

Use of Eutectic Mixture of Local Anesthetics in Children

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Abstract. The Eutectic Mixture of Local Anesthetics (EMLA) is a topical application, which has proved to be a useful medication for providing pain relief among children. It is an emulsion containing a 1 : 1 mixture of lidocaine and prilocaine. The high concentration of the uncharged anesthetic base in the microdroplets of the emulsion ensure effective skin penetration. In the pediatric population EMLA has been shown to be efficacious when it is used prior to venipuncture, cannulation, lumbar puncture, laser treatment of port wine stains, curettage of molluscum contagiosum or vaccination. For several of these indications, the efficacy has been documented by double blind controlled trials, that have used objective and quasi-objective scales for assessing pain relief. The dose of EMLA is between 0.5 to 1 gram, and the cream should be applied half to one hour prior to the procedure. Local side effects are very mild, and the only systemic side effect of importance is the risk of methemoglobinemia in young infants. The literature has conflicting reports about the safety of EMLA in neonates. (*Indian J Pediatr 1999; 66 : 707-715*)

Key words : *Local anesthesia; Pain; Neonates.*

Pain is a distressing experience at all ages. Reducing the pain of injections and overcoming a child's fear of needles is imperative in eliciting the co-operation of a child and thus improving his or her medical management. This has led to the search for a suitable topical local anesthetic agent which can effectively reduce pain. Many attempts have been made to produce local anesthesia by the topical application of drugs. Topical 40% lidocaine or 20% benzocaine have been tried, but they have drawbacks of local irritation, systemic toxicity and inadequate analgesia¹. A major problem with previous methods of topical an-

esthesia was that the keratinised epidermis formed an effective barrier to drug penetration and when the concentration of the drug was increased to overcome this barrier it resulted in greater side-effects. In contrast the eutectic mixture of two local anesthetics, lidocaine and prilocaine, in the form of a cream for topical application (EMLA) has proved to be a useful medication.

Composition

The local anesthetics of the amide type, such as lidocaine and prilocaine, can exist in two forms-either a water soluble salt which in the presence of water dissociates into cations, anions and a small fraction of uncharged base; or in the form of an oil soluble uncharged base. Only the uncharged

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form can penetrate the skin. It was found that if the uncharged lidocaine base is dissolved in oil and an emulsifier is added, the oil microdroplets in the oil-in-water emulsion contain a very high concentration of the active base although the total concentration in the emulsion remains low. Another finding was that a specific mixture of crystalline bases of lidocaine and prilocaine had a lower melting point than the

melting point of the individual drugs¹. Such mixtures are called eutectic mixtures.

A 1:1 mixture of lidocaine and prilocaine was found to be liquid at room temperature whereas the individual drugs would have been solid. On adding an emulsifier to this eutectic mixture an emulsion could be created which had small (1 μm) microdroplet size, a high concentration of uncharged base in the

TABLE 1. Use of EMLA Cream Prior to Venipuncture

Authors	Study design	Number of patients	Results
Ehrenstrom Reiz <i>et al</i> ⁷	Double blind placebo controlled	60	EMLA superior ($p < 0.001$) by both nurse and child
Cooper <i>et al</i> ⁸	Double blind placebo controlled	40	EMLA superior on child verbal and visual scales ($p < 0.001$, $p < 0.01$)
Wahlstedt <i>et al</i> ⁹	Double blind controlled	60	EMLA superior ($p < 0.001$)
Young <i>et al</i> ¹⁰	Double blind placebo controlled		EMLA superior in reducing pain and anxiety
Lander <i>et al</i> ¹¹	Double blind placebo controlled	258	EMLA superior to placebo. Success higher of venipuncture (84%) than cannulation (51%)
Brislin <i>et al</i> ¹²	Double blind; nitrous oxide alone or with EMLA or lidocaine	60	No difference in pain and sedation between 3 groups
Cassinello <i>et al</i> ¹³	Double blind placebo controlled	100	EMLA superior on behavioural pain scale ($p < 0.05$)
Lurngnateetape and Tritrakarn ¹⁴	Double blind placebo controlled	60	No difference between EMLA and placebo
Hopkins <i>et al</i> ¹⁵	Double blind placebo controlled	111	EMLA superior on verbal rating ($p < 0.05$) and visual analogue scale ($p < 0.0005$)

