Effect of Lidocaine-Prilocaine Cream (EMLA®) on Pain of Intramuscular Fluzone® Injection

Anna Taddio, Irena Nulman, Ellen Reid, June Shaw and Gideon Koren

ABSTRACT

The efficacy of lidocaine-prilocaine cream (EMLA® — Eutectic mixture of Local Anesthetics) in alleviating the pain of intramuscular injections was investigated in a randomized, double-blind, placebo-controlled, parallel group trial. EMLA® or placebo cream was applied to the arms of 60 adult volunteers before receiving influenza virus vaccine (Fluzone®). Twenty-nine subjects received approximately 2.5 g of EMLA® cream and 31 subjects received approximately 2.5 g of an inert placebo cream under occlusion for 60-90 minutes. The cream was then removed and each subject received one 0.5 mL intramuscular injection of influenza virus vaccine using a 22 gauge one inch needle. Pain of needle puncture and pain of injection were both assessed by the subjects using a visual analog scale. EMLA® was associated with decreased needle puncture pain ($p < 0.0002$) and decreased pain of injection when compared to placebo ($p = 0.0139$). There was a significant correlation between scores of needle puncture pain and injection pain. Mild skin pallor was a common skin reaction from EMLA®. While the efficacy of EMLA® to alleviate pain of venipuncture is well documented, this is the first study to show the efficacy of EMLA® for intramuscular injections.

Key Words: *EMLA®, intramuscular injection, lidocaine-prilocaine, pain, vaccination*

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RÉSUMÉ

Une étude randomisée à double insu, en contrôle parallèle avec placebo a permis d'évaluer la capacité de la Lidocaïne-Prilocaïne (crème EMLA® — mélange eutectique d'anesthésiques locaux) à soulager la douleur causée par les injections intramusculaires. On a appliqué la crème EMLA® ou un placebo sur le bras de 60 volontaires adultes avant de leur injecter un vaccin viral contre la grippe (Fluzone®). Vingt-neuf (29) sujets ont été traités avec la crème EMLA® et 31 avec le placebo. Tous ont reçu une application d'environ 2,5 g de crème sous un pansement occlusif pendant 60 à 90 minutes. Après l'élimination de la crème, on leur a injecté 0,5 mL de vaccin par voie intramusculaire au moyen d'une aiguille calibre 22 d'un pouce. Les sujets ont évalué la douleur causée par l'insertion de l'aiguille et par l'injection au moyen d'une échelle visuelle analogique. Comparativement au placebo, la crème EMLA® a atténué la douleur associée à l'insertion de l'aiguille ($p < 0.0002$) et à l'injection ($p = 0.0139$). On a noté une corrélation significative entre les cotes se rapportant à la douleur provoquée par l'insertion de l'aiguille et celles relatives à la douleur causée par l'injection. L'apparition d'une légère pâleur fut une réaction cutanée courante à l'application de la crème EMLA®. Il est bien établi que cette dernière soulage la douleur due à la ponction veineuse, mais la présente étude est la premièree à démontrer son efficacité en cas d'injection intramusculaire.

Mots clés: *douleur, EMLA®, injection intramusculaire, Lidocaïne-Prilocaïne, vaccination*

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INTRODUCTION

EMLA® 5% cream (Astra Pharma Inc., Canada) is a eutectic mixture of equal parts of lidocaine and prilocaine. It is currently available in Europe and in Canada while it is not yet available in the U.S. EMLA®, used topically to produce surface anaesthesia, has been studied for many clinical indications, including the pain associated with needle puncture,[1,2,3,4,5] superficial skin surgery,[6] and removal of molluscum contagiosum lesions.[7,8] The depth of its effect may be up to 5 mm and persists after its removal.[9]

We have recently studied EMLA®'s effectiveness in reducing the pain associated with subcutaneous injections of normal saline in adult volunteers, showing decreased needle pain compared with placebo[10]. As injections are

commonly utilized for administering vaccinations, EMLA® may be useful in alleviating some of the pain associated with this procedure. The objective of the present study was to evaluate EMLA®'s ability to alleviate pain associated with intramuscular injections of influenza virus vaccine in adult volunteers.

METHODS

After approval by our Human Subject Review Committee, and obtaining written informed consent, 60 healthy adult volunteers participated in a randomized, double-blind, prospective trial. The study was held on the day when the influenza virus vaccine was being offered to hospital employees. All study subjects were informed of the study objectives and design through an information summary sheet which was distributed to them. Exclusion criteria for the study included: subjects with a history of sensitivity or allergy to amide anaesthetics; any contraindication to influenza vaccine including allergy to eggs, neurological disorders, concurrent upper respiratory tract infection, and pregnancy; or receipt of any anaesthetic or sedative within two hours of the study. Each subject received either one application of approximately 2.5 g of EMLA® cream or approximately 2.5 g of placebo cream (Miglyol® 812 oil, Dynamit Nobel, Sweden) covered by a transparent occusive dressing on the arm to be vaccinated, in the middle of the deltoid muscle. The placebo cream contained the same ingredients as the active cream, except that the active ingredients were substituted with a coconut oil. Both formulations are cosmetically and visually identical.

