Is lidocaine-prilocaine cream (EMLA®) always useful for venous puncture in preoperative autologous blood donation ?

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Purpose: *The goal of the present study was to evaluate in adults the benefit of the Eutectic Mixture of Local Anesthetics (EMLA®) for preoperative autologous blood donation.*
Methods: *Twenty-six adult patients requiring three blood samples were studied. The pain of venipuncture was assessed by the patient using a 100 mm Visual Analogue Scale (VAS) and a four-category Verbal Rating Scale (VRS). The first puncture was performed without anaesthesia, as a "reference puncture." The second and third punctures were performed with EMLA® and placebo in a double-blind cross-over randomization. For statistical analysis, the patients were allocated to two groups according to the VAS scores of the reference puncture: (Group 1) $VAS_{ref} < 20$ mm; (Group 2) $VAS_{ref} \geq 20$ mm.*
Results: *For the whole 26 patients, the VAS and the VRS pain scores were lower for EMLA® puncture than for both the placebo and reference punctures ($P < 0.05$). Twenty patients had a $VAS_{ref} < 20$ mm and six patients a $VAS_{ref} \geq 20$ mm. In Group 1, there was no difference between EMLA® and placebo for both the VAS and VRS scores. In contrast, in Group 2, the VAS score was lower for EMLA® than for both the placebo and the reference punctures (respectively 11 ± 7.1 , 28.9 ± 7.9 , 29.1 ± 6.4; $P < 0.01$) ; the VRS score was also lower for EMLA® puncture than for placebo puncture ($P < 0.05$).*
Conclusion: *In adults requiring repeated venous punctures, pain from cannulation may be evaluated at the first puncture with a Visual Analogue Scale, thus indicating or not the need for EMLA®.*

But: *Le but de cette étude est d'évaluer chez l'adulte l'efficacité de la crème EMLA® lors des prélèvements sanguins de transfusion autologue préopératoire.*
Méthode: *Vingt-six patients nécessitant trois prélèvements ont été étudiés. La douleur lors de la ponction veineuse a été quantifiée par le patient selon une Echelle Visuelle Analogique (EVA) et une Echelle Verbale de quatre niveaux (RV). La première ponction a été pratiquée sans aucune anesthésie, servant de "ponction de référence." La deuxième et la troisième ponctions ont été réalisées après application d'EMLA® et de placébo dans un ordre randomisé en double aveugle. Pour l'analyse statistique, les patients ont été séparés en deux groupes selon le score EVA de la ponction de référence: (groupe 1) $EVA_{ref} < 20$ mm; (groupe 2) $EVA_{ref} \geq 20$ mm.*
Résultats: *Sur l'ensemble des 26 patients, les scores EVA et RV étaient abaissés pour EMLA® vis-à-vis du placébo et de la ponction de référence ($P < 0,05$). Vingt patients avaient un score $EVA_{ref} < 20$ mm et six patients un score $EVA_{ref} \geq 20$ mm. Dans le groupe 1, il n'a pas été observé de différence entre EMLA® et placébo au niveau des scores EVA et RV. Dans le groupe 2, le score EVA était abaissé pour EMLA® tant vis-à-vis du placébo que de la ponction de référence (respectivement 11 ± 7,1 , 28,9 ± 7,9 , 29,1 ± 6,4; $P < 0.01$); de même, le score RV était abaissé pour EMLA® en comparaison de la ponction sous placébo.*
Conclusion: *Dans le cas de ponctions veineuses répétées chez*

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ANAESTHETICS, LOCAL: EMLA®;
PAIN: measurement;
TRANSFUSION: preoperative autologous blood transfusion;
VEINS: venipuncture.

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l'adulte, la douleur lors de l'insertion du cathéter peut être évaluée lors de la première ponction à l'aide d'une Echelle Visuelle Analogique, permettant de poser ou non l'indication ultérieure d'EMLA®.

EMLA® 5% (Eutectic Mixture of Local Anesthetics) has previously been shown to produce dermal anaesthesia for superficial vascular punctures in children and in adults.[1-3] Superficial venous punctures in adults are currently performed without anaesthesia, because they are considered easier and less painful than in children. However, even in adults, venous puncture may be especially painful, more so when frequently repeated. Therefore local anaesthesia with a skin wheal of local anaesthetic is performed in some countries, especially for the placement of 16-gauge venous cannulae. To our knowledge, pain associated with repeated punctures of preoperative autologous blood donation and the preventive role of EMLA® in alleviating pain of placement of a 16-gauge venous cannula has not been evaluated.

