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KEY WORDS
preterm, pain, PIPP, DAN, sucrose, EMLA, venipuncture

ABBREVIATIONS
DAN—Douleur Aigüe Nouveau-ńe
PIPP—Premature Infant Pain Profile

This trial has been registered at www.clinicaltrials.gov (identifier NCT00470080).

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WHAT'S KNOWN ON THIS SUBJECT: Venipunctures are painful in preterm neonates. Oral sucrose has a moderate effect on reducing venipuncture-induced pain in neonates. Sucrose should be combined with other analgesic methods to improve analgesia. Data on the analgesic efficacy of EMLA cream in neonates are conflicting.

WHAT THIS STUDY ADDS: The combination of sucrose plus EMLA cream was more effective than sucrose alone in reducing venipuncture-induced pain in preterm neonates. The use of this combination analgesic strategy will improve pain management of venipuncture in preterm neonates.

abstract

OBJECTIVE: The goal of this study was to compare the analgesic effect of sucrose with that of the combination of sucrose and the local anesthetic cream EMLA during venipuncture in preterm neonates.

METHODS: This randomized, double-blind prospective study included infants younger than 37 weeks' gestational age during 1 routine venipuncture for blood sampling. Each child randomly received either sucrose plus application of a placebo cream (S group) or sucrose plus EMLA cream (S+E group) before venipuncture. Venipuncture-induced pain was assessed through videotapes of the procedures by using the Douleur Aiguë Nouveau-né (DAN) behavioral scale. Pain was assessed at 2 phases: during venipuncture (from needle introduction to its removal) and during the recovery period (30 seconds after needle removal). Pain scores over time and between treatments were compared by using repeated-measures analysis of variance.

RESULTS: The study included 76 children (37 in the S group, 39 in the S+E group). Mean (SD) DAN pain scores for the S group and the S+E group were 7.7 (2.1) and 6.4 (2.5), respectively, during venipuncture and 7.1 (2.8) and 5.7 (3.3) during the postinjection period. A significant time and treatment effect in favor of the S+E group was observed.

CONCLUSION: The combination of sucrose and EMLA cream revealed a higher analgesic effect than sucrose alone during venipuncture in these preterm infants. *Pediatrics* 2011;128:e63–e70

During routine care of neonates, some painful invasive procedures are usually inevitable in both healthy and sick neonates. Alleviation of pain caused by minor invasive procedures in neonates is important for humane reasons as well as for avoiding the acute physiologic instability, such as hypoxemia or hemodynamic variations, associated with invasive interventions.[1] Research suggests that pain experienced in the neonatal period might have long-term effects later in life.[2–4] For these reasons, pharmacologic and nonpharmacologic pain prevention techniques have been recommended for painful procedures such as venipuncture,[5,6] which is the preferred method for blood sampling in neonates.[7,8]

A number of studies have shown that orally administered sweet-tasting solutions reduce signs of pain during minor invasive procedures in premature and term newborns.[9–11] Although effective at reducing pain, the efficacy of these solutions is moderate for various infant populations.[12,13] Thus, other strategies or combinations of analgesic methods are necessary to further reduce neonatal procedure-related pain. For venipuncture, 1 such option is combining sweet solutions with EMLA (Astra, Stockholm, Sweden), which has been demonstrated to be effective in children and infants.[14] Studies have shown EMLA to be safe for use in neonates, and its use has therefore been recommended for term newborns.[15,16] However, studies on EMLA-induced pain relief during venipuncture in newborns have led to conflicting conclusions. Larsson et al[17] and Lindh et al[18] found that EMLA reduced signs of pain caused by venipuncture in healthy newborns, but Acharya et al[19] did not observe any behavioral or physiologic differences between healthy preterm infants treated with EMLA and those given placebo.