After 60-90 minutes, the dressing was removed and creams were wiped off using a paper tissue. Any local skin reactions, (i.e., pallor, edema or redness at the treated site), were recorded by one investigator blinded to the treatment within two minutes of the removal of the cream, using a four point rating score of none, mild, moderate or severe. The area was then wiped with an alcohol swab and each subject then received one 0.5 mL intramuscular injection of influenza vaccine (Fluzone® subvirion vaccine, Connaught Laboratories, Canada) a two to eight degrees centigrade using a 22 gauge, one inch needle by a registered nurse in the Occupational Health Unit of our hospital. For each injection, the needle was inserted in the middle of the deltoid area at a 90 degree angle to the skin. The vaccine was injected over five seconds, as counted by the nurse. All injections were performed by two nurses familiar with the study protocol. The nurses were blinded to the treatments.

The pain associated with the procedure was scored by each subject by drawing a perpendicular line through a 100 mm ungraded line (Visual Analogue Scale (VAS)) where zero denoted "no pain" and 100 mm denoted "worst possible pain". All patients were pretested for understanding of the VAS, by scoring the pain they would feel during the following situations: mosquito bite; falling in the snow; falling on the pavement; and slamming the door on their fingers. A trend toward increasing pain constituted adequate understanding of this test. Each subject was instructed to score the pain felt by the needle entering the skin and the pain felt by the injection of the vaccine on two separate VAS. All subjects also participated in a short questionnaire after receiving their vaccinations. The investigator administering both the test scores and questionnaire was blinded to the treatments.

Differences in patient characteristics between the two groups were analyzed using Chi square and t-test for unpaired data whenever appropriate. The differences between the pain scores in the two groups were calculated using the nonparametric Mann-Whitney U test for unpaired data. Differences in pain scores within each group were calculated using the Wilcoxon signed rank sum test. A two tailed p value of ≤ 0.05 was considered significant. Correlation between the puncture and injection scores was studied by the nonparametric Spearman method.

RESULTS

Patient characteristics are listed in Table I; no statistically significant differences between the groups were observed. Twenty-seven subjects (93%) in the EMLA® group and 26 subjects (84%) in the placebo group reported no history of skin allergies. Seven out of sixty subjects (12%) reported allergies to perfumes, metal, acrylic, formaldehyde and one specific brand of adhesive tape. Four other patients in the placebo group reported having general skin sensitivity or allergies which resulted in skin manifestations, but without identifying the causative agent or agents.

Table II shows the pain scores from the intramuscular injection with EMLA® versus placebo. EMLA® was associated with significantly lower pains scores during needle prick when compared to placebo ($p < 0.0002$). EMLA® was also associated with significantly lower pain scores during injection with the vaccine compared with placebo ($p = 0.0139$). The pain scores associated with the needle prick were significantly lower than the pain from the injection of the vaccine for both the EMLA® and placebo group ($p < 0.01$ and $p = 0.046$, respectively).

Analysis of the correlation between the pain scores from the needle prick and the pain scores from injection from the vaccine

Table I: Patient characteristics

	EMLA® (N=29)		PLACEBO (N=31)		p value
Sex (% female)	20	(69.0)	26	(83.9)	0.2897[a]
Mean Age (yr) (SD) (range)	34	(10.5) (23-62)	37	(11.6) (22-65)	0.2783[b]
Weight (kg)(SD)	64	(10.4)	67	(17.2)	0.4928[b]
Race (%)					
caucasian	25	(86.2)	28	(90.3)	0.6211[a]
negroid	2	(6.9)	1	(3.2)	
oriental	2	(6.9)	1	(3.2)	
asian	0	(0.0)	1	(3.2)	
Vaccination Site					
left arm (%)	24	(82.8)	27	(87.1)	0.9136[a]

[a] Chi square test
[b] t-test for unpaired data

Table II: Visual Analog Scale (VAS) Pain Scores for EMLA® (N=29) and Placebo (N=31) after Intramuscular Injections of Influenza Virus Vaccine (0=no pain; 100=worst possible pain)

	Mean VAS pain score (mm) ± SD (median, range)	p value[a]
EMLA® Needle[b]	4.62 ± 7.77 (1, 0-29)	$p < 0.0002$
Placebo Needle[b]	15.19 ± 16.49 (8, 1-64)	
EMLA® Injection[c]	9.52 ± 13.65 (3, 0-50)	$p = 0.0139$
Placebo Injection[c]	18.45 ± 19.64 (13, 0-92)	

[a] Mann-Whitney test
[b] refers to assessment of pain from needle prick
[c] refers to assessment of pain from influenza virus vaccine injection