The aims of the present study were firstly, to investigate the analgesic effect of EMLA® cream when used to alleviate pain from the insertion of the autologous blood donation cannula, and secondly, to determine if it is possible to predict those patients in which EMLA® is beneficial.

Methods

Approval for this double-blind, randomized clinical study was obtained from the local clinic research ethics commitee. Thirty adult patients undergoing surgery and requiring three blood samples at one week intervals for preoperative autologous blood transfusion were asked to participate. All patients were informed about the nature of the trial and gave their written consent to participate in accordance with the recommendations of the Helsinki Declaration. Patients were excluded if they (1) had a contraindication to EMLA®, (2) had a history of atopy, (3) were pregnant or lactating women, (4) were using major analgesics, (5) had already used EMLA®, (6) could not understand the trial or scales, (7) were unable to apply the cream at home. EMLA® 5% cream consists of a mixture of lidocaine base 25 $mg \cdot ml^{-1}$ (107 $mmol \cdot L^{-1}$) and prilocaine base 25 $mg \cdot ml^{-1}$ (113 $mmol \cdot L^{-1}$). The remaining ingredients are an emulsifier, a viscosity increasing agent, and water. The placebo cream, a mixture of light liquid paraffin, white soft paraffin, and wool fat, was visually identical to EMLA®. For each patient, a vein at the antecubital fossa was selected for the three punctures, and the following sequence was performed: on day one, the puncture was performed without anaesthesia, as a "reference puncture" by an experienced nurse after poviodine disinfection; then the patient was instructed to apply half a tube of cream (approximately 2.5 g) under an occlusive dressing (Opsite®) at home on the selected vein, one to four hours before the puncture; the second and third punctures (respectively one and two weeks later) were performed with EMLA® and placebo in a double-blind cross-over manner. The occlusive dressing and the cream were removed just before the insertion of the cannula and the application time noted. The skin was wiped dry and observed for any local reactions, such as erythema, pallor or oedema. Any other spontaneously reported reaction or untoward event was also recorded. Thereafter the skin was disinfected with poviodine solution and venous cannulation was performed with a 16-gauge cannula by the same nurse who had performed the first puncture of the patient. Immediately after each cannulation, the pain of venipuncture was assessed by the patient using a 100-mm Visual Analogue Scale (VAS) with "0" signifying no pain and "100" unbearable pain.[4] For data analysis, the patients were allocated to two groups according to the VAS scores of the reference puncture: (Group 1) $VAS_{ref} < 20$ mm; (Group 2) $VAS_{ref} \geq 20$ mm. In the second and third punctures, the patients were also asked to evaluate the pain using both the VAS and a 4-category Verbal Rating Scale (VRS) of (0) no pain at all, (1) some pain but less than for the first puncture, (2) same pain as the first puncture, (3) more pain than for the first puncture. A new scale was used for each evaluation. The ease of cannulation was subjectively evaluated by the nurse who performed the procedure as "easier than usual," "as usual" or "more difficult than usual." The number of attempts at needle insertion was also documented.

All values are reported as mean ± SD. For the analysis of difference of application time for EMLA® and placebo, the paired t test was used. The VAS scores for the three punctures were tested by a two-way analysis of variance, one way repeated (the three measures) and the other way testing the order of treatments. Comparisons of VRS scores between EMLA® and placebo were made using the Wilcoxon T test. After the separation into two groups (patients with a reference VAS pain scale <20 mm or ≥20 mm), the same tests were used as previously with the exception that a third way (group) was added to the ANOVA. Multiple comparisons were performed using the Newman-Keuls test.[5] Demographic data were compared between the groups using the Student t test, and sex ratio using the chi-square test. A P value < 0.05 was considered to show statistical significance.

Results

No patient among the 30 questioned refused to partici-

TABLE I Subjective evaluation of the ease of cannulation by the nurse who performed the procedure

	Reference puncture	*EMLA® puncture*	*Placebo puncture*
Easier than usual	15/3	15/3	16/4
As usual	5/3	5/2	4/2
More difficult than usual	0/0	0/1	0/0
Total	20/6	20/6	20/6

Number of subjects for each assessment in Group 1 (VAS_{ref} < 20 mm)/ Group 2 (VAS_{ref} ≥ 20 mm). There was no statistically difference between the three punctures.

pate in the study. Two patients were excluded because they had forgotten to perform the second application of cream, one patient because the Transfusion Centre had not given the second tube of cream to the patient, and a fourth patient did not complete the study because his haemoglobin concentration was too low to allow the third blood sample. No patient was excluded from the study because of adverse reaction to the treatment. The results from 26 patients (21 men and 5 women, age 61.5 ± 11.4 yr) were investigated. Two patients in Group 1 failed to complete the VRS score for the placebo puncture.

