Use of lidocaine-prilocaine cream for vaccination pain in infants

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***Purpose*: To determine whether use of lidocaine-prilocaine 5% cream (EMLA) decreases pain associated with diphtheria-pertussis-tetanus (DPT) vaccination in infants.**

***Methods*: Randomized, double-blind, controlled trial in outpatient pediatric practice, Toronto, Ontario, Canada. Before vaccination, parents applied 2.5 gm of EMLA or placebo to the infant's leg and covered it with an occlusive dressing for at least 60 minutes. The infant received a 0.5 ml intramuscular injection of DPT at 2° to 8° C with a 1.6 cm 25-gauge needle; the infant was videotaped. The Modified Behavioral Pain Scale (MBPS) was used to assess baseline and postvaccination pain scores. Latency and duration of infant cry were also measured.**

***Results*: A total of 49 evaluable infants received EMLA, and 47 infants received placebo. There were no significant differences in demographic data; mean age was 5 months; and 50% of the subjects were male. The median difference in prevaccination and postvaccination MBPS scores was lower for EMLA than for placebo ($p = 0.001$). The latency to the first cry was longer for subjects who were treated with EMLA ($p = 0.0004$), but the total crying time was shorter (10.3 seconds vs 25.2 seconds; $p = 0.027$). Of the study group, 90% (45/50) of subjects treated with EMLA and 12% (6/49) of subjects treated with placebo had local skin reactions ($p < 0.0001$), mainly skin blanching.**

***Conclusions*: Pretreatment with EMLA decreases infant pain from DPT vaccinations. Application of these data is limited to healthy infants receiving DPT vaccinations. (J PEDIATR 1994;124:643-8)**

Although routine intramuscular vaccinations are the most common source of iatrogenic pain in infants and children, methods to reduce this pain have not yet been adequately tested. Pretreatment with lidocaine-prilocaine cream, 5% strength (EMLA, Astra Pharma Inc.), has become a useful tool in this regard. Composed of equal parts of lidocaine and prilocaine, EMLA has been shown in pediatric clinical trials to decrease the pain of venipuncture,[1-4] lumbar puncture,[4] and removal of molluscum contagiosum lesions.[5,6] A comprehensive review of pretreatment with EMLA for the management of procedure-related pain in children was recently published.[7] Before evaluating EMLA's efficacy in children, we tested its effect in adults in two double-blind, randomized, clinical trials.[8,9] In both instances, pretreatment with EMLA decreased the pain from skin penetration by the needle.

DPT	Diphtheria-pertussis-tetanus [vaccine]
EMLA	Eutectic mixture of local anesthetics, composed of equal parts of lidocaine and prilocaine (also proprietary name)
MBPS	Modified Behavioral Pain Scale
VAS	Visual Analogue Scale

The purpose of this study was to determine whether use of EMLA cream could decrease the pain associated with

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intramuscular diphtheria-pertussis-tetanus vaccination in infants.

METHODS

Subjects participated in a double-blind, randomized (in blocks of two) clinical trial between April 30, 1992, and Feb. 11, 1993. Two team members recruited subjects from their shared pediatric outpatient clinic in Toronto, Ontario. Study subjects included healthy infants receiving their 4-month or 6-month regular DPT vaccination. Exclusion criteria included a history of sensitivity to amide local anesthetics, use of analgesics within 4 hours of the vaccination procedure, fever, or illness that prevented administration of the vaccine.

Each subject received either EMLA or placebo cream before the administration of the vaccine. The parent(s) were given one 5 gm tube of EMLA or a placebo cream that was visually and cosmetically identical to EMLA, except that the active ingredients were replaced by coconut oil (Miglyol 812 Oil; Nobel Industries AB, Stockholm, Sweden).