microdroplet (80%), but a low concentration of uncharged base in the emulsion (5%) and a satisfactory release rate²⁻⁴. The composition of EMLA is as follows—lidocaine 25 mg, prilocaine 25 mg, arlactone 289 (emulsifier) 19 mg, carbopol 934 (thickener) 10 mg, sodium hydroxide to pH 9.6 and distilled water to produce a total of 1 gm EMLA cream.

Pharmacobiology

The major clinical effects of amide local anesthetics can be explained by their reversible inhibition of ion flux through the voltage-dependent sodium channels in peripheral nerves. These anesthetic agents

are metabolised to inactive products by the liver.

Skin thickness and blood flow, duration of application, and the presence of skin pathology are important factors effecting the onset, efficacy and duration of EMLA analgesia. On the forehead the onset of analgesia is fastest and lasts the shortest duration because of higher blood flow. When applied on diseased skin, for instance childhood atopic dermatitis, the onset of action is faster than on normal skin because of quicker absorption⁵. It has been suggested that it is the thickness of the stratum corneum which adversely affects the efficacy of EMLA cream. In a study on healthy adult volunteers it was found that the max-

TABLE 2. Use of EMLA Cream Prior to Intravenous Cannula Insertion

Author	Study design	Number of patients	Results
Maunuksela and Korpela ¹⁹	Double blind placebo controlled	60	EMLA superior on anesthetist score ($p < 0.001$) and child score ($p < 0.05$)
Manner <i>et al</i> ²⁰	Double blind placebo controlled and a no-treatment group	40	EMLA superior vs placebo ($p < 0.001$) and vs no-treatment ($p < 0.01$)
Hallen and Uppfeldt ²¹	Double blind placebo controlled	111	EMLA superior ($p < 0.001$) on nurse score and child score ($p < 0.01$)
Vetter <i>et al</i> ²²	Open randomised	50	Nitrous oxide inhalation provides better anxiolysis and superior analgesia ($p < 0.001$) than EMLA
Arts <i>et al</i> ²³	Double blind stratified placebo controlled	180	EMLA superior ($p < 0.001$) on child score
Wig and Johl ²⁴	Blinded placebo controlled	75	EMLA superior to placebo ($p < 0.005$)
Hopkins <i>et al</i> ¹⁵	Double blind placebo controlled	111	EMLA superior on verbal rating ($p < 0.05$) and visual analogue scale ($p < 0.0005$)

imum depth of analgesia achievable was upto 5 mm below skin surface at 30 min after a 90 min application of EMLA⁶.

Clinical Uses in Children

Venipuncture : EMLA cream has been shown to reduce the venipuncture pain in several studies in children⁷⁻¹⁵ (Table 1). This reduction has been documented both in terms of subjective assessments made by the children as well as objective scales used by observers and patients. Only 2 studies have failed to show beneficial use of EMLA^{12,14}. In a double blind controlled trial on 258 children and adolescents, EMLA was found to have a higher success rate for venipuncture than for cannulation¹¹. In this study the other factors which predicted success of EMLA were duration of drug application and pre-procedure anxiety. Age of the child was not a factor. There are 2 modes of application of EMLA: by patch or as a cream covered by an occlusive dressing. Both the methods are equally efficacious; there is no difference in the side effects and the patch method has been found to be less adhesive¹⁶.

Most workers have used an application time of 60 minutes which has provided adequate analgesia. However, in one study

on 111 subjects aged 1-5 years, the pain of venipuncture was alleviated after 30 minutes of application of EMLA¹⁵. In adults, a statistically significant reduction in pain scores has been noted after applying EMLA for only 5 minutes.

The application of EMLA does not affect the results of common laboratory tests. However, EMLA should not be used to prevent the pain of intra-dermal skin tests for hypersensitivity, because it reduces the flare response and may produce false negative results¹⁷.

