

# A Randomized Trial of Eutectic Mixture of Local Anesthetics During Lumbar Puncture in Newborns

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**Objective:** To determine the efficacy of a topical anesthetic cream, eutectic mixture of local anesthetics (EMLA), in alleviating pain associated with lumbar puncture in newborns.

**Design:** Randomized double-blind placebo-controlled trial.

**Setting:** Neonatal intensive care unit of a university teaching hospital.

**Patients:** Sixty consecutive newborns (gestational age,  $\geq 34$  weeks) undergoing diagnostic lumbar puncture.

**Intervention:** Topical application of 1 g of EMLA or placebo 60 to 90 minutes before lumbar puncture.

**Main Outcome Measures:** Heart rate, transcutaneous oxygen saturation level, and total behavioral score recorded on a video camera and graded according to the Neonatal Facial Coding System.

**Results:** Compared with baseline, all newborns experienced pain as evidenced by increased heart rate, decreased oxygen saturation level, and total behavioral score (all within-groups differences were significant using repeated-measures analysis of variance;  $P < .001$ ) during the procedure. Compared with placebo, EMLA significantly attenuated the pain response as shown by a lower mean  $\pm$  SE heart rate (per minute), particularly at needle insertion (EMLA:  $159.3 \pm 2.3$ ; placebo:  $175.2 \pm 2.7$ ;  $P < .001$ ) and needle withdrawal (EMLA:  $153.8 \pm 2.6$ ; placebo:  $167.3 \pm 2.5$ ;  $P < .001$ ), and a lower mean  $\pm$  SE total behavioral score, again at insertion (EMLA:  $4.0 \pm 0.3$ ; placebo:  $5.0 \pm 0.0$ ;  $P = .004$ ) and withdrawal (EMLA:  $1.8 \pm 0.3$ ; placebo:  $3.9 \pm 0.3$ ;  $P < .001$ ). There was no statistically significant difference between groups with regard to oxygen saturation level.

**Conclusions:** Lumbar puncture in newborns produces pain responses. Eutectic mixture of local anesthetics is an efficacious agent for reducing the pain associated with needle insertion and withdrawal during lumbar puncture in newborns.

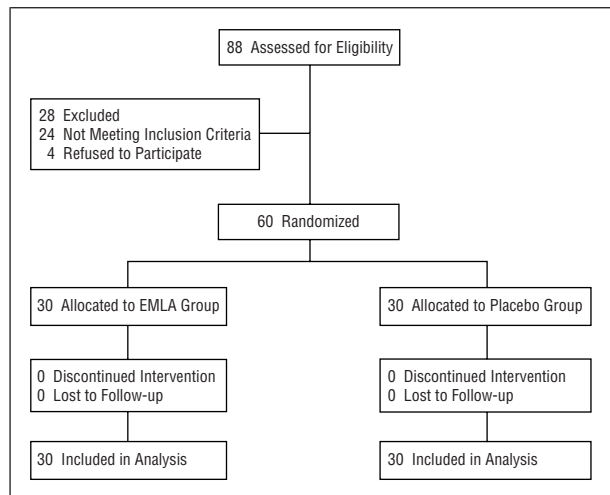
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**L**UMBAR PUNCTURE in neonates without the benefits of anesthesia or analgesia is common practice in neonatal intensive care units. This practice is being questioned by recent evidence that neonates are capable of both perceiving and exhibiting reproducible responses to noxious stimulation. Newborns not only experience pain and stress, but their pain responses may even influence their subsequent social and behavioral development. Repetitive painful stimuli have been associated with behavioral and emotional problems during childhood, major psychosis, altered responses to pain, and intractable pain states in later life.<sup>1-5</sup> Thus, reducing the pain of needles is imperative in neonatal intensive care treatment protocols.

