Upsala J Med Sci 90: 293–298, 1985

A Lignocaine-prilocaine Cream Reduces Venipuncture Pain

Christian Möller

Department of Pediatrics, University Hospital, Umeå, Sweden

ABSTRACT

A new, topical anaestetic formulation, EMLA 5% cream (Eutectic Mixture of Local Anaesthetics), and placebo have been compared in a randomized double-blind study of 51 children. The objectives were to test if EMLA diminishes pain from venipuncture, to evaluate possible adverse reactions, and to determine if there is any influence upon the ease with which the insertion procedure is carried out. Pain was evaluated using a three-graded verbal rating scale. EMLA relieved pain significantly better than placebo ($p < 0.001$), and the procedure was considered to be easier after EMLA treatment. No oedema occurred, but a few cases of local redness and paleness were observed after EMLA treatment. However, these reactions were clinically insignificant. It is concluded that EMLA significantly reduces pain from venipuncture, and sideeffects are mild and transient.

INTRODUCTION

Fear and pain can make the insertion of i.v. needles for blood sampling a traumatic experience for the child and a difficult and time-consuming task for the physician and nurse. A topical preparation that can be applied to the skin without discomfort and which alleviates pain from needle puncture would be helpful to both patients and staff.

The solid, pure bases of lidocaine and prilocaine, if mixed in equal amounts, form an oil at temperatures above 16°C, i.e. they constitute an eutectic mixture. This mixture, called EMLA (Eutectic Mixture of Local Anesthetics), has been formulated as an oil-in-water emulsion cream and tested in experimental and clinical studies in adults and children. The present study reports the results of tests performed in children with the objectives of answering the following questions; Does the cream diminish the pain from insertion of intravenous needles for blood sampling? Facilitates the insertion of i.v. needles? Causes any adverse reactions?

PATIENTS AND METHODS

Sixty children aged 5-15 years were selected for study as they appeared at the Department of Pediatrics at the Regional Hospital, Umeå. They were scheduled for venous blood sampling, mostly in connection with investigations for allergy. Patients with known or suspected allergy to local anesthetics, however, were considered ineligible for the study. The cream consisted of a eutectic mixture of lidocaine base and prilocaine base together with an emulsifier (Arlatone®) and a thickener (Carbopol®) to obtain a suitable consistency. The concentration of the active ingredients were 107 mmole/litre (25 mg/ml) of lidocaine and 113 mmol/litre (25 mg/ml) of prilocaine. A placebo cream in which the active substances were substituted with Miglyol® oil was prepared so that both formulations were visually and cosmetically identical. The active and the placebo creams were packen in identical aluminium tubes marked with numbers according to a randomization list, and the study was carried out in a double-blind manner. At least one hour before the venous blood sampling, EMLA cream or placebo was applied to the skin over a suitable vein in the decubital fossa. The cream was covered with either Blenderm tape 1525 (3M Company) or a thin plastic wrap to form an occlusive dressing. Just before the sampling procedure the bandage was removed and the skin wiped dry and evaluated for any adverse reactions. Thereafter the skin was disinfected with 0.5% chlorhexidine in 70% ethanol, the cannula was inserted, and the pain was assessed by the attending nurse or physician and by the patient himself. The ease with which the procedure was carried out and adverse reactions were also evaluated.

Pain was assessed according to a three-graded verbal rating scale: no pain, slight pain or severe pain. The same rating scale was used by both the staff and the patients. The staff subjectively evaluated how easy it was to perform the procedure according to a three-graded scale: easier than usual, as usual or more difficult than usual - particularly observing anxiety of the child and reflex movements during the procedure. Oedema, redness and paleness of the treated skin were assessed according to a four-graded scale: no, slight, moderate or severe. Any spontaneously reported reactions were noted.

The differences between EMLA and placebo were tested by the Mann-Whitney tests with rank sums and variances corrected for ties. The patients and their parents were verbally informed about the aim and nature of the study according to a standard text formulated to comply with the Helsinki declaration. Verbal consent by the patients and parents was essential for participation. The investigation was approved by the peer review committee of the University of Umeå and the Swedish National Board of Health and Welfare.

