgesics and anaesthetics, and is highly used today.\(^1,2\) This simple, safe technique requires patient collaboration as the patient has to be in a foetal position and immobile for the time it takes to perform, and it is not exempt from complications or undesirable effects, such as pain during puncture and the possibility of headaches, localised back pain, haemorrhages or post-puncture infections.\(^1\) Patients consider lumbar puncture to be a painful technique, and prior to it ask about the level of pain the puncture produces. Fear of pain from lumbar puncture is a reason for up to 24% of patients who are to undergo surgery to reject epidural anaesthesia.\(^2\)

To measure pain intensity pain evaluation scales are used since they enable us to quantify the subjective perception of pain of a patient who in this case had been submitted to a lumbar puncture, which may lead to temporary numbness in the legs or pain in the lower back. One of the most standard scales for measuring is the Visual Analogue Scale (VAS), whereby the intensity of pain can be measured with maximum reproducibility from observers.\(^3\)

The VAS consists of a 10 cm horizontal line, at the ends of which are the extreme expressions of a symptom. On the left is the absence of lowest intensity of pain and on the right the greatest intensity. The patient is asked to mark on the line the point which indicates the intensity and this is measured with a millimetre ruler. Intensity is expressed in centimetres or millimetres.\(^3\) Pain is frequently assessed numerically, resulting in a value between 0 and 10, with 0 being the equivalent of no pain and 10 unbearable pain. There is good correlation between the levels of pain valued continuously and discreetly.\(^4\)

To avoid the pain produced by puncture in children it is recommended that an anaesthetic be administered previously, either through infiltration or as a topical anaesthesia, bearing in mind that topical administration requires greater time for obtaining the anaesthetic effect (usually between 30 and 60 min), resulting in sufficient anaesthesia of the

Conclusions: There were no significant differences in the patients who were treated with EMLA and patients treated with placebo, compared to the studies reviewed previously. More studies need to be carried out with larger patient sample, and to take into account other variables, such as anxiety level, skin thickness, and time of exposure to the product.

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However, was 9 and In The existing protocol for lumbar puncture in our centre is no exception, and there is no use of anaesthetic prior to puncture.

The EMLA® anaesthetic cream contains 2 active agents called lidocaine and prilocaine. They belong to a group of drugs called local anaesthetics. EMLA® acts by numbing the skin’s surface temporarily. It is applied on the skin before some medical interventions5 and helps to stop pain in the skin. Several studies conclude that its use is effective in pain reduction during lumbar puncture,7-11 but the majority were carried out on the paediatric population10,11 or newborns,9 and there is no confirmation that EMLA® is effective in adults. Several of these studies assessed pain reduction relating to treatments which combine EMLA® with another drug (propofol),7 and it cannot therefore be confirmed that EMLA® was the cause of pain reduction. The variability of the tools for measuring the level of pain used in each study, among which we found the use of the VAS scale, behavioural scales or alteration of physical parameters such as heart rate or oxygen saturation hinders assessment of outcome obtained.

With regard to the effectiveness of EMLA® in lumbar punctures in adults, only a few studies refer to lumbar puncture used for anaesthetic purposes, showing a lower level of pain, of up to 50% difference, using the EMLA® anaesthetic cream compared with infiltration of lidocaine or placebo.2,9 One study was carried out in patients with a mean age of 28 ± 5, who had been submitted to postpartum tubal ligation, and compared the level of pain in the lumbar puncture for the administration of surgical anaesthesia using EMLA® anaesthetic cream or lidocaine. The patients treated with EMLA® recorded a global mean pain level (assessed from the VAS scale) 2 points below that recorded with lidocaine. This reduction and a higher percentage of satisfied patients with EMLA® analgesia presented statistical significance.7 In the same study pain was evaluated by being classified according to the time prior to the application of the anaesthetic cream EMLA®: 30–44 min, 45–59 min and 60–75 min, with no statistically significant differences being found between the 3 groups, nor any existence of correlation between application time and pain level.9 In the other study, with 180 patients divided into 3 equal groups (EMLA®, lidocaine and placebo), apart from detecting a lower level of pain (50% less) with the application of EMLA® it was confirmed that it helped to lower fear of the lumbar puncture technique.2

There is a scarcity of articles on the effectiveness of EMLA® on the pain of lumbar puncture compared with a large number of studies on its analgesic effectiveness in infants and children. These studies2,7,8,10 were conducted in patient groups who had undergone surgery where the use of lumbar puncture was for anaesthetic purposes, not for diagnosis. Studies are scarce possibly because in the case of therapeutic/anaesthetic ends, the puncture was programmed, or in the case of diagnostic lumbar punctures it was performed as an emergency measure, and possibly the perception was that there was no time to administer a topical anaesthesia.