Local anesthetics such as 40% lidocaine hydrochloride or 20% benzocaine

have been used for the relief of procedural pain, but they have produced drawbacks such as local irritation, systemic toxic effects, and inadequate analgesia. A major problem with previous methods of topical anesthesia was that the keratinized epidermis formed an effective barrier to drug penetration; any increase in the concentration of the drug to overcome this obstacle resulted in greater adverse effects. Since the advent of eutectic mixture of local anesthetics (EMLA), a 1:1 oil-in-water emulsion of a low (5%) concentration of lidocaine and prilocaine hydrochloride, effective topical analgesia of intact skin is now feasible without the need for subcutaneous injections or exposure to high concentrations of local anesthetics. The efficacy of EMLA for the treatment of procedural pain in children and adults is well established.<sup>6</sup>



**Figure 1.** Study flowchart. EMLA indicates eutectic mixture of local anesthetics.

In neonates, EMLA has been shown to diminish pain during circumcision,<sup>7,8</sup> venipuncture, arterial puncture,<sup>9</sup> and percutaneous venous catheter placement.<sup>10</sup> However, the efficacy data for these procedures is limited.<sup>11</sup> Although 3 trials<sup>12-14</sup> have shown the usefulness of EMLA in alleviating the pain of lumbar puncture in older children, only 1 randomized controlled study<sup>15</sup> has evaluated its use in newborns.

Our study was designed to test the efficacy of topical EMLA in diminishing pain during lumbar puncture in newborns. A control placebo group was included, in keeping with the current practice of not using anesthesia or analgesia for this procedure.

## METHODS

### PATIENTS

The study was carried out during a period of 12 months in a 32-bed neonatal intensive care unit of a tertiary care hospital. Sixty consecutive newborns undergoing diagnostic lumbar puncture were enrolled in the study following informed consent from their parents. The criteria for inclusion in the study were postnatal age younger than 4 weeks, gestational age of 34 weeks or older, uncomplicated vaginal or cesarean delivery, 5-minute Apgar score of 7 or higher, no history of maternal medication use, absence of structural neurodevelopmental anomalies, and a rectal temperature of  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ . The neonates should not have been receiving any sedatives or analgesics. Lumbar puncture was performed to rule out meningitis in sick newborns with seizures or sepsis, according to intensive care treatment protocol.

### STUDY DESIGN

These 60 selected newborns were randomized using a computer-generated simple random-number table. Thirty numbers (generated between 1 and 60) were assigned to the study (EMLA) group; the rest were given to the placebo group. These neonates received either EMLA (Astra Pharmaceuticals, Hertfordshire, England) or the placebo cream in a double-blind manner. **Figure 1** depicts the study flowchart. The placebo cream consisted of an inert oil that was not differentiable from EMLA with respect to appearance and odor. Written informed consent was obtained from the parents, and the study was approved by the institutional research board, including ethical clearance.

## PROCEDURE

The cream (1 g) was uniformly applied to an area of 1 sq in at the site of the procedure and covered with an occlusive dressing 60 to 90 minutes before the scheduled time of the lumbar puncture. The newborn was then placed in a servomechanism-controlled open care system. The dressing was removed immediately prior to the procedure, and any local reactions were noted. The skin was wiped dry, disinfected, and draped according to standard aseptic procedures. The lumbar puncture was performed in the left lateral position with a 24-gauge needle. The procedure comprised the following 8 events: baseline (preprocedural 60 to 90 minutes before EMLA application), preparation, positioning, needle insertion, needle in place, needle withdrawal, 5-minute postprocedural period (5 minutes after needle withdrawal), and 1-hour postprocedural period. All lumbar punctures were carried out by the same person (G.K.).

## OUTCOME VARIABLES

Physiological responses (ie, heart rate and transcutaneous oxygen saturation level) were quantified and monitored using a compact vital signs monitor (BP-88; Colin Corporation, Komaki, Japan). The measurement accuracy (SD) for the heart rate was  $\pm 1$  beat per minute, and the display update was within 1.2 seconds. The measurements could be performed at a particular point in time. It was also possible to generate a trend and list all of the vital parameters of a particular neonate in the last 24 hours. The mean value for each event was used for comparisons between groups.