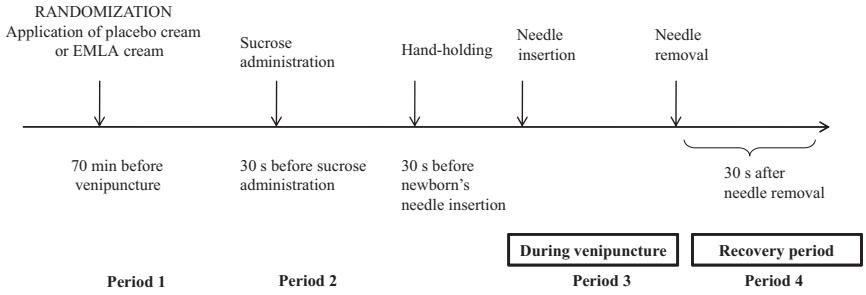

FIGURE 1
Schematic time line of events depicting the experimental protocol used in this study. Schematic time points are not proportional to actual duration.

Reducing venipuncture-induced pain is important because it has been shown that pain scores observed in neonates are very high if venipuncture is performed without treatment.[20] One study found that the median score on the Douleur Aiguë Nouveau-né (DAN) behavioral scale, which ranges from 0 to 10, was 10 (interquartile range: 7.5–10) in term neonates undergoing venipuncture after receiving an oral placebo.[20] Furthermore, venipuncture is a frequent procedure in hospitalized neonates; an epidemiologic prospective study reported that 430 neonates admitted to NICUs underwent a mean of 3.1 venipunctures or venous cannula insertion during their first 2 weeks of admission.[21]

We hypothesized that the analgesic effectiveness of EMLA cream would be additive with the effect of orally administered sucrose during venipuncture in preterm neonates. The aim of the present study was to compare the analgesic effect of the combination of EMLA cream and oral sucrose with that of oral sucrose alone.

METHODS

Participants

Neonates from the NICUs of 2 French hospitals (Hôpital Armand Trousseau and Centre Hospitalier de Meaux) were enrolled in the study. The study protocol and parental consent forms were approved by the local ethics committee for the protection of human subjects in medical research. Written informed consent was obtained from parents of each child before inclusion.

Eligibility criteria were a postnatal, corrected gestational age younger than 37 weeks at entry in the study and last feeding within the previous 30 minutes or having continuous enteral feeding. Exclusion criteria were mechanical assisted ventilation or administration of continuous positive airway pressure; abnormal neurologic clinical examination; administration of sulfonamides, metoclopramide, sedatives, or analgesia within 24 hours before inclusion; known allergy to local anesthetics; porphyria; clinical instability; methemoglobinemia; Apgar scores of <7 at 1 or 5 minutes; and parents who did not understand the study protocol or French language.

Procedure

The study was prospective, controlled, randomized, and double-blind. The sequence of events is depicted in Fig 1. All venipunctures were performed for clinical purposes in a quiet observation room. Each child was included only once. The infant was placed on a preheated nursing table, and a pulse oximeter probe (Siemens 7000 monitor [Siemens Healthcare Diagnostics, Deerfield, IL]) was placed on the infant's foot. The infant's legs and feet

were uncovered to allow for observation of movements.

Infants were allocated to 1 of 2 groups: group 1 was given 30% sucrose solution orally and placebo cream (S group) and group 2 received 30% sucrose solution orally and EMLA on the skin (S+E group). No pacifier was used in this study. The research assistant placed 0.5 g of EMLA or placebo cream (Bepanthen [Bayer HealthCare, Morristown, NJ] containing vitamin B_5 and lanoline) on the dorsal aspect of the hand and covered it with a nonocclusive dressing (plastic wrap).[22] After 60 minutes, the dressing and cream were removed by the research assistant. After waiting for an additional 10 minutes to allow recovery from any constriction of the vein or any stress associated with removal of the dressing, a 0.5-mL dose of 30% sucrose solution was inserted, using a syringe, into the mouth of all infants by 1 of the 10 experienced nurses trained for this study. Participating nurses had viewed a presentation of the study, with a detailed explanation of the sequence of events they had to follow. All venipunctures were performed as standard care. Two minutes after sucrose administration, the nurse gently took the newborn's hand to visualize the vein, cleaned the skin with a local disinfectant, and performed the venipuncture with a 23-gauge needle. After blood collection, a nonadhesive bandage was applied on the puncture site, and the infant was left undisturbed on the nursing table for 3 minutes. Any parent wishing to be present during the blood sampling was allowed to do so but was asked not to talk to or comfort the infant.