RESULTS

Fifty-one patients out of the original 60 were subjected to statistical evaluation. The reasons for excluding these 9 patients were the following; five did not receive the intended treatment, three had application times shorter than the required 60 minutes, and for one patient no application time registrered. Six patients were included although they did not strictly fulfil the inclusion criteria. In the placebo group there were two patients aged 16 years and one aged 17. In the EMLA group there was one patient aged 16 and one 17 and one patient with an application time of 55 minutes.

The number of patients in the placebo group was 26 (12 males) with a median age of 13 years (range 8-17) and a median application time of 75 minutes (range 60-130). In the EMLA group there were 25 patients (9 males) with a median age of 13 years (range 9-17) and a median application time of 75 minutes (range 55-135). There were no statistical differences between the groups regarding sex, age or application time.

Treatment with EMLA resultet in significantly lower pain scores than treatment with placebo as judged by the patients (Table 1). The evaluation

Table 1. Number of patients in each pain score group according to the pain evaluation by the patient.

	No pain	Slight pain	Severe pain	Total
Placebo	2	23	1	26
EMLA	16	9	0	25

$z = 4.07$ $p < 0.001$

by the staff was almost identical. The only difference was that one patient in the EMLA group was evaluated by the staff as having no pain and by the patients as having slight pain.

The evaluation of the influence on the procedure showed a statistically significant difference in favour of EMLA versus placebo (Table 2).

Table 2. Evaluation of the ease with which the procedure could be carried out. Number of patients in each score group.

	Easier than usual	As usual	More difficult than usual	Total
Placebo	5	19	2	26
EMLA	13	12	0	25

$z = 2.61$ $p < 0.01$

No cases of oedema occurred. A comparison between the placebo and EMLA treatment regarding the frequency of redness and paleness is presented in Table 3. There was a statistically significant difference regarding redness

Table 3. Frequency of redness and paleness after placebo and EMLA treatments (number of patients).

		No	Slight	Moderate	Severe	Total
Redness	Placebo	25	1	0	0	26
	EMLA	17	2	4	2	25
Paleness	Placebo	25	1	0	0	26
	EMLA	22	2	1	0	25

($z = 2.61$ $p < 0.01$) but not paleness. The reactions posed no clinical problems and usually disappeared within an hour. Blenderm tape was used for the first six patients but caused redness in four of them an petechiae in one. It was abandoned and the plastic wrap was used in the remaining patients. Two of the patients with redness also had some itching and one of these had a somewhat pale area around the red area. One patient had slight burning pain after the application but no visible skin reaction. These effects were mild and transient.

DISCUSSION

Many attempts have been made to obtain a suitable formulation for effective topical anesthesia. Examples of preparations that have been tested are lidocaine (9, 10) benzocaine (3), combinations of local anaesthetics with dimethylsulphoxide (DMSO) (2, 8) and ketocaine in alcoholic solutions (11). Physical methods such as iontophoresis have also been tried to increase the penetration (12, 13). No formulation has yet gained wide acceptance mainly due to either poor pain relieving effect, inconveniant application, irritation or toxic reactions.

In adults EMLA has been shown to penetrate intact skin and abolish the pain response to pin-prick. It has even been possible to perform superficial skin surgery without any other analgesia (7). The eutectic mixture of lidocaine and prilocaine in a 1:1 ratio is more effective than either base alone in a corresponding oil-in-water preparation. The main reason for the greater effectiveness of the mixture, compared with the individual active components, is the higher concentration of the local anaesthetic bases in the emulsion droplets. In the ELMA emulsion, 80% of each droplet consists of lidocaine and prilocain in contrast to only 20% active substance (base) in the single component formulation (7).