No side effects were noted and there was no marked erythema, scaling, oedema, or allergic reaction either for the EMLA® application or for the placebo application. Successful venipuncture was always achieved on the first attempt in all patients, except for one patient who needed two attempts for the reference puncture. For an individual patient, the three punctures were performed both at the same vein site and by the same nurse. The subjective evaluation by the nurse of the ease with which the procedure was performed did not show any difference for the three punctures (Table I). There was no difference between the application time for EMLA® (170 ± 32 min) and for placebo (179 ± 55 min). The VAS and the VRS pain scores were lower for EMLA® puncture than for both the placebo and reference punctures, without any effect of the order of treatments (P < 0.05) (Figures 1 and 2). The patients were allocated to two groups according to the VAS score of the reference puncture. Twenty patients had a VAS_{ref} < 20 mm (Group 1) and six patients a VAS_{ref} ≥ 20 mm (Group 2). Both groups were similar with respect to age, sex ratio, weight, height, application time of EMLA® and placebo (Table II). In Group 1, there was no difference between the VAS scores for the three punctures whereas in group 2, there was a difference in VAS scores between EMLA® and both the placebo and the reference puncture (P < 0.01) (Figure 3). The VRS scores for EMLA® were similar to placebo in Group 1, and statistically lower for EMLA® than placebo in Group 2 (P < 0.05) (Figure 4).

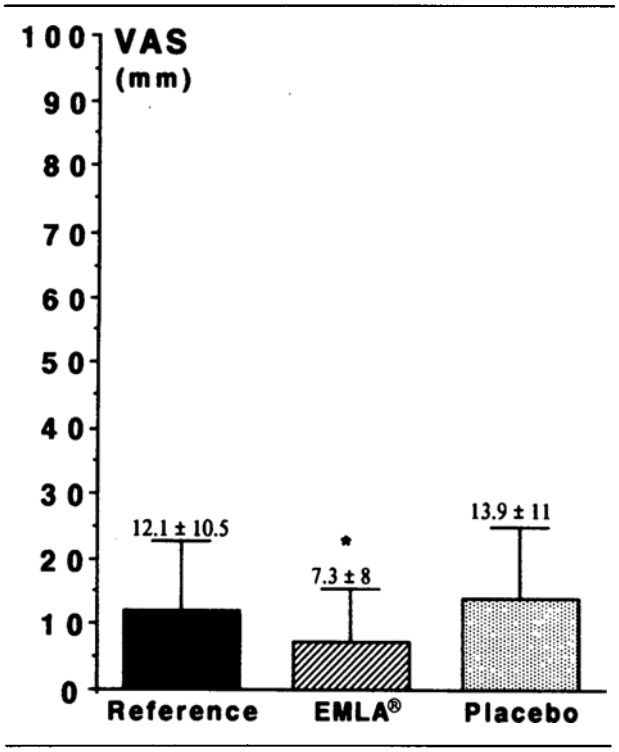

FIGURE 1 Visual Analogue Scores for the three punctures (Mean ± SD). Number of patients = 26. (P < 0.05 : EMLA® vs reference and placebo).

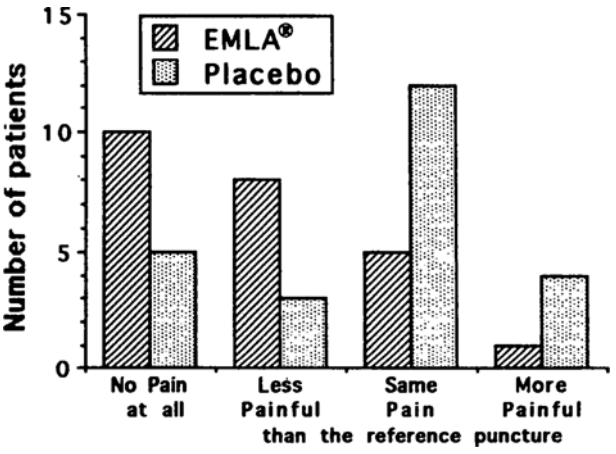

FIGURE 2 Verbal Rating Scores of the two punctures with EMLA® and placebo. Number of patients = 24. (P < 0.05 : EMLA® vs placebo).

Discussion

Several clinical trials have shown that EMLA® cream gives sufficient analgesia to prevent pain induced by a

TABLE II Patients characteristics for the two groups according to the VAS score of the reference puncture.