All the venipunctures were videotaped with a color digital camera by the research assistant. Facial actions, body movements, physiologic parameters, behavioral state, and crying time were captured on the camera, which included a real-time counter. The time periods of the procedure were identified by voice as they occurred and recorded on the videotape. For the purpose of the study, only the first venipuncture attempt was videotaped and analyzed. The rate of successful sampling (measured as obtaining blood in the needle), the time needed for successful completion of the procedure, and the number of attempts were recorded.

TABLE 1 DAN Behavioral Scale for Rating Acute Pain in Neonates

	Score
Facial expressions	
Calm	0
Snivels and alternates gentle eye opening and closing	1
Intensity of eye squeeze, brow budge, or nasolabial furrow	
Mild, intermittent to return to calm[a]	2
Moderate[b]	3
Very pronounced, continuous[c]	4
Limb movements	
Calm or gentle movements	0
Intensity of pedaling, toes spread, legs tensed and pulled up, agitation of arms, withdrawal reaction	
Mild, intermittent with return to calm[a]	1
Moderate[b]	2
Very pronounced, continuous[c]	3
Vocal expression	
No complaints	0
Moans briefly (for intubated child, looks anxious or uneasy)	1
Intermittent crying (for intubated child, expression of intermittent crying)	2
Long-lasting crying, continuous howl (for intubated child, expression of continuous crying)	3

[a] Present during less than one-third of the observation periods.
[b] Present during one-third to two-thirds of the observation periods.
[c] Present during more than two-thirds of the observation periods.

Pain Assessment

When all inclusions were completed, 2 specially trained observer nurses independently assessed the recordings to assess the arousal state, the pain induced by the procedures using the DAN scale (which was the primary outcome measure [Table 1]), the Premature Infant Pain Profile (PIPP) scale (which was the secondary outcome measure), and crying time. These observer nurses had not participated in the venipunctures. They were not members of the unit staff and were unaware of the design or treatment assignments, or the objective of the study.

For the purpose of the assessment, the procedure was divided into 3 observation periods. The baseline period was the 30-second period that preceded the holding of the newborn's hand. For the PIPP score, the physiologic values of the first second of this period served as the reference for the changes during the rest of the baseline period. The venipuncture period was the second period (the time from skin puncture until removal of the needle). The last period, the recovery period, was the first 30 seconds after the removal of the needle. The recovery period was included in the analysis because it is well known that during painful procedures, pain continues for a variable time after the noxious stimulus stops.

Observers assessed arousal state by using Prechtl's observational rating system: (1) eyes closed, regular respiration, no movements; (2) eyes closed, irregular respiration, gross movements; (3) eyes open, no gross movements; (4) eyes open, continual gross movements, no crying; and (5) eyes open or closed, fussing or crying.[23]

The DAN scale is a behavioral scale developed to rate acute pain in term and preterm neonates. Scores range from 0 (no pain) to 10 (maximum pain).[24] The scale is used to evaluate 3 items: facial expressions, limb movements, and vocal expression (Table 1). This scale has been presented elsewhere.[20] In the validation study, painful procedures yielded scores from 1 to 10, with 95% of scores $\geq$3.[24] No study has yet established cutoff points for mild, moderate, or severe pain with this scale, but DAN median pain scores can reach 10 for venipunctures performed without analgesic treatment in neonates.[20]

The PIPP scale is a multidimensional measure developed to assess acute pain in preterm and term infants.[25] It is based on gestational age, behavioral state, heart rate, oxygen saturation, and 3 facial reactions (brow bulge, eye squeeze, and nasolabial furrow). The range of scores for the PIPP scale is different from the DAN scale. In preterm infants, scores range from 0 (no pain) to 21 (maximum pain). Observer nurses could stop and restart the videotape as many times as they needed to establish a score. Observers determined a pain score for the baseline, venipuncture, and recovery periods. As recommended by the authors of both the DAN and PIPP scores, the percentage of time that signs were exhibited during each observation period determined the score of behavioral items (Table 1). Physiologic and behavioral parameters were obtained from videotapes. Each observer conducted an independent assessment, and then the 2 observers reevaluated all the procedures for which each observer's scores had not been identical during their first assessment. This yielded final sets of pain scores that reflected perfect agreement between the 2 observers.