Intravenous cannulation : EMLA has been found superior to placebo for reducing the pain of cannula insertion in several studies^{15,19-24} (Table 2). However, one study showed that nitrous oxide administration by face mask provided greater anxiolysis and thereby superior pain relief scores than EMLA in presurgical children²². EMLA has been shown to be as effective as intradermal infiltration with lidocaine, in producing analgesia prior to cannulation. The advantage of EMLA over infiltration with lidocaine is that the pain of infiltrating with a 26 gauge needle is avoided, and EMLA does not distort the skin anatomy thus making it easier to cannulate. This study also showed that patient cooperation

TABLE 3. Use of EMLA Prior to Lumbar Puncture

Authors	Study design	Number of patients	Results
Halperin <i>et al</i> ²⁵	Double blind placebo controlled	14	EMLA superior on visual analogue scale (p < 0.01)
Kapelushnik <i>et al</i> ²⁶	Double blind placebo controlled / open crossover	28	EMLA has a favourable effect in 2 different study designs
Gimenez <i>et al</i> ²⁷	Double blind placebo controlled	11	EMLA superior on first attempt at lumbar puncture (p < 0.05)

does not necessarily improve after analgesia. Another study showed that levels of biochemical markers of stress, such as plasma catecholamine and arginine vasopressin, remained the same regardless of the application of EMLA and the consequent reduction in pain perception²⁰. This evidence suggests that anxiety and the anticipation of pain rather than pain itself may influence patient behaviour.

The addition of nitroglycerine to the EMLA cream increases the ease of venous cannulation by producing venodilatation.

Lumbar puncture : In 3 randomised, placebo-controlled studies, EMLA reduced the pain associated with lumbar puncture in children with malignancies²⁵⁻²⁷ (Table 3). One of these studies showed that this advantage with EMLA is apparent only in patients who undergo a successful lumbar puncture in the first attempt²⁷. In another study on children with malignancies, the

EMLA patch and the EMLA cream were found equally effective. The EMLA patch however, simplified and speeded up the application of EMLA and allowed for control of dose per application. Thus, in children with malignancies who require multiple lumbar punctures EMLA is invaluable.

Removal of port wine stains : Children with port wine stains are often treated with laser²⁸⁻³⁰ (Table 4). This is painful and the lesion may necessitate multiple sessions of therapy. Two double blind randomised placebo controlled studies demonstrated that EMLA is superior to placebo^{28,29}. In a study on 8 patients, it was shown that although EMLA may cause some vasoconstriction, it does not adversely affect the efficacy of pulsed dye laser therapy.

Curettage of Molluscum contagiosum : Superficial skin surgery for removal of Molluscum contagiosum can be done after

TABLE 4. Use of EMLA Prior to Laser Treatment of Port Wine Stains

Author	Study design	Number of patients	Results
Tan and Stafford ²⁸	Double blind, placebo controlled and no treatment	73	EMLA superior to placebo and no treatment ($p < 0.0001$)
Sherwood ²⁹	Double blind placebo controlled	73	EMLA significantly reduced pain ($p < 0.0001$)
Taieb et al ³⁰	Open	74	EMLA aids repeated therapy and at young age

TABLE 5. Use of EMLA Prior to Curettage of Molluscum contagiosum

Authors	Study design	Number of patients	Results
Rosdahl et al ³¹	Double blind	55	No/little pain in 93% children
de Waard-van der Speak et al ³²	Double blind placebo controlled	83	EMLA effective ($p < 0.01$) at 15, 30 or 60 min application times

applying EMLA^{31,32} (Table 5). In a double blind placebo controlled study it was shown that although effective analgesia could be achieved in 15 minutes, the proportion of pain-free children increased from 36% in the 15 min group to 61% in the 60 min group³².

Miscellaneous uses of EMLA: Two studies examined the effect of pre-treatment with EMLA on pain associated with vaccination. In a double blind, randomised, placebo-controlled trial on 118 ten to fifteen year olds receiving the measles-mumps-rubella vaccine there was no difference in pain perception between the EMLA and the placebo group³³. On the contrary, in a double blind, randomised, placebo-controlled trial on 96 infants receiving the diphtheria-pertussis-tetanus vaccine the "Modified Behavioural Pain Scale" scores were lower in the EMLA group than the placebo group ($p < 0.001$) and the latency to the first cry was longer in subjects treated with EMLA³⁴.