Children are often afraid of needles and syringes and the pain associated with punctures (1). The present study shows that EMLA cream reduces the pain of needle puncture in older children and facilitates the procedure of venous blood sampling. It is reasonable to assume that a corresponding effect could be obtained in very young children, and a study to confirm this is recommended, although evaluation of pain is associated with methodological problems, verbal communication being both difficult and unreliable. It is thus, necessary to choose other methods of evaluation. The adverse reactions observed were mild and transient despite the fact that most of the patients had a disposition for allergy. However, no hypersensitivity reactions were expected as the cream has not shown any allergic properties in earlier studies, and it is known that the frequency of allergic reactions to local anesthetics of the amide type is extremely low (5). The definite frequency of side-effects evidently cannot be determined in a single study like this but has to be derived from a large number of trials.

The disadvantages associated with the use of the cream are the comparatively long application time and the need for an occlusive dressing. However, application of the cream could with relative ease be included in the preparatory procedures for in-patients scheduled for sampling. For out-patients regularly attending a clinic for various sampling procedures or treatments, the practical problem with the application time can be solved by giving the patient a tube with cream at the first visit and instructing him to apply the cream one hour before coming to the clinic. The application time makes the cream less usefull in acute cases. The occlusive tape caused some problems such as redness and discomfort at removal but the thin plastic sheet wrapped around the arm was fully acceptable.

The results of the present study is in agreement with two other studies recently published (4, 6).

ACKNOWLEDGEMENT

The author thanks Dr. Catharina Wahlstedt, Prof. Hans Kollberg, Mr Anders Uppfeldt, Mr Olov Stockman and Dr. Ian Jones for help with various parts of the study.

REFERENCES

1. Blom, G.E.: The reactions of hospitalized children to illness. Pediatr 22: 590-600, 1958.
2. Brechner, V., Cohen, D., Pretsky, I.: Dermal anesthesia by the topical application of tetracaine base dissolved in dimethyl sulphoxide. Ann New York Acad Sci 141:524-531, 1967.
3. Dalili, H., Adrinani, J.: The efficacy of local anesthetics in blocking the sensations of itch, burning and pain in normal and "sunburned" skin. Clin. Pharmacol Ther 12:913-191, 1971.

4. Ehrenström-Reiz, G., Reiz, S.L.A.: EMLA - an eutectic mixture of local anaesthetics for topical anaesthesia. Acta Anaesthesiol Scand 26:596-598, 1982.
5. Giovannetti, J.A., Bennet, C.R.: Assessment of allergy to local anesthetics Am Dent Assoc 98:701-706, 1979.
6. Hallén, B., Uppfeldt, A.: Does lidocaine-prilocaine cream permit painfree insertion of i.v. catheters in children? Anesthesiology 57:240-342, 1982.
7. Juhlin, L., Evers, H., Broberg, G.: A lidocaine-prilocaine cream for superficial skin surgery and painful lesions. Acta Derm Veneroeol (Stockh) 60:544-546, 1980.
8. Kligman, A.M.: Topical pharmacology and toxicology of dimethyl sulphoxide-part 1. JAMA 193:140-148, 1965.
9. Lubens, H.M., Ausdenmoore, R.W., Shaffer, A.D., Reece, R.M.: Anesthetic patch for painful procedures such as minor operations. Am J Dis Child 128:192-194, 1974.
10. Monash, S.: Topical anaesthesia of the unbroken skin. A M A Arch Dermatol 76:752-756, 1957.
11. Pettersson, L.-O.: Percutaneous anaesthesia for taking split skin grafts. Scand J Plast Reconstr Surg 11:79-82, 1977.
12. Rapperport, S.: Adjunctive uses for iontophoresis. In: transactions of the 5th International Congress of Plastic and Reconstructive Surgery. Australia: Butterworth, 797-802, 1971.
13. Russo, J.Jr, Lipman, A.G., Comstock, T.J., Page, B.C., Stephen, R.L.: Lidocaine anaesthesia: Comparison of iontophoresis, injection, and swabbing. Am J Hosp Pharm 37:843-847, 1980.

Address for reprints:

Dr Christian Möller
Department of Pediatrics
University Hospital
S-901 85 Umeå
Sweden