Assessment of Adverse Effects

Local skin reactions, chocking, coughing, vomiting, sustained tachycardia (heart rate: >200 beats per minute), bradycardia (heart rate: <80 beats per minute), sustained tachypnea (respiratory rate: >80 breaths per minute), bradypnea (respiratory rate: <20 breaths per minute), and oxygen desaturation (<80%) for >15 seconds after the administration of sucrose were determined by the research assistant.

Assignment

An assistant not involved in the study performed the randomization in advance in blocks of 8 using a random number table. Forty infants were allocated to the S group and 40 to the S+E group. Placebo or EMLA cream syringes were covered with identical stickers. Treatment allocations were placed in opaque sealed envelopes, and the syringes were numbered 1 to 80; investigators were blinded to these allocations. Codes of allocation were kept secret by the assistant who performed randomization, and they were uncovered only after all videotape assessments were accomplished.

Sample Calculation

Calculations were conducted with the NCSS-PASS 2002 (Number Cruncher Statistical Systems, Kaysville, UT) statistical software using the module designed for 2-sample *t* test power analysis to approximate the sample needed for a repeated-measure analysis, including a between-group analysis. We calculated that a sample size of 37 for each group would achieve 80% power to detect a difference of 2 points in the group means in the primary outcome measure, with estimated SDs of 3.0 for each group and an α risk of 0.05 using a 2-sided 2-sample *t* test. We decided to randomly assign 40 infants to each group to cover potential problems with video recordings and dropouts after venipuncture.

Statistical Analysis

Pain scores over time and between treatments were compared by using repeated-measures analysis of variance. Before this analysis, we verified whether baseline pain scores (ie, before hand holding) were similar between the 2 analgesic interventions. The model included 1 within-subject factor (time) that had 2 levels (venipuncture period and recovery period) and 1 between-subject factor (treatment) that had 2 levels corresponding to each of the 2 analgesic interventions. In all analyses, $P < .05$ was considered statistically significant. The statistical analysis was conducted by using SPSS 14 for Windows (SPSS Inc, Chicago, IL).

RESULTS

From July through September 2007, 80 infants were randomly assigned to treatment. Four infants were excluded after randomization (3 in the S group and 1 in the S+E group) because of technical video problems; thus, the final analysis included 37 infants in the S group and 39 in the S+E group. Figure 2 shows the flow of study participants. The demographic characteristics of the participating children are shown in Table 2. Because the mean postnatal age at venipuncture was lower ($P = .031$) in the S+E group compared with the S group (34.4 vs 35.1 weeks), we analyzed the correlation between postnatal age at venipuncture and DAN pain scores during venipuncture. The Spearman ρ coefficient was 0.207 ($P = .073$). Parents were present during procedures performed in 7 infants for both the S group (mothers for 5 infants, and both parents for 2 infants) and the S+E group (mothers for 6 infants, and both parents for 1 infant).