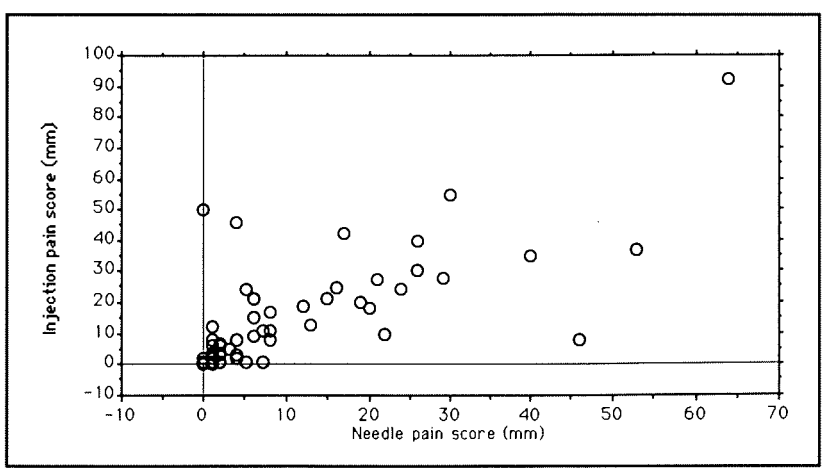

Figure 1: Correlation between VAS pain scores from needleprick and injection: EMLA and placebo groups combined. (Spearman correlation coefficient = 0.746, $p < 0.001$)

revealed that in the EMLA® group, the correlation coefficient was 0.543 ($0.002 < p < 0.01$). In the placebo group, the correlation coefficient was 0.815 ($p < 0.001$). Overall, the correlation coefficient was 0.746 ($p < 0.001$), (Figure 1).

All patients reported that they would be able to properly apply EMLA® at home one hour prior to having their next injection. Eighty-seven percent reported that the one hour application time would not be difficult to fit into their schedule.

No serious adverse events were reported (Table III). Fifteen subjects (48%) in the placebo group and 28 (97%) in the EMLA® group experienced local skin reactions ($p < 0.0001$). Mild pallor of the skin was the most frequent reaction in the EMLA® group, occurring in 68% of subjects with skin reactions. Other adverse effects included reactions such as heat or burning sensation, numbness, skin blotchiness (i.e., red spots), goosebumps, or mild redness at site of adhesive tape. Seven patients experienced more than one adverse effect.

DISCUSSION

This is the first blinded, placebo controlled study to show the efficacy of EMLA® in alleviating pain associated with vaccination. We chose to score the pain from the procedures using a visual analogue scale. This method has been used successfully in similar settings where EMLA® has been studied.[2,4,7,8,10,11] When compared to placebo, EMLA® decreased the pain of needle penetration into the skin. These results are consistent with our previous study where twenty adult volunteers were administered 1.0 mL of normal saline subcutaneously in both arms after receiving EMLA® and placebo creams in a randomized, double-blind fashion[10]. EMLA® was associated with statistically lower pain scores from needle prick.

Table III: Frequency of Adverse Effects

Signs	Severity	EMLA® (N=29)	PLACEBO (N=31)	p value
No. subjects with adverse effects (%)		28 (96.6)	15 (48.4)	$p < 0.0001$[a]
Type of reaction				
Pallor	mild	19	6	
	moderate	2	—	
Edema		—	—	
Redness	mild	7	8	
Other[b]	mild	6	4	
Total No. Reactions		34	18	

[a] Chi square test
[b] see text

When compared to placebo, EMLA® also decreased the pain of injection from influenza virus vaccine as well. This was not shown in our previous study, where EMLA® was associated with statistically lower pain scores associated with skin penetration compared to placebo, but not during the injection of normal saline[10]. This difference between the two studies is not surprising as there are many variables that affect the amount of pain caused by various solutions. Differences may be due to the properties of the solutions used such as: temperature, volume, pH, and osmolality; method of administration; and setting. For example, in our current study, 0.5 mL of plasma was administered using a 22 gauge needle, whereas the preliminary study involved administration of 1.0 mL of saline using a 25 gauge needle.

In the present study, the pain elicited by the needle prick was less than from injecting the vaccine. The quality of pain associated with needle insertion, however, may be different from that caused by the injection of vaccine. The needle elicits anxiety and is commonly described as causing a sharp pain. The injection, however, is described as causing a dull pain. The observed correlation between the needle and injection pains suggests that the two events are not totally independent, and the pain elicited by the needle may affect the pain perception from the injection. This observation may be of high clinical relevance, because the use of skin anaesthesia may thus modulate pain perception of much deeper procedures.

Our subjects were confident they could administer EMLA® at home, and that based on their experience, it would not interfere with their schedules. This study suggests that adults perceive needles as painful and they would be willing to accommodate their routines to avoid or attenuate this pain.

EMLA® cream was associated with more local skin reactions than the placebo, but the reactions were mild, and consisted mainly of skin pallor, consistent with previous studies.[1,2,4,8,10]

In summary, we have shown that EMLA® cream decreases pain associated with intramuscular vaccinations in adults. Since intramuscular injections are commonly used in children for administration of routine vaccinations and since children and parents often perceive needles as painful, EMLA® may be also useful in this setting. These results support continuing research into the usefulness of EMLA® for vaccination pain in children.

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