	Group 1	*Group 2*	
	$EVA_{ref} < 20$ *mm*	$EVA_{ref} \geq 20$ *mm*	
Number of patients	$n = 20$	$n = 6$	
Sex Ratio Men/Women	16/4	5/1	NS
Age (yr)	63 ± 10	57 ± 16	NS
Weight (kg)	71 ± 11	78 ± 8	NS
Height (cm)	167 ± 7	171 ± 7	NS
EMLA® application time (min)	171 ± 30	64 ± 41	NS
Placebo application time (min)	178 ± 57	179 ± 51	NS

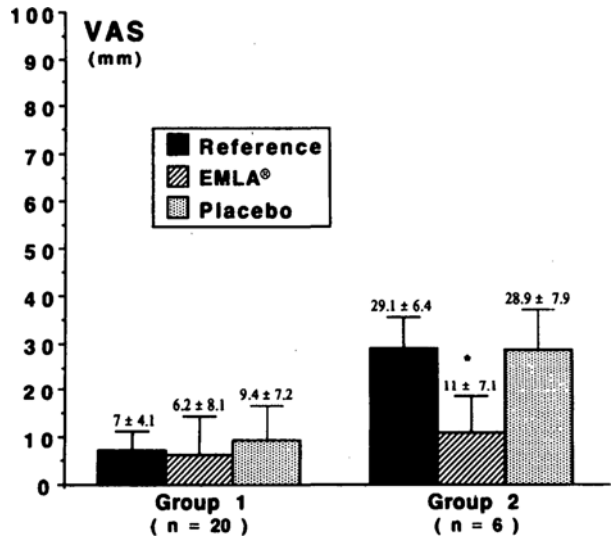

FIGURE 3 Visual Analogue Scores of the three punctures for the two groups of patients according to the VAS score of the reference puncture (Mean ± SD). (Group 1: $VAS_{ref} < 20$ mm; Group 2: $VAS_{ref} \geq 20$ mm; $P < 0.01$: EMLA® vs reference and placebo).

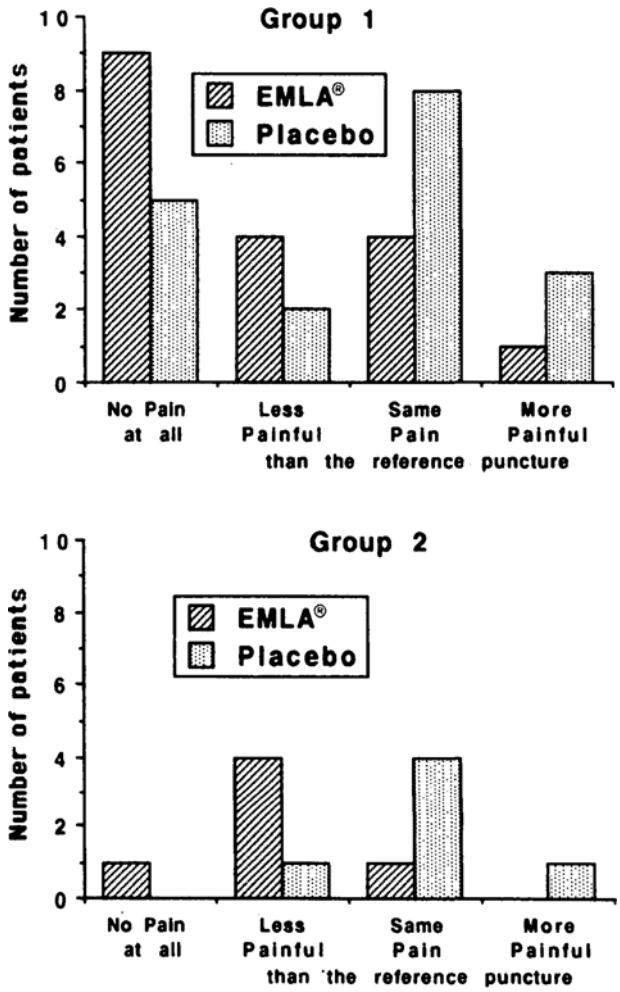

FIGURE 4 Verbal Rating Scores of the two punctures with EMLA® and placebo for the two groups of patients according to the VAS score of the reference puncture. (Group 1: $VAS_{ref} < 20$ mm; Group 2: $VAS_{ref} \geq 20$ mm; $P < 0.05$: EMLA® and placebo vs reference).

single venipuncture. To our knowledge, this is the first study in which EMLA® has been used for the alleviation of pain from multiple autologous transfusion blood samples with large gauge venous cannulae. This clinical trial shows that, although EMLA® is efficient in alleviating pain as estimated by mean VAS and VRS scores in our 26 patients, individual efficiency must also be considered. Twenty patients did not suffer discomfort from venous puncture when it was performed without anaesthesia, and therefore EMLA® was no more efficient than placebo, whereas six patients suffered from venous puncture, and obviously EMLA® alleviated pain on both VAS and VRS scores.