For all of these reasons we believed it was necessary to carry out a study to determine the effectiveness of the anaesthetic cream EMLA® for reducing pain in diagnostic lumbar punctures in adults, compared with non application.

Objectives

The aim of this study was to determine the effectiveness of the anaesthetic cream EMLA® for pain reduction in lumbar punctures in adults, compared with a placebo (moisturising cream).

Material and method

Study design

Simple blind clinical trial with placebo.

Description of the groups

Intervention group patients on whom EMLA® was applied and control group patients on which a placebo was applied, a moisturising cream with a similar appearance and consistency.

Study sample

Patients over 18 who had been hospitalised in the Neurology Unit of the General University Hospital Santa Lucía, and who were to undergo a lumbar puncture.

Exclusion criteria

Patients with serious liver dysfunction, pregnant women, those allergic to local amide type anaesthetics, with methyoglobinemia, complicated puncture (2 or more punctures or incorrect position of the patient for physiological reasons), breach of cutaneous integrity in the L3–L5 area and changes to the spine.

Sample size

Estimation of the number of patients needed for the study was carried out using the Grandaria Mostral (GranMo) software programme from the Institut Municipal d’Investigació Médica de Barcelona. Standard deviation of 0.8 points in pain after application of EMLA® 60–75 min prior to puncture9 was assumed. There were 11 patients in each group to detect a difference equal to or higher than one unit on the VAS, with an alpha risk of 0.05 being accepted and a beta risk of 0.2 in bilateral contrast.

After obtaining authorisation to conduct the study from the Ethical Committee of Clinical Research in our centre, we started to include the patient participants, once informed consent had been given.

Inclusion and randomisation of subjects

A consecutive sample was carried out for the necessary sample size in each group, including all patients who met with the inclusion criteria and who agreed to participate.
The assignment of patients to each group was made randomly and systematically: the main researcher made a list where the intervention groups were alternated and randomly determined that the first patient would be included in the intervention group (EMLA®), the second into the control (placebo) group, the third in the intervention group and thus successively, up to the total of 11 patients in each group. The nurses in charge of administering EMLA or placebo was previously aware of the group into which the patient was assigned but not his or her identity.

Both the patient and the neurologist who carried out the lumbar puncture did not know whether EMLA or placebo cream had been used on the patient.

The study was conducted between November 2015 and March 2016 in the Neurology Unit of the Hospital Santa Lucía in Cartagena.

### Intervention

Once the neurologist had been notified that a puncture was to be carried out on a patient who had met with the inclusion criteria, the main researcher requested informed consent and, if the patient accepted to participate in the study, randomly assigned them to a group. Later, the nurse in charge was informed about which group the patient had been assigned to and the nurse was in charge of carrying out all the interventions and measurements of the study, confirming firstly the integrity of the skin between vertebrae L3–L5 (area of application of the EMLA® or placebo cream). If there was no concomitant one hour prior to puncture, 2 g of cream (EMLA® or placebo) was applied, being spread in a circular manner from inside to out and covered with a transparent 3M® dressing. The placebo was of the same consistency and appearance as the EMLA® cream to avoid any distinction by the patient. Measurement of following variables also took place at that time: blood pressure and heart rate, in addition to pain using the VAS scale.

The patient was subsequently put into a foetal lateral position with chin and knees flexed, the residues of the cream were removed and the antiseptic was applied. The neurologist (who was unaware of the type of cream administered) then performed the lumbar puncture. As soon as the needle had been removed, a new measurement of the constants and degree of pain was carried out. Finally, one hour after lumbar puncture, pain level, blood pressure and heart rate were again assessed.

The only difference in the intervention carried out on both groups was the type of cream applied: EMLA® in the experimental group and a moisturising cream in the control groups.

In addition to the variables mentioned (blood pressure, systolic and diastolic pressure, heart rate and degree of pain) the following variables were recorded: age, gender, medical reason for performing the puncture, administration of anxiolytics by medical prescription prior to puncture to lessen the patient’s anxiety, the nature of the pain (according to VAS scale: mild if 1–3, moderate 5–7 or intense if 8–10), location of pain (puncture point, irradiation of lower extremity), physical complexon (according to the BMI: underweight if <20, normal weight if 20–24.9, overweight if 25–29.9, obese if over or equal to 30) and any diagnosed disease of the spinal column (yes or no).