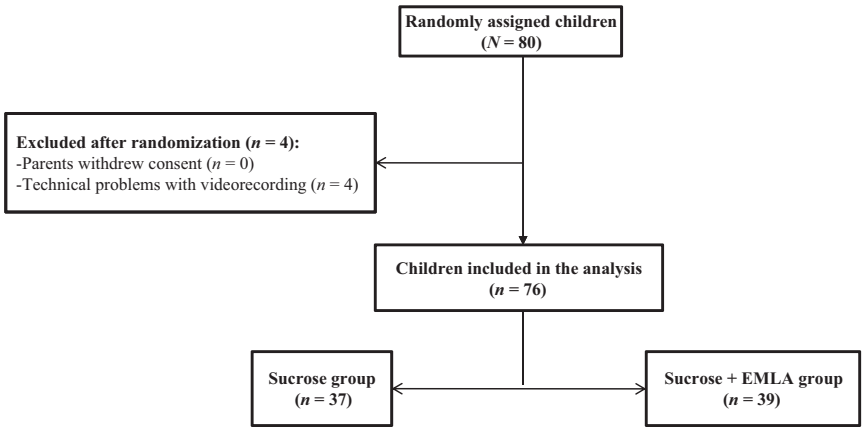

FIGURE 2
Flow diagram of the trial profile.

TABLE 2 Demographic Data of the Study Newborns

	S Group ($N = 37$)	S+E Group ($N = 39$)	P
Gestational age, wk			.587
Mean (SD)	32.6 (2.33)	32.3 (2.01)	
Range	25.4–36.5	28.4–36	
Postnatal age at venipuncture, wk		.031	
Mean (SD)	35.1 (1.38)	34.4 (1.31)	
Range	30–36.8	32–36.7	
Days of life at venipuncture			
Mean (SD)	17.1 (13.7)	14.3 (13.9)	.372
Range	1–49	1–68	
Male gender, *n* (%)	26 (70.2)	19 (48.7)	.06
Birth weight, g		.366	
Mean (SD)	1727 (519)	1831 (477)	
Range	810–3050	1019–2030	
Apgar score at 1 min, mean (SD)	8 (0–10)	8 (1–10)	.753
Apgar score at 5 min, mean (SD)	10 (3–10)	10 (6–10)	.643
Vaginal delivery, *n* (%)	21 (56.8)	14 (36.0)	.07
Principal diagnosis			
Suspected perinatal infection	12	15	
Jaundice	27	32	
Transient tachypnea of the newborn	7	5	
Hyaline membrane disease	6	5	

DAN and PIPP Pain Scores

The 2 independent observer nurses initially agreed on 75 of 76 DAN assessments and on 74 of 76 PIPP assessments. They then together assessed the 1 DAN and 2 PIPP conflicting assessments to reach a final common score.

Baseline DAN and PIPP scores were similar for the 2 interventions. For the S group and S+E group, respectively, the mean (SD) baseline DAN scores were 2.2 (2.4) and 2.1 (2.5) ($P = .843$) and the mean baseline PIPP scores were 4.2 (1.9) and 4.5 (2.2) ($P = .645$).

Mean DAN and PIPP scores for the 3 periods are summarized in Table 3. In terms of the primary outcome measure, mean (SD) DAN pain scores for S and S+E treatments were 7.7 (2.1) and 6.4 (2.5), respectively, during the venipuncture period and 7.1 (2.8) and 5.7 (3.3) during the recovery period. Analysis of scores from serial measurements showed a significant time ($P = .047$) and treatment ($P = .018$) effect in favor of the S+E treatment; DAN mean (SE) values were 7.0 (0.262) and 6.4 (0.347) for the venipuncture and recovery periods, respectively, and 7.4 (0.386) and 6.0 (0.376) for the S and S+E groups, respectively. Regarding the secondary outcome measure, mean (SD) PIPP pain scores for the S and S+E treatments were 8.5 (3.1) and 7.2 (3.2), respectively, during the venipuncture period and 7.7 (2.9) and 7.1 (3.0) during the recovery period. Analysis of scores from serial measurements showed neither a time ($P = .241$) nor a treatment ($P = .112$) statistically significant effect; PIPP mean (SE) values were 7.8 (0.359) and 7.4 (0.335) for the venipuncture and recovery periods, respectively, and 8.0 (0.419) and 7.2 (0.408) for the S and S+E groups.