Facial expressions were recorded during all events on a video camera mounted on a tripod at the newborn's bedside. The camera provided a continuous close-up view of the neonate's face. Videotapes were then coded by a single person in a blinded manner, according to the Neonatal Facial Coding System developed by Grunau and Craig<sup>16</sup> and simplified by Rushforth and Levine.<sup>17</sup> The coding and scoring were carried out using a slow-motion and stop-frame playback system. Four items of facial action (brow bulge, eye squeeze, nasolabial furrow, and open mouth) and the presence of crying were used as measures of behavioral response to pain. Each response was given a score of 1 if present and 0 if absent, for a possible total ranging from 0 to 5.

The physiological and behavioral measures were serially recorded at all 8 events during a single lumbar puncture procedure. Following the procedure, the newborn was closely monitored for a period of 24 hours for the presence of any local or systemic adverse effects linked to EMLA application, particularly central cyanosis suggestive of methemoglobinemia.

## STATISTICAL ANALYSIS

The sample size was estimated according to a formula for hypothesis testing<sup>18</sup> for the difference between 2 population means with an equal sample size in both groups. A mean  $\pm$  SD heart rate difference of at least  $15 \pm 15$  beats per minute was considered clinically important. Setting an  $\alpha$  value of .05 and a  $\beta$  value of .10, 21 newborns per group were needed. Demographic characteristics between groups were compared using an unpaired *t* test for equality of means and the  $\chi^2$  or Fisher exact test for equality of proportions.

A 1-sample Kolmogorov-Smirnov test was used to investigate whether heart rate and oxygen saturation values were normally distributed. Repeated-measures analysis of variance was fit to the outcome variables (means of heart rate, oxygen saturation level, and total behavioral score), with group (EMLA vs placebo) as a between-subject factor and event (baseline, preparation, positioning, needle insertion, needle in place, needle withdrawal, 5-minute postprocedural period, and 1-hour postpro-

**Table 1. Heart Rate in EMLA Group vs Placebo Group Before, During, and After Lumbar Puncture in Newborns\***

Event	Heart Rate, beats/min		
	EMLA Group (n = 30)	Placebo Group (n = 30)	Mean Difference (95% CI)
1. Preprocedural (1 h before)	144.0 ± 2.69	140.6 ± 2.36	3.43 (-3.73 to 10.6)
2. Preparation	156.3 ± 2.16	164.5 ± 2.75	-8.2 (-15.2 to -1.20)
3. Positioning	164.9 ± 2.16	171.0 ± 2.96	-6.07 (-13.4 to 1.27)
4. Needle insertion	159.3 ± 2.34	175.2 ± 2.66	-15.93 (-23.0 to -8.83)
5. Needle in place	144.8 ± 2.61	147.2 ± 2.59	-2.4 (-9.77 to 4.97)
6. Needle withdrawal	153.8 ± 2.57	167.3 ± 2.49	-13.47 (-20.63 to -6.31)
7. Postprocedural (5 min after)	144.8 ± 2.61	147.2 ± 2.59	-2.4 (-9.76 to 4.97)
8. Postprocedural (1 h later)	140.9 ± 2.40	139.0 ± 1.85	1.9 (-4.17 to 7.97)

Abbreviations: CI, confidence interval; EMLA, eutectic mixture of local anesthetics.

\*Data are presented as mean ± SE unless otherwise indicated. Between-subjects effects were calculated using repeated-measures analysis of variance ( $P < .001$  for overall differences within groups;  $P = .04$  for overall differences between groups). Events 2, 3, 4, and 6 are significantly different ( $P < .05$ ) from respective baseline (event 1) values in both the EMLA and placebo groups. Additionally, events 5 and 7 are significantly different ( $P < .05$ ) from event 1 in the placebo group.