The protocol was approved by our hospital's research ethics committee. Parents were informed of the study objectives and design through an information summary sheet. Parental consent to infant participation in the trial was obtained during the prior clinic appointment (i.e., before the infant's 4- or 6-month appointment). A study nurse explained and showed the parents how to apply the cream, which was then covered by an occlusive transparent dressing (Tegaderm; 3M Health Care, St. Paul, Minn.). The parents then practiced applying the cream and dressing. Parents were given an instruction sheet to keep for reference. Parents were also contacted by one of the investigators within 1 or 2 days of the study day to review the protocol.

On the day of vaccination, the parent applied approximately 2.5 gm to the upper part of the infant's thigh approximately 60 minutes before the scheduled appointment. The parent noted the time that the cream was applied or wrote the time directly on the dressing. The dressing and cream were both removed in the clinic by one of the investigators after 60 to 120 minutes. The cream was wiped from the skin with a paper tissue; a water-soluble marker was used to mark four dots on the skin where the cream had been applied.

Within several minutes of removal of the cream, the infant was placed in a supine position on the examining table. If the infant was unsettled, he or she sat on the table or was held by a parent. Immediately before the injection, the site was wiped with an alcohol swab by a pediatrician who then administered one 0.5 ml intramuscular injection of DPT vaccine at 2° to 8° C with a 1.6 cm 25-gauge needle. Two pediatricians unaware of the treatments performed all vaccinations.

The vaccination procedures were videotaped with a color camera. A mirror was mounted on the wall behind the examining table so that the videographer could film the infant's reaction both face on and from the mirror image. The videographer stood approximately 3 feet from the infant and did not interfere with the procedure. The entire vaccination procedure was taped until the baby settled down. Parents were told that "[they could do] whatever they normally would do after the vaccine was given, and that [they] did not have to do anything different because of the video camera."

Parents also completed two questionnaires. The revised Carey Infant Temperament Questionnaire[10] for infants 4 to 8 months of age was completed within 2 weeks of the scheduled vaccination appointment. According to the scoring method, infants were assigned to one of five possible categories: easy, intermediate low, slow to warm up, intermediate high, and difficult. These five categories were then ranked in increasing order from 1 to 5 for statistical analyses. A questionnaire regarding parental opinion of the cream was completed on the study day.

The pain from the vaccination was assessed according to two methods: the Modified Behavioral Pain Scale and a 100 mm unmarked Visual Analogue Scale. On the VAS, a score of 0 denotes no pain, and 100 mm denotes maximal possible pain. The VAS was scored by an uninformed investigator at the time of the procedure, within 15 seconds of the injection. After the videotapes were reviewed, the infant pain scores were assessed by the same investigator according to the MBPS (Table I), which was modified from the Children's Hospital of Eastern Ontario Pain Scale[11] to score pain in infants.

The MBPS was used to score baseline pain and postvaccination pain for each vaccination procedure. The main outcome measure was the difference between the pre- and post-MBPS pain scores (i.e., the net increase in pain). In all instances, the prevaccination pain scores were assessed within 5 seconds of the vaccination, and the postvaccination pain scores were assessed within 15 seconds (i.e., maximal pain response) by one investigator. The same investigator also scored whether the infant had a general "startle" reaction after receiving the vaccination. Finally, infants' cry patterns were also analyzed by viewing the videotapes. With a handheld stopwatch, the investigator recorded the latency to the first cry after the injection, the duration of the first cry, and the total crying time.

The infant's reaction to removal of the Tegaderm dressing was assessed according to three categories: no reaction, mild reaction (i.e., movement), or severe reaction (i.e., crying). Within 1 to 5 minutes after the removal of the cream, local skin reactions were also assessed according to a four-point rating scale (none, mild, moderate, severe).