### Statistical analysis

Once data on all subjects was obtained and the data base had been filtered, a descriptive analysis was made using central tendency statistics and the dispersion of quantitative variables, and frequencies of qualitative variables. With regard to the level of pain, the mean and standard deviation was calculated for the level of pain during puncture, and the median and interquartile range in pain prior and subsequent to puncture was made, since in these 2 variables the values obtained did not follow a normal distribution pattern. The percentage of patients who presented with slight pain was also estimated (VAS ≤ 4) as was that of moderate/high pain (VAS > 4). Comparison of percentages in qualitative variables was carried out through an exact Fisher test.

Mean pain of the 2 groups during puncture was compared, and age, systolic blood pressure, mean blood pressure and heart rate before and after lumbar puncture were compared using the Student’s t-test. Comparison of pain before and after puncture was performed using the Mann–Whitney U test due to non normal distribution.

The statistical software programme SPSS v.19 was used for statistical analysis.

### Results

The study was performed with all patients hospitalised in the neurology unit who had undergone lumbar puncture (n=22), with the same number of patients assigned to each group (Fig. 1). They all met with the inclusion criteria, suffered from no incidents in puncture or losses in collection of the proposed variables.

The EMLA or placebo cream was applied to each patient, according to the group. Patient characteristics of those included in the intervention group (EMLA) and the control group (placebo) were similar (Table 1), with no significant differences between either groups.

When EMLA or placebo cream was applied—an hour before lumbar puncture (Table 1)—and on performing the puncture (Table 2), the puncture pain showed no statistically significant differences between groups. One hour after puncture (Table 2) both groups presented the same pain median. With regards to blood pressure, both systolic and mean were higher at all times in the control group. In contrast, the mean of heart rate was lower in the intervention group, although none of these differences were statistically significant.

On classifying pain evaluation into slight (score under 4) and moderate or strong (score from 4 to 10) it was determined that 2 patients out of the 11 in the group on whom EMLA® had been applied presented with moderate or strong pain (n=2, 18%), compared to nobody in the control group, assessing 60 min prior to puncture. When lumbar puncture was performed the degree of pain rose in both groups, although, again, the group treated with EMLA® recorded a higher number of patients with pain (EMLA®: n=5, 45% vs. placebo: n=3, 27.27%) compared to the group treated with a placebo. However, one hour after puncture only one patient in the group treated with placebo...
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Figure 1 Flow diagram of the study.

Table 1 Comparison of baseline data of patients from intervention (EMLA<sup>®</sup>) and control groups (placebo).

<table>
<thead>
<tr>
<th>Baseline variables</th>
<th>Placebo (n = 11)</th>
<th>EMLA&lt;sup&gt;®&lt;/sup&gt; (n = 11)</th>
<th>p value</th>
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<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
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<tr>
<td>Female, n (%)</td>
<td>6 (54.55)</td>
<td>6 (54.55)</td>
<td>0.242</td>
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<tr>
<td>Male, n (%)</td>
<td>5 (45.45)</td>
<td>5 (45.45)</td>
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<tr>
<td><strong>Age in years (mean ± SD)</strong></td>
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<tr>
<td>51.18 ± 21.23</td>
<td>48.18 ± 19.24</td>
<td>0.732</td>
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<tr>
<td><strong>Takes anxiolytic, n (%)</strong></td>
<td></td>
<td></td>
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<tr>
<td>3 (27.28)</td>
<td>2 (18.18)</td>
<td>0.490</td>
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<tr>
<td><strong>Pain (VAS) 60 min prior to puncture, median (IQR)</strong></td>
<td></td>
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<tr>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0.166</td>
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<tr>
<td><strong>HR 60 min prior to lumbar puncture (mean ± DE)</strong></td>
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<tr>
<td>71.18 ± 14.78</td>
<td>74.64 ± 13.51</td>
<td>0.573</td>
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<td><strong>systolic BP 60 min prior to lumbar puncture (mean ± SD)</strong></td>
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<tr>
<td>123.36 ± 17.18</td>
<td>129.36 ± 17.5</td>
<td>0.389</td>
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<tr>
<td><strong>mean BP 60 min prior to lumbar puncture (mean ± SD)</strong></td>
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<td></td>
</tr>
<tr>
<td>96.81 ± 12.42</td>
<td>94.95 ± 11.09</td>
<td>0.714</td>
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<tr>
<td><strong>Constitution n (%)</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Thin</td>
<td>6 (54.55)</td>
<td>9 (81.82)</td>
<td>1.000</td>
</tr>
<tr>
<td>Stocky</td>
<td>5 (45.45)</td>
<td>2 (18.18)</td>
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</tr>
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</table>

SD: standard deviation; n: sample size; IQR: interquartile range; BP: blood pressure.

recorded moderate or strong pain (n = 1, 9.09%), compared to none in the group treated with EMLA. None of these differences in percentages was statistically significant.