**Table 2. Oxygen Saturation Level in EMLA Group vs Placebo Group Before, During, and After Lumbar Puncture in Newborns\***

Event	Oxygen Saturation Level, %		
	EMLA Group (n = 30)	Placebo Group (n = 30)	Mean Difference (95% CI)
1. Preprocedural (1 h before)	96.0 ± 0.53	95.6 ± 0.51	0.47 (-1.01 to 1.95)
2. Preparation	86.8 ± 1.04	85.8 ± 1.42	0.97 (-2.54 to 4.48)
3. Positioning	83.9 ± 1.56	80.2 ± 1.62	3.70 (-0.79 to 8.20)
4. Needle insertion	83.7 ± 1.80	78.6 ± 2.13	5.07 (-0.52 to 10.66)
5. Needle in place	85.1 ± 1.63	84.0 ± 1.50	1.07 (-3.37 to 5.50)
6. Needle withdrawal	89.0 ± 1.64	84.9 ± 1.51	4.13 (-0.33 to 8.60)
7. Postprocedural (5 min after)	94.5 ± 0.68	93.6 ± 0.74	0.87 (-1.14 to 2.88)
8. Postprocedural (1 h later)	95.8 ± 0.53	96.0 ± 0.52	-0.13 (-1.62 to 1.35)

Abbreviations: CI, confidence interval; EMLA, eutectic mixture of local anesthetics.

\*Data are presented as mean ± SE unless otherwise indicated. Between-subjects effects were calculated using repeated-measures analysis of variance ( $P < .001$  for overall differences within groups;  $P = .35$  for overall differences between groups). Events 2, 3, 4, 5, and 6 are significantly different ( $P < .05$ ) from respective baseline (event 1) values in both the EMLA and placebo groups.

cedural period) as the within-subject factor. Mean baseline values were individually compared with each of the other 7 values. The EMLA and placebo groups were also compared at all 8 events with the help of an unpaired *t* test for equality of means. Significance was set at  $P = .05$  (2-tailed test); however, if multiple comparisons were involved, the significance was set at  $P = .01$ . Analysis was conducted using Windows-based SPSS version 10.0 statistical software (SPSS Inc, Chicago, Ill).

## RESULTS

Sample characteristics for the 60 selected newborns satisfying the inclusion criteria were comparable for both groups. The mean ± SD birth weight was 2219 ± 577 g for the EMLA group and 2190 ± 599 g for the placebo group, and the mean gestational age was 37.4 weeks for the EMLA group and 37.2 weeks for the placebo group. Lumbar puncture was performed at a mean postconceptional age of 3.5 days for the EMLA group and 3.2 days for the placebo group. The male-female ratio was 19:11 in the EMLA group and 13:17 in the placebo group. In the EMLA group, 16 newborns were an appropriate weight for their gestation period as compared with 14 who were small for their gestational age; this ratio was 21:9 in the placebo group.

Mean ± SE heart rate, oxygen saturation level, and total behavioral score for the EMLA group vs placebo group at different events are presented in **Tables 1, 2, and 3**. Mean ± SD heart rate, oxygen saturation level, and total behavioral score for the 2 groups are pictorially compared in **Figures 2, 3, and 4**.

Heart rate for both groups was significantly higher from baseline at all events except in resting states; that is, when the needle was placed and at both the 5-minute and 1-hour postprocedural time points (Table 1). Heart rate was significantly different between groups ( $P = .04$ ) and between events ( $P < .001$ ). Differences in heart rate ranged from 13 to 16 beats per minute and 12 to 35 beats per minute between groups and events, respectively (Figure 2). The difference from baseline value was significantly lower for the EMLA group compared with the placebo group at insertion and withdrawal of the needle ( $P < .001$ ).