From a previous study,[1] we calculated a sample size of 48

Table I. Modified Behavioral Pain Scale (MBPS)

Behavior observed	Score (0-10)
Facial expression	
Definite positive expression (i.e., smiling)	0
Neutral expression	1
Slightly negative expression (i.e., grimace)	2
Definite negative expression (i.e., furrowed brows, eyes closed tightly)	3
Cry	
Laughing or giggling	0
Not crying	1
Moaning, quiet vocalizing, or gentle or whimpering cry	2
Full-lunged cry or sobbing	3
Full-lunged cry, clearly more than baseline full-lunged cry*	4
Movements	
Usual movements and activity	0
Resting and relaxed	0
Partial movement or attempt to avoid pain by withdrawing the limb where the puncture is done	2
Agitation with complex movements involving the head, torso, or the other limbs, or rigidity	3

*Used only for postprocedural pain.

subjects in each group to show a 50% difference in pain scores with a standard deviation that was twofold this difference. Differences in infants' characteristics between subjects who were treated with EMLA and subjects who received placebo were analyzed by means of the chi-square test, Mann-Whitney U test, or Student *t* test, where appropriate. Differences in pain scores, cry characteristics, and adverse effects were similarly analyzed. Correlations between pain scores and infant cry patterns were assessed according to the Spearman method. Backward elimination multiple linear regression was used to assess the contribution of potential confounding factors on pain scores and duration of infant cry. The significance level (probability) was 0.05.

RESULTS

There were 112 participants randomly assigned to the study groups, but 12 withdrew from the study or did not come on a scheduled study day for vaccination. Of the 100 study subjects, 51 were randomly assigned to the EMLA group and 49 to the placebo group. For two subjects in each group, there was deviation from the study protocol (i.e., the parent did not apply enough cream, cream was applied for <60 minutes, or occlusive dressing did not cover the skin adequately). Thus 96 subjects were available for study.

The mean age of the infants was 5 months. Of the infants, 50% were male, and 96% were white. There were no significant differences between the groups in any of the demographic characteristics, temperament scores, or other factors measured (data available on request). In the EMLA group, the cream was applied on the skin for an average of 83 minutes (SD = 14 minutes).

Table II. MBPS and VAS pain scores for EMLA and placebo groups

Pain scores (SD)	EMLA group (n = 49)	Placebo group (n = 47)	p*
MBPS score			
Before vaccination	2 (0-4)	2 (0-5)	0.975
After vaccination	7 (3-9)	8 (3-9)	0.001
Difference between before and after scores	5 (1-8)	6 (1-9)	0.001
VAS score (mm)	26.0 (0-94.0)	48.0 (0-97.0)	0.002

Values (except *p* values) are expressed as median (range).
*Mann-Whitney U test.

The pain scores for the EMLA and placebo groups are shown in Table II. The prevaccination MBPS scores did not differ between the two groups ($p = 0.975$); however, both the postvaccination MBPS scores and the difference between prevaccination and postvaccination MBPS scores were lower for the EMLA group ($p = 0.001$). Similarly, the VAS scores were lower in the subjects treated with EMLA ($p = 0.002$). Correlation of the differences in prevaccination and postvaccination MBPS scores with VAS scores yielded a Spearman correlation coefficient of 0.608 ($p < 0.001$). The incidence of startle reaction in the infants who received EMLA was 22 (44.9%) compared with 25 (53.2%) in the placebo group ($p = 0.416$).

A backward elimination multiple regression analysis was performed to determine whether magnitude of pain (defined by the difference in the pre- and post-MBPS scores) could be attributed to the infant's sex, age, or temperament; the physician who administered the vaccine; or preadministration of EMLA versus placebo cream. Administration of EMLA cream and female sex were the only two factors associated with lower pain scores ($F = 8.31$; $df = 2, 93$; $p = 0.001$). The multiple correlation coefficient *(R)* was 0.390 ($R^2 = 0.152$). There was no interaction between infant sex and randomization code in regard to the difference in the pain scores ($F = 0.34$; $df = 1$; $p = 0.563$).