Several methodological aspects of our study must be discussed: (1) dose of EMLA® used, (2) application time, (3) use of a reference puncture, (4) sex ratio of the patients studied and (5) the reference threshold used. (1) The dose of EMLA® used in this study was half a tube of cream, approximately 2.5 g, as in other studies on superficial venipuncture.[6,7] Lower doses are effective in alleviating pain from venipuncture, but larger volumes increase the dermal analgesia parallel to a decrease in the variability in response between the volunteers, indicating a more reliable effect with the higher dosage.[8] (2) Since most of the patients went to the Transfusion Centre in the early morning, we decided to let them apply EMLA® cream at home with an application time ranging from one to four hours. The minimal effective EMLA® application time is know to be 45 min on intact skin in adults,[1] although the current minimal application time is 60 min in most studies.[6,9–11] Ninety to 120 min application of the EMLA® cream increases the effect

and simultaneously provides even more reliable dermal analgesia if applied to the lower arms of volunteers; dermal analgesia is still pronounced when application time is increased to four hours.[8] (3) The first puncture, performed without anaesthesia, was considered as the "reference puncture." This is contestable, because pain of venous cannulation results from numerous factors, and can change according to the operator, individual patient factors, surgical context, etc. In our study, venous cannula, vein site and operator were standardized for the three punctures of each patient, but it was impossible to standardize others factors... However, as shown in Figure 1, pain from the reference and placebo punctures was not different. This finding allows us to validate our proposal of "reference puncture." (4) There were considerably more men (21) than women (5) in our study. This reflects the sex distribution at the Transfusion Centre due to greater numbers of urological (prostate) than orthopaedic procedures in our hospital. (5) We allocated the patients to two groups according to the VAS scores of the reference puncture, with an arbitrary threshold set at 20 mm. The range 0–30 mm is often thought of a "zone of analgesic success" in postoperative pain measurement.[5] However, pain is considered as "normal" by the patient during this perisurgical period. Venipuncture is a procedure for which pain is more unacceptable than after surgery. Considered in this light, a VAS score of 30 mm for venipuncture reflects a higher and more unacceptable level of pain, than a similar score in the postoperative period. Hence we chose a threshold of 20 mm to separate patients.

EMLA® was found to be effective in alleviating the pain of venous puncture for the 26 patients, both on VAS and VRS scores. This confirms the results of other studies.[1–3] The two groups of patients according to the VAS scores of the reference puncture weren't different regarding sex ratio, age, weight, height, EMLA® and placebo application time. It is, therefore, impossible to predict the value of pain of the reference puncture. In Group 1, venipuncture was painless, with a VAS score less than 20 mm: neither EMLA® nor placebo was effective. In contrast, in Group 2, this procedure was painful, with a VAS score equal or superior to 20 mm, and EMLA® through its anaesthetic effect was efficient, by reducing pain both on VAS and VRS scores.

No serious local reaction was observed in any patient, as reported by Sunderraj.[12] This is in marked contrast with most other studies, in which erythema or paleness are often present.[2,8–10] We can offer no explanation other than a subjective difference in appreciation of intensity of cutaneous reactions.

EMLA® cream has the disadvantage of increased cost (the price of one tube of EMLA® 5% cream in France is about eight dollars US) and the need for it to be applied at least one hour before to needle insertion. Currently, in France, preoperative autologous blood sampling is performed without anaesthesia. Applying EMLA® for all venous punctures would be expensive, and useless in three quarters of the patients, according to our findings. Applying EMLA® only to those patients who suffer from venous puncture is useful, but again suffers from increased cost. However, the cost consideration should be weighed against improved patient comfort and confidence. Preoperative autologous blood donation is of benefit to the patient, but may be both inconvenient and painful. Most patients find it easy to apply the cream at home before attending the hospital, and so the slow onset of action of EMLA® cream is not a problem in practice. Since EMLA® is efficient in alleviating pain for venipuncture, it would be unethical not to use this very easy and safe anaesthetic method for patients who really suffer when undergoing venipuncture, especially when it is frequently repeated.

In conclusion, venous punctures with 16-gauge cannulae may be painful in about one quarter of patients in whom EMLA® will be efficient in alleviating pain. Consequently, the indications for EMLA® use must take account of both the type of puncture performed and subjective patient criteria. In patients requiring repeated punctures, as for preoperative autologous blood sampling, pain from cannulation may be evaluated at the first puncture with a Visual Analogue Scale, thereby providing or not an indication for EMLA® use.

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