TABLE 3 DAN and PIPP Pain Scores Before Venipuncture (Baseline), During Venipuncture, and During the Postinjection Period (Recovery)

Group	S Group ($N = 37$), Mean (SD)	S+E Group ($N = 39$), Mean (SD)
DAN score		
Baseline	2.2 (2.4)	2.1 (2.5)[a]
Venipuncture	7.7 (2.1)	6.4 (2.5)
Recovery	7.1 (2.8)	5.7 (3.3)
PIPP score		
Baseline	4.2 (1.9)	4.5 (2.2)[b]
Venipuncture	8.5 (3.1)	7.2 (3.2)
Recovery	7.7 (2.9)	7.1 (3.0)

For DAN scale analysis of scores from serial measurements (including venipuncture and recovery periods), there was a significant time effect ($P = .047$) and a treatment effect ($P = 0.018$) in favor of the S+E group. For PIPP scores, the corresponding values were $P = .241$ and $P = .112$.

[a] $P = .083$ for the baseline comparison between the S group and the S+E group.

[b] $P = .645$ for the baseline comparison between the S group and the S+E group.

Twenty-nine of the 37 (78.4%) infants in the S group and 23 of 39 (59.0%) infants in the S+E group cried during venipuncture ($P = .20$). Mean (SD) crying times during all the procedures for the S group ($n = 39$) and the S+E group ($n = 37$), respectively, were 50.51 (56.90) and 41.82 (61.69) seconds ($P = .52$).

A successful sampling at first attempt, defined as obtaining blood in the nee-

dle, was observed in 30 of 37 (81.1%) infants in the S group and 34 of 39 (87.2%) infants in the S+E group ($P = .466$). Mean (SD) time needed to gain vein access in these patients was 25.7 (32.3) seconds in the S group and 27.3 (33.2) seconds in the S+E group ($P = .844$).

Adverse Effects

All observed adverse effects were minor. A mild blanching was noted in 2 of 37 (5.4%) infants in the S group, and 28 of 39 (71.8%) infants in the S+E group ($P < .001$). No erythema at the site of cream application and no adverse effects after sucrose administration were observed.

DISCUSSION

To our knowledge, this is the first study to report the additive analgesic efficacy of EMLA cream and oral sucrose during venipuncture in preterm infants. This study revealed that pain scores, as assessed by using the primary outcome measure (ie, the DAN behavioral pain scale), were lower during both the venipuncture and the recovery periods in infants receiving EMLA cream plus oral sucrose compared with those receiving only oral sucrose. On a scale of 0 to 10, the mean (SD) DAN pain scores for the S and S+E groups were 7.7 (2.1) and 6.4 (2.5), respectively, during venipuncture and 7.1 (2.8) and 5.7 (3.3) during the postinjection period. These figures showed a statistically significant treatment effect ($P = .018$). It should be noted, however, that although pain scores assessed with the secondary outcome measure (ie, the PIPP score) were also lower in the S+E group, they did not reach statistical significance. Similarly, the number of infants who cried during the procedure showed a trend to be lower in the S+E group without reaching statistical significance.