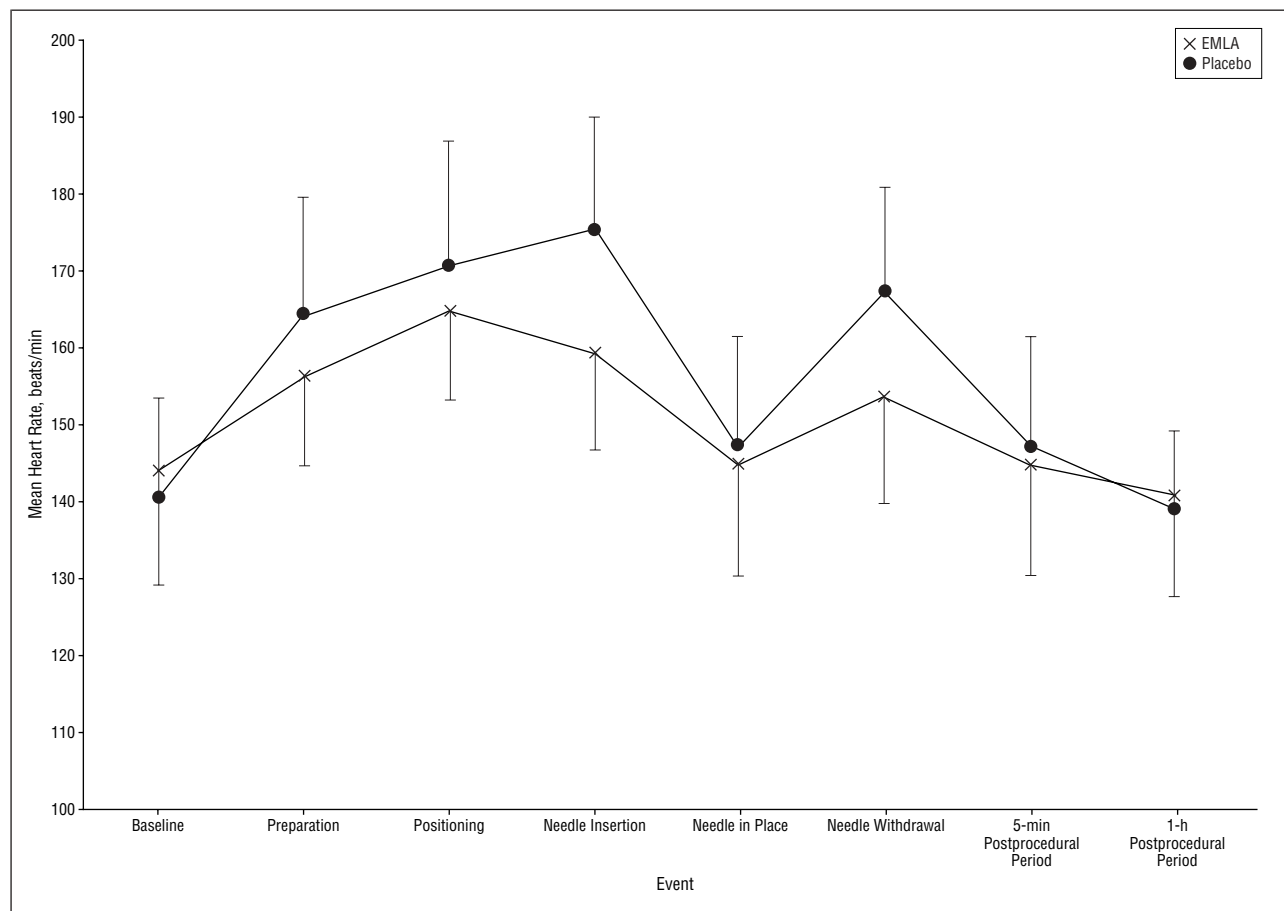
Oxygen saturation level (Table 2) was significantly different between events ( $P < .001$ ) but comparable between groups ( $P = .35$ ). The magnitude of the mean difference between events ranged between 7% and 17% (Figure 3). Both groups showed significant decreases in oxygen saturation level across all events from baseline except for the postprocedural time points (Table 2). The percentage change

**Table 3. Total Behavioral Score in EMLA Group vs Placebo Group Before, During, and After Lumbar Puncture in Newborns\***

Event	Total Behavioral Score		
	EMLA Group (n = 30)	Placebo Group (n = 30)	Mean Difference (95% CI)
1. Preprocedural (1 h before)	0.70 ± 0.15	0.27 ± 0.08	0.53 (0.20 to 0.87)
2. Preparation	3.50 ± 0.33	4.27 ± 0.27	-0.77 (-1.62 to 0.09)
3. Positioning	4.20 ± 0.28	4.97 ± 0.03	-0.77 (-1.34 to -0.20)
4. Needle insertion	4.00 ± 0.32	5.00 ± 0.00	-1.00 (-1.65 to -0.35)
5. Needle in place	1.87 ± 0.31	3.60 ± 0.34	-1.73 (-2.66 to -0.81)
6. Needle withdrawal	1.83 ± 0.30	3.90 ± 0.33	-2.07 (-2.96 to -1.17)
7. Postprocedural (5 min after)	0.70 ± 0.20	0.90 ± 0.24	-0.20 (-0.82 to 0.42)
8. Postprocedural (1 h later)	0.13 ± 0.06	0.07 ± 0.04	0.07 (-0.09 to 0.22)

Abbreviations: CI, confidence interval; EMLA, eutectic mixture of local anesthetics.