The subjects who were treated with EMLA had a longer latency period between needle puncture and the start of crying ($p = 0.0004$). The total time that infants cried after the vaccination procedure was less for the EMLA group than for the placebo group ($p = 0.027$). The difference in prevaccination and postvaccination MBPS scores was correlated with the latency to the first cry (Spearman rho = −0.22; $p = 0.031$) and total duration of infant crying (Spearman rho = 0.509; $p < 0.001$) (Table III).

Table III. Duration of cry characteristics of subjects receiving EMLA and placebo

Characteristic	Duration (seconds) EMLA group (n = 49)	Placebo group (n = 47)	p*
Mean (SD) latency of first cry†	3.4 (1.2)	2.5 (1.0)	0.0004
Median‡	3.3 (1-6.4)	2.4 (0.53-5.5)	
Mean (SD) duration of first cry§	4.7 (2.8)	6.0 (3.4)	0.073
Median‡	4.7 (0.6-10.3)	5.9 (0.7-14.2)	
Mean (SD) total duration of cry‖	31.2 (37.4)	35.4 (29.5)	0.027
Median‡	10.3 (0-145.1)	25.2 (0-117.4)	

*Mann-Whitney U test.
†One subject in the EMLA group and two subjects in the placebo group did not cry and are not included in the analysis.
‡Values in parentheses are ranges.
§Data also not available for one subject in the EMLA group.
‖Data not available for one subject in the EMLA group.

Multiple regression was again used to identify factors associated with duration of crying. The log of the total duration of infant crying was analyzed with the same factors tested in the previous analysis. Only pretreatment with EMLA was associated with decreased duration of infant crying ($F = 6.64$; $df = 1, 90$; $p = 0.012$, $R^2 = 0.069$).

The parent who accompanied the infant to the clinic appointment was usually the mother; a father comforted the infant after the vaccination instead of the mother in only two instances. Most infants were touched by the parent during the vaccination procedure. The parent usually held the infant's hand(s), but some parents touched other parts of the infant. Only four infants in the placebo group and one in the EMLA group were not touched by a parent ($p = 0.199$). After the injection, 26 parents (55.3%) in the placebo group picked up their infants compared with 23 (46.9%) in the EMLA group ($p = 0.411$). Picking up the child was correlated with the duration of the infant crying (Spearman correlation coefficient = 0.340; $p = 0.001$); infants whose mothers picked them up cried longer than those whose mothers did not.

Adverse effects could be evaluated in 50 subjects in the EMLA group and 49 subjects in the placebo group; 92 subjects (93.0%) did not react to removal of the patch. Only three infants cried when the dressing was removed. Thirty subjects (30.3%) had minor skin redness where the dressing had been applied. Of the subjects in the EMLA group, 90% had local skin reactions compared with 12% of subjects in the placebo group ($p < 0.0001$). The most common adverse reaction to pretreatment with EMLA was minor skin blanching (60%) followed by redness (30%).

When parents were asked whether they thought the cream was difficult to apply, 87 (90.6%) responded that it was not. When asked whether it was difficult to fit application of the cream into their schedules, 84 parents (87.5%) responded that it was not.

DISCUSSION

Current methods of measuring infant pain include observations of infant behavior, physiologic responses, or both.[12] We used a behavioral approach to measure the pain of the vaccination procedure. Other investigators have used similar techniques to measure infant pain.[1, 11, 13] Our data are limited to healthy infants and DPT vaccines. Further research will be necessary to determine whether pretreatment with EMLA is effective with other vaccines and in other patient populations.

We scored the MBPS pain scores by means of video analysis. This provided a precise way of observing infant behavior. The MBPS scores obtained from video analysis were significantly correlated with VAS pain scores obtained from direct observation, suggesting that both scales measured similar responses.