Sucrose has been largely reported to be effective at soothing procedural pain in preterm and term neonates,[11] and its use is currently recommended by many scientific societies.[26] A recent Cochrane systematic review found 20 studies that included preterm neonates.[11] These studies revealed the analgesic efficacy of sucrose in this population. Despite the proven efficacy of sucrose, it should be emphasized that its analgesic effect is moderate. Taddio et al[12] reported a moderate effectiveness to reduce pain in newborns of both diabetic and nondiabetic mothers when sucrose was used for all medical procedures performed in the first 2 days after birth. The authors stated that sucrose should not be used as the sole "analgesic" agent before procedural pain. The moderate analgesic effect of oral sucrose observed in different studies highlights the necessity to use supplemental therapeutic interventions for pain relief during venipuncture. In this context, the association of EMLA with oral sweet solutions seems an interesting option to further reduce venipuncture-induced pain. Compared with sucrose alone, in our study, the combination of sucrose plus EMLA reduced mean pain scores by 1.3 and 1.4 DAN score points during the venipuncture and recovery periods, respectively. One may wonder at the clinical significance of this reduction, because scores of 6 to 7 of 10 still indicate that the infant is experiencing moderate-to-severe pain. Nonetheless, we feel that even interventions that cause modest reductions of neonatal pain are worth considering in clinical practice. The question of the minimal clinically important difference is not yet clearly elucidated, and this task is still more challenging in neonates. According to Stevens et al,[11] this minimal clinically important difference is somewhere between 10% and 20% of the scale range. Powell et al[27] found, in older children, that a reduction of 10 points on a 0 to 100 point scale is considered clinically significant by these children. In terms of neonatal pain, we consider that all effective and safe analgesic means should be used to further reduce procedural pain in neonates. Although there is considerable interest in the use of EMLA in neonates, few studies have been conducted in this population, and these studies have yielded conflicting results. A lack of efficacy was found by Acharya et al,[19] who assessed 19 infants of 26 to 33 weeks' gestational age in a double-blind, placebo-controlled crossover study. They found no significant difference in efficacy between EMLA and placebo creams in physiologic and behavioral responses. Gradin et al[28] reported that oral glucose was more effective than EMLA to reduce venipuncture pain in term neonates. However, some other studies have shown EMLA to be effective in neonates. Lindh et al[18] observed, in term neonates, that EMLA attenuates increases in heart rate and its variability during venipuncture and concluded that EMLA was effective in this context to reduce stress. Gourrier et al[29] reported that EMLA cream was effective and safe in term and preterm neonates undergoing venipunctures and arterial punctures.

There is concern about the safety of the use of EMLA in neonates, however. The main concern is the possibility of increased methemoglobin concentrations after EMLA application. However, in various studies,[19,29–33] the regular monitoring of methemoglobin concentrations have the levels to be safe in this population.[34] In studies assessing a single application, methemoglobin concentrations were higher in the EMLA groups compared with placebo groups; these concentrations were below 5% to 6%.[34] There are currently insufficient data to determine the safety of repeated EMLA administration. In

preterm neonates, single doses ranging from 0.5 to 1.25 g applied for 30 to 180 minutes have not been reported to cause methemoglobinemia.[35] EMLA should not be used with other methemoglobin inducers. No adverse effects occurred in our study, except for a temporary blanching of the skin (28 of 39 infants in the S+E group), reflecting vasoconstriction. This adverse effect disappeared within a few minutes. The use of EMLA did not make the puncture harder to accomplish. The frequency of successful sampling was 81% in the S group and 87% in the S+E group.

The advantages of combining different analgesic strategies have been stressed in recommendations to alleviate procedural pain in neonates.[5,36] One of the most common approaches for minor procedures is the combination of sucrose and nonnutritive sucking. Its efficacy has been clearly shown.[28,37,38] From the published literature and the results of our study, it would seem useful during venipuncture in neonates to combine oral sweet solutions (which have a pharmacologic action through a likely opioid-mediated mechanism), a pacifier (which acts through a nonopioid mechanism),[39] and EMLA (which is a local anesthetic).[40]

Interpretations of these results should acknowledge 3 limitations. First, our random assignment was not computerized, and we used opaque sealed envelopes for treatment assignment. This created the risk of treatment identification by study participants. Second, we did not include a placebo group that would have allowed us to determine the absolute efficacy of each analgesic intervention. However, we felt that it would be unethical to deny children analgesia for the purposes of our study. Third, we only powered our study to detect a 2-point difference in the main outcome measure, the DAN scale. We used the PIPP scale because we had considered that the same 2-point difference would be observed with the PIPP scale. Thus, our study lacked enough power to detect a 1.2 difference in the PIPP score. Because the PIPP scores range from 0 to 21 in preterm infants, we considered that a 1-point difference within this range would probably be of very little clinical significance. This discrepancy also highlights the difficulties in assessing pain in neonates. Nonetheless, because the DAN scale is based on behavioral responses (especially facial action), which have been shown to be highly correlated with cortical pain responses,[41] we consider the results observed with this scale to be robust.

CONCLUSIONS

The results of our study add to the current evidence that the combination of EMLA cream and oral sweet solutions is additive to reduce pain during venipuncture in preterm neonates.

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