\*Data are presented as mean ± SE unless otherwise indicated. Between-subjects effects were calculated using repeated-measures analysis of variance ( $P < .001$  for overall differences within groups;  $P < .001$  for overall differences between groups). Events 2, 3, 4, 5, and 6 are significantly different ( $P < .05$ ) from respective baseline (event 1) values in both the EMLA and placebo groups.

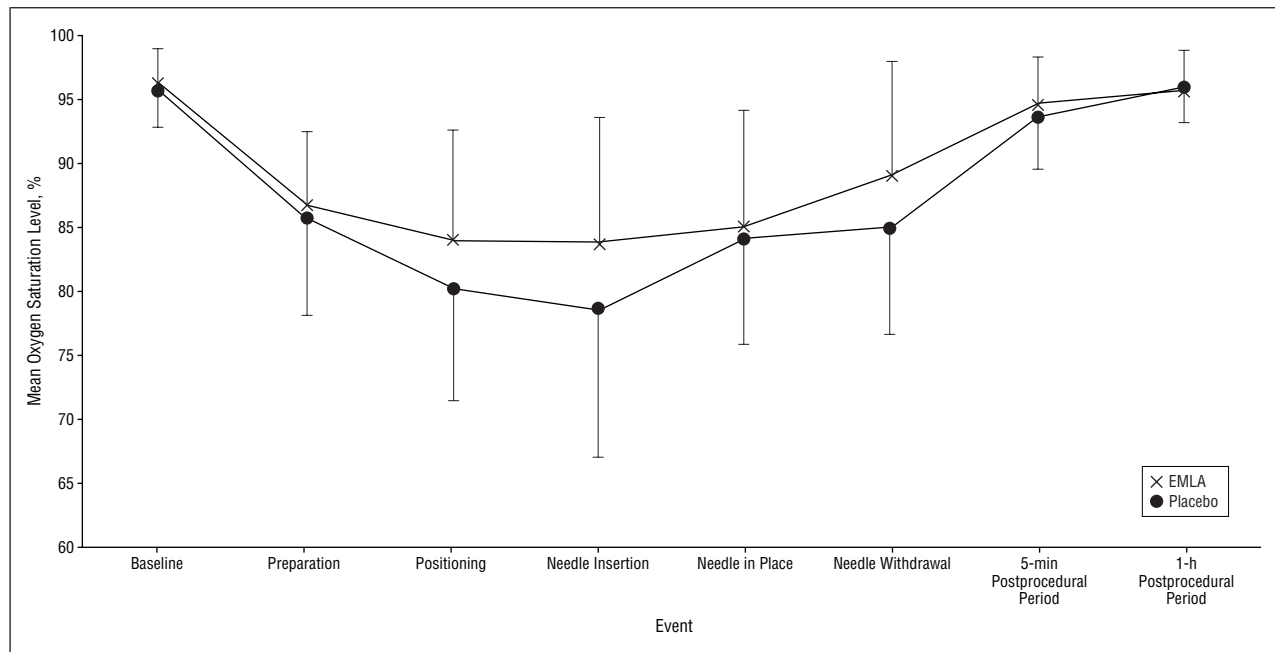


**Figure 2.** Comparison of mean ± SD heart rate between the eutectic mixture of local anesthetics (EMLA) group and placebo group before, during, and after lumbar puncture in newborns.