There were no significant differences in degree of pain in the 3 measurements, according to the intake of anxiolytics, constitution and gender between both groups (EMLA<sup>®</sup> and placebo). However, when stratifying by gender it became clear that the women presented with a higher degree of pain than the men (5.50 ± 2.96 vs. 3.20 ± 2.14) p < 0.047 (Table 3).

**Discussion**

The degree of pain due to lumbar puncture in hospitalised patients in a neurology unit did not present with any significant differences using EMLA<sup>®</sup> or placebo, unlike previous studies, especially those conducted with infant and child samples. These studies concluded that use of the EMLA<sup>®</sup> cream reduces the degree of pain. We found 2 studies with an adult sample: the first compared 180 adults who had undergone surgery and who were to receive anaesthesia by epidural, and who were divided into 3 groups, one with EMLA<sup>®</sup> application, another with subcutaneous lidocaine administration and a third with placebo. In the first group the median score on the VAS scale of pain was 0.75, in the second 1.75 and in the third 1.80. The author therefore determined the effectiveness of the use of EMLA<sup>®</sup>, but clarified that this was due more to reducing patient anxiety prior to the intervention.
In the second study we found there had also been a comparison of lumbar puncture pain in a total of 41 women who had been referred for tubal ligation. In one group EMLA® was applied and a mean pain score of 1.5 was recorded as soon as the needle was removed. In the other group an infiltration of lidocaine was administered and a score of 3.5 was recorded as soon as the needle was removed. The outcome was thus again favourable for the application of EMLA® in our study, and it would therefore be pertinent to increase the sample size to be able to detect treatment effects.

When the lumbar puncture was performed the women generally recorded a higher level of pain than the men which was statistically significant (p < 0.047), in compliance with studies that show there are quantitative and qualitative differences in pain perception according to gender, with higher pain levels being recorded by women. Despite this being considered a possible limitation affecting the study outcome, the fact that the randomised distribution of patients by gender between the two groups was the same (6 women and 5 men) minimises possible bias.

In our study we hardly observed any increases in heart rate at the time of lumbar puncture compared with those recorded an hour before, in contrast to that detected in previous research studies where a lower alteration of heart rate during insertion and removal of the needle was detected compared with children treated with placebo and, in general, a lower behavioural change in the children who had been administered EMLA®.

There are variables, such as the thickness of skin and anxiety, which we have not taken into account and which could be the reason why the result was not as satisfactory as that of previous studies.

With regards to skin thickness, this should be taken into consideration, according to the manufacturer of EMLA® topical anaesthetic. For the cream to penetrate 2 mm a 60 min application time is required and for a 3 mm penetration, 120 min. Considering that the dermis in adults has a thickness of up to 3 mm, the application time in our study (60 min) may have influenced the EMLA® cream’s effectiveness compared with placebo, especially in relation to the studies carried out with children, since the dermis in children is approximately 1.2 mm. With regard to the application time of EMLA® several studies indicate effectiveness in adults with a time under 60 min, whilst others establish that 90–120 min is required to obtain maximum penetrability (5 mm).
Anxiety about the procedure to be carried out may influence the perception of pain by the study participants, and this is therefore a variable to which attention should be paid in future research studies.

The recruitment of participants up to the estimated study sample (n=22) lasted 4 months. During this period 369 patients were hospitalised in the neurology unit, and lumbar puncture was performed on 22 of them. In future studies there should be consideration for the inclusion of other services, such as the emergency and intensive care units, where diagnostic lumbar punctures are also performed, so as to reduce the inclusion time of patients and increase participant numbers.

Conclusions

It is not possible to determine whether the application of EMLA® cream prior to lumbar puncture in adults in the neurology unit reduced pain, compared with the placebo. It is therefore not possible to recommend or reject the use of the topical anaesthetic cream EMLA® for pain reduction.

Further studies need to be conducted to minimise the methodological limitations of our study, with a larger sample size, and the establishment of mechanisms to conceal the intervention for the professional, and control variables which could affect the outcome, such as level of anxiety, application time of the EMLA® cream, gender or skin thickness.

Conflict of interests

The authors have no conflict of interests to declare.

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References