In pediatric outpatients, EMLA has been used as an alternative to general anesthetics to separate preputial adhesions³⁵.

Dose

A dose of one gram per 10 sq.cms surface area is suggested by some authors, with a total of not more than 2 grams being applied in infancy^{36,37}. The dose of EMLA that has been used to reduce the pain of circumcision in newborns is 0.5 grams. There is a paucity of studies comparing the efficacy of various doses at different ages.

Use in Newborns

EMLA has been found to be effective in

reducing iatrogenic pain in various studies which looked at pain response during procedures like heelprick, percutaneous line insertion, lumbar puncture and circumcision.

Complications

Local skin reactions such as pallor, erythema, alteration in temperature sensation, edema, itching and rash are generally mild and transient as observed in a study on an adult population. Complications seen with systemic use of lidocaine, such as seizures and arrhythmias have not been reported with EMLA. Children may swallow the cream if left unsupervised after the application of EMLA.

The biggest concern with the use of EMLA has been the risk of methemoglobinemia, particularly in infants less than 3 months of age. Two metabolites of the prilocaine component have been implicated in the causation of methemoglobinemia by direct oxidation of hemoglobin. Clinically significant methemoglobinemia has been reported in a 3 month old infant who became cyanosed after 5 grams of the cream was applied for a total of 5 hours. The methemoglobin concentration was 28% although it may have been compounded by the concomitant use of a sulfonamide in this patient³⁸. In a study on 22 infants aged 3 to 12 months who received 2 grams EMLA application beneath an occlusive dressing, the methemoglobin levels were all found to be normal and plasma levels of the anesthetics were within safe limits³⁶. In another study on infants less than 3 months of age who received 2 grams EMLA application, a small increase in methemoglobin levels (median 2.24%) was detected which was inversely correlated

with erythrocyte methemoglobin reductase activity³⁷. The erythrocyte methemoglobin reductase levels did not reach adults levels till after 3 months. In children aged 1 to 6 years, small but significant increases in methemoglobin levels have been seen following application of 5 grams of EMLA cream³⁹. In this study the finding of raised levels of methemoglobin upto 24 hours after application suggests that cumulative effects may occur with daily application. In a study on term newborns who received 1 gram EMLA before circumcision, a statistically significant rise in methemoglobin levels was noted 8 hours later, but this was well below the toxic levels⁴⁰. In a study on preterm neonates the application of 0.5 grams of EMLA cream before heelpricks did not result in a significant rise of methemoglobin levels. It can be appreciated that there are conflicting and incomplete data on its use in newborns.

Contraindications

EMLA cream should not be used in patients with congenital or idiopathic methemoglobinemia, or in infants receiving therapy with methemoglobin inducing agents. It should be used with caution in infants less than 3 months age and particularly so in newborns. EMLA is contraindicated in patients with hypersensitivity to local amide anesthetics.

Conclusion

The eutectic mixture of local anesthetics (EMLA) has undergone extensive trials in the pediatric age group. It is a valuable tool for ameliorating the pain in procedures such as venipuncture, intravenous cannulation, lumbar puncture, laser treatment of

port wine stains, and curettage of *Molluscum contagiosum*. It is, by and large, safe but some concerns remain regarding its potential to cause methemoglobinemia in early infancy. Areas for further research include determining the minimum efficacious dose of EMLA, particularly in infancy, determining the risk of clinically significant methemoglobinemia after single dose and multiple dose application, finding a formulation that has a faster onset of action and a greater depth of penetration.

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WHY IS THERE NO TRAINING FOR PARENTHOOD?

“Even today (1950) almost everywhere, parenthood is perhaps the only job, if I may say so, which is supposed not to require any training or knowledge such as is required in any other profession...”

-Dr J. Oren (Israel) : address to the Third World Health Assembly, 1950

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