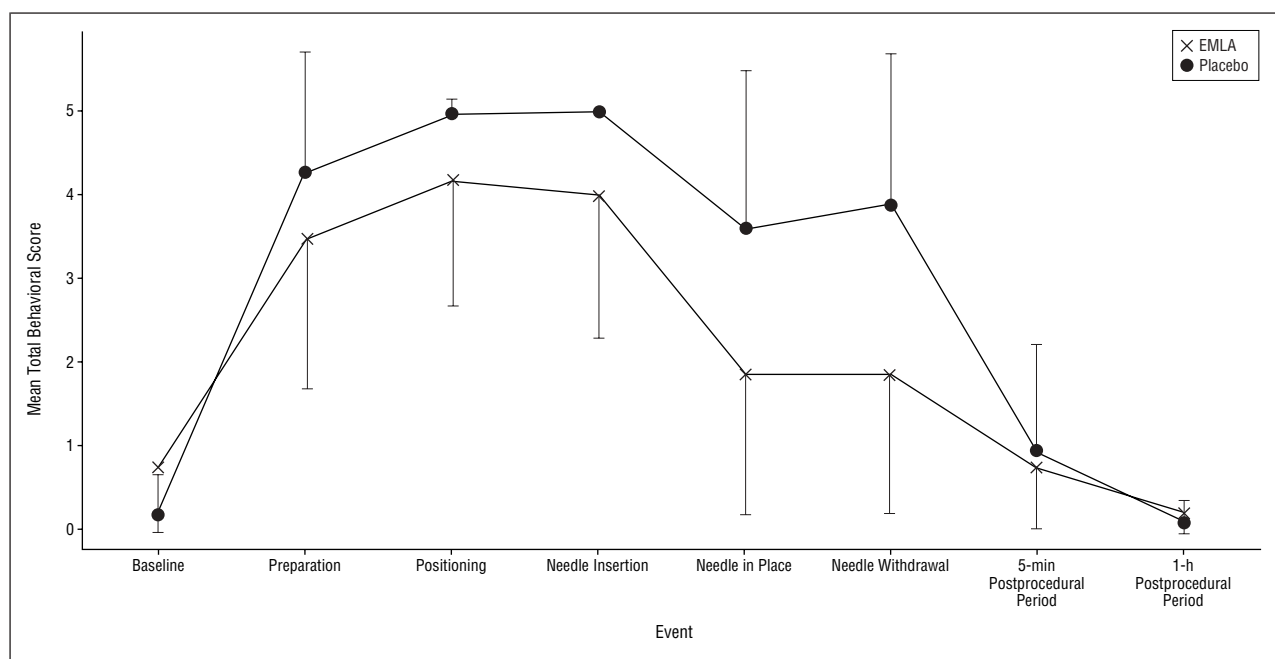
from the initial baseline value was found to be smaller in the EMLA group compared with the placebo group during positioning, needle insertion, and needle withdrawal; differences were not statistically significant. The maximum dip in oxygen saturation level compared with baseline was observed at needle insertion, the magnitude being 12% in the EMLA group and 17% in the placebo group.

Total behavioral score, comprising facial actions and crying, was significantly different between groups (range,

15%-35%;  $P < .001$ ) and events (range, 22%-95%;  $P < .001$ ) (Table 3). Behavioral score for both groups was significantly higher from baseline at all events except the 2 postprocedural periods (5 minutes and 1 hour). Behavioral score was significantly higher from baseline for the placebo vs EMLA group at needle insertion, needle in place, and needle withdrawal ( $P < .001$ ). The maximum response for all 5 behavioral parameters was seen during positioning and needle insertion in the placebo group, whereas



**Figure 3.** Comparison of mean  $\pm$ SD oxygen saturation level between the eutectic mixture of local anesthetics (EMLA) group and placebo group before, during, and after lumbar puncture in newborns.



**Figure 4.** Comparison of mean  $\pm$ SD total behavioral score between the eutectic mixture of local anesthetics (EMLA) group and placebo group before, during, and after lumbar puncture in newborns.

in the EMLA group, the maximum response was seen during positioning only (Figure 4). Another interesting observation was the presence of 100% positivity in the placebo group during needle insertion for all 5 parameters; in the EMLA group, none of the events were characterized by the presence of all 5 behavioral parameters.