Our study could not discriminate between the pain from the needle prick and that from the injection of the vaccine; however, the longer latency between the first cry for the subjects in the EMLA group suggests that this agent causes superficial anesthesia. The overall lower pain scores suggest that pretreatment with EMLA also minimizes the pain from the entire procedure. There was a large variation in the VAS and MBPS pain scores obtained between subjects. In fact, scores varied from minimal pain to almost maximal pain for subjects in both groups. Pretreatment with EMLA may not have substantially reduced pain in all infants because it penetrates to about 5 mm below the skin surface[14] and vaccination involved needle insertion into the muscle.

In addition to the behavioral scores and VAS scores, we measured differences between the subjects in the EMLA and placebo groups in the latency to the infant's first cry, duration of first cry, and total crying time, which are regarded as important measurements in the overall assessment of infant pain.[14a, 14b] Skin anesthesia with EMLA cream was associated with a longer latency to the first cry, suggesting that infants who received EMLA, similar to adults, had not felt the needle penetrating the skin. Similarly, subjects in the EMLA group cried for a shorter period than subjects given placebo, indicating that use of EMLA decreased the pain from the entire procedure, not just the needle penetration. Some investigators have suggested that stressful events in infancy can affect develop-

mental outcome.[15, 16] Pretreatment with EMLA may thus affect an infant's long-term conditioning to painful procedures. Decreasing infant pain may also lead to a decrease in parental anxiety during vaccination. The psychologic consequences of decreasing pain during procedures warrants further study.

Most parents in the study were able to apply the cream correctly before the child's vaccination. Although this implies that EMLA cream may be routinely used at home before the infant's arrival at the physician's office, our results are limited to the sample of parents studied and their level of understanding. The pediatric practice setting was in an upper-class neighborhood with mature mothers (average age, 33 years).

In this study, female sex was associated with lower pain scores. Other investigators have not consistently found this to be true.[13, 17] The effect of gender on pain behavior requires more study. Infant temperament was measured to try to explain infant pain behavior; no statistical associations were found. Perhaps the limitations of temperament scales are partially responsible, or infant temperament may not predict pain behavior.

Minor local skin reactions were observed in almost all subjects who received EMLA cream. The most common reactions were minor pallor and redness, which are recognized reactions to EMLA cream.[18] No serious adverse reaction was observed in any study subject.

EMLA is not currently licensed in the United States for use in neonates because there is a lack of safety data in this population, together with a concern about possible development of methemoglobinemia from the prilocaine metabolite *o*-toluidine. Systemic bioavailability of EMLA is believed to be small in adults but has not been studied in children. There is one report of methemoglobinemia in a 3-month-old infant treated with trimethoprim-sulfamethoxazole and a large dose of EMLA cream (5 gm for 5 hours),[19] suggesting significant absorption of EMLA, but a variety of other agents may cause methemoglobin formation in neonates and the concurrent use of the sulfonamide may have contributed to the observed toxic effects.[20] Para-aminophenol derivatives, such as acetaminophen, can also cause methemoglobin formation.[21] In infants exposed to one or more of these agents there may be a potential for drug interactions with EMLA. Practitioners who treat infants with EMLA should be aware of these concerns.

We limited our study to infants more than 3 months of age who were not using other medications known to cause methemoglobin formation, because published data show that for these patients the risk of methemoglobinemia is small.[22] Until there is more evidence of EMLA's safety in younger infants, however, it should not be recommended for routine use in those patients.

The wholesale U.S. price of one 5 gm tube of EMLA cream, which yields two doses, is $5.25. The preparation is available only with a prescription; the added cost of a pharmacy dispensing fee can make it a relatively expensive alternative. Conversely, the cost of pain has yet to be defined and may be much greater in the infants who experience it than the cost of the medication.

We conclude that skin anesthesia with EMLA was associated with lower pain scores and less crying in infants vaccinated with DPT vaccine. The EMLA cream may thus be useful for premedication of infants before such procedures. The method of administration is crucial to the efficacy of EMLA; the fact that most parents were able to use it correctly suggests that it can be utilized in this setting.

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