No adverse effects, either local (except temporary blanching of the skin observed during removal of the occlusive dressing) or systemic, were observed with EMLA or placebo. Lumbar puncture was traumatic on the first

attempt in 2 and 3 cases in the EMLA and placebo groups, respectively. No case required more than 2 attempts.

#### COMMENT

This study substantiates the previous observations: lumbar puncture is a stressful procedure, and neonates exhibit demonstrable pain responses in the form of increased heart rate, decreased oxygen saturation level, and presence of facial responses and crying during the proce-



### What This Study Adds

Reducing procedural pain in newborns is gaining recognition. Eutectic mixture of local anesthetics, a topical agent, has been successfully used during circumcision and in obtaining vascular access in newborns. However, its efficacy in reducing the pain of needles during lumbar puncture is unproven.

This study establishes that EMLA is an efficacious agent for reducing the pain associated with needle insertion and withdrawal during lumbar puncture in newborns, evidenced by lower heart rate and less facial actions and crying in the intervention group.

ture. Destabilization was greatest during positioning of the newborn and insertion of the needle. Because it is a good superficial anesthetic agent,<sup>14</sup> EMLA attenuated the pain responses during insertion and withdrawal of the needle but did not affect the handling and positioning of the neonate. This was shown by maximum pain responses occurring during insertion of the needle in the placebo group in contrast to the EMLA group, in which the variation in outcome measures was greatest during positioning.

The stress associated with lumbar puncture could not be eliminated; significant changes from baseline to most events occurred even in the EMLA group. A significant difference was noticed for all parameters between baseline and positioning. Positioning the newborn for the procedure resulted in crying, facial grimacing, a significant increase in heart rate, and a diminished oxygen saturation level before the needle was inserted. A previous study<sup>19</sup> has demonstrated that handling and immobilization significantly alter the magnitude of the neonate's responses to a painful stimulus. Positioning is an integral part of lumbar puncture and cannot be avoided; although EMLA could do nothing about the stress imposed on the newborn during positioning, it helped reduce the pain during needle insertion.

To our knowledge, only 1 earlier study has evaluated the efficacy of EMLA for lumbar puncture in newborns. Enad et al<sup>15</sup> randomly assigned 49 neonates to 1 g of EMLA or placebo in a blinded manner for 60 minutes before lumbar puncture. Heart rate, oxygen saturation level, and behavioral response (scored from 0 to 3) were assessed. Percent change from baseline values did not differ between groups, suggesting that EMLA is ineffective for the treatment of pain from lumbar puncture. The lack of efficacy was attributed to the destabilizing nature of the procedure, inadequate amount of cream, or inadequate duration of application. No details of the study were provided, and only an abstract is currently available; thus, a critical analysis of the methods and results is impossible.

Our study has its own limitations. Although no statistically significant differences were noted between groups, the study population was not entirely homogeneous. Subjects included a mix of neonates who were both term and preterm, healthy and small for their gestational age, and weighing less or more than 2500 g (the cutoff for low birth weight). The severity of illness was not graded, and responses were not analyzed accordingly. Although no adverse effects were noted in any of

the subjects, the serum levels of lidocaine and prilocaine were not measured. The efficacy of EMLA was tested but not compared with other methods of pain control. Another potential limitation is the higher baseline pre-procedural behavioral score in the EMLA group compared with the placebo group. However, the clinical significance of this chance difference is limited. A higher baseline score in the EMLA group would only help to validate our claim for rejecting the null hypothesis.

This study shows that EMLA is an effective agent for reducing the pain of needles during lumbar puncture in neonates. Further studies are required in a homogeneous group of subjects because the effectiveness of EMLA may differ with gestation, weight, thickness of the skin, and presence of subcutaneous fat. This agent needs to be compared with other modalities of neonatal pain control such as pacifiers, oral sucrose, or topical tetracaine. Other interventions in conjunction with EMLA such as less stressful positioning, environmental manipulation, and other nonpharmacological or behavioral measures should be investigated to prevent, reduce, or eliminate the stress and pain associated with lumbar puncture in sick newborns.

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