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A Systematic Review of Lidocaine-Prilocaine Cream (EMLA) in the Treatment of Acute Pain in Neonates

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ABSTRACT. *Objective.* Neonates routinely undergo painful cutaneous procedures as part of their medical treatment. Lidocaine-prilocaine 5% cream (EMLA) is a topical anesthetic that may be useful for diminishing the pain from these procedures. EMLA is routinely used in children and adults. There is substantial apprehension about its use in neonates because of concerns that it may cause methemoglobinemia. The objective of this review was to determine the efficacy and safety of EMLA as an analgesic for procedural pain treatment in neonates and provide evidence-based recommendations for clinical practice.

Methods. Systematic review techniques were used. Studies were identified using manual and computer-aided searches (Medline, EMBASE, Reference Update, personal files, scientific meeting proceedings). Behavioral (eg, facial action, crying) and physiologic (eg, heart rate, oxygen saturation, blood pressure, respiratory rate) outcome data from prospective nonrandomized controlled studies and randomized controlled trials in full-term and preterm neonates were accepted for inclusion to establish efficacy of EMLA. The risk of methemoglobinemia (defined as methemoglobin concentration >5% and requiring medical intervention) was estimated from all prospective studies.

Results. Eleven studies of the efficacy of EMLA were included in the analysis. Infant gestational age at the time of delivery ranged from 26 weeks to full-term. Two studies included data from both neonates and older infants. The following procedures were studied: circumcision (n = 3), heel lancing (n = 4), venipuncture (n = 1), venipuncture and arterial puncture (n = 1), lumbar puncture (n = 1), and percutaneous venous catheter placement (n = 1). Nine studies were randomized controlled trials. The total sample size for each study ranged from 13 to 110 neonates. The dose of EMLA used was 0.5 g to 2 g in 9 studies, and was not specified in the others. The duration of application ranged from 10 minutes to 3 hours. The three studies that investigated the efficacy of EMLA for decreasing the pain of circumcision used a randomized controlled trial design. All of them demonstrated significantly reduced crying time during the procedure in the infants in the EMLA group compared with the

infants in the control group. Facial grimacing, assessed in two of the studies, was also significantly lower in the EMLA group. Using meta-analytic techniques, the heart rate outcome data for two studies was summarized. Increases in heart rate compared with baseline values were 12 to 27 beats per minute less for the EMLA group than in the placebo group during various stages of the surgical procedure. Three studies that investigated the pain from heel lancing were randomized controlled trials; the other was a nonrandomized controlled study. None demonstrated a significant benefit of EMLA for any of the outcome measures used to assess pain (ie, behavioral pain scores, infant crying, heart rate, blood pressure, respiratory rate, oxygenation parameters). One randomized controlled study of the pain from venipuncture showed that infants treated with EMLA had significantly lower heart rates and cry duration compared with infants treated with a placebo. In one nonrandomized study, a significantly lower behavioral pain score was observed for infants treated with EMLA compared with the control group. Infant heart rate, however, did not differ between the groups. In one randomized controlled study of pain from percutaneous venous catheter placement, EMLA resulted in a significantly lower increase in heart rate and respiratory rate. Behavioral pain scores were significantly lower during arterial puncture in one nonrandomized controlled study. EMLA did not reduce physiologic changes or behavioral pain scores in one randomized controlled trial in infants undergoing lumbar puncture. Meta-analytic techniques revealed that methemoglobin concentrations did not differ between EMLA-treated and placebo-treated infants (weighted mean difference, -0.11%; 95% confidence interval, -0.31% to 0.10%). The incidence of clinically important methemoglobinemia from all prospective studies was 0% (95% confidence interval, 0.0% to 0.2%). There was insufficient data to assess the risk with multiple doses of EMLA. Four studies measured concentrations of lidocaine in the plasma of neonates who had been treated with EMLA. In all cases, concentrations were <0.3 µg/mL. Three studies that measured prilocaine detected <0.1 µg/mL.

Conclusions. EMLA diminishes pain during circumcision. It may also diminish the pain from venipuncture, arterial puncture, and percutaneous venous catheter placement; however, efficacy data for these procedures are limited. EMLA does not diminish the pain from heel lancing. Based on available data, EMLA is recommended for the treatment of pain from circumcision but not heel lance. There is insufficient data to recommend its use for other procedures. Single doses do not cause methemoglobinemia. Additional research is recommended in neonates before EMLA is used routinely for procedures other than circumcision and to determine the safety of repeated administration. *Pediatrics* 1998;101(2). URL: <http://www.pediatrics.org/cgi/content/full/101/2/e1>; *sys-*

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ABBREVIATIONS. LP, lumbar puncture; PVC, percutaneous venous catheter; EMLA, lidocaine-prilocaine 5% cream; GA, gestational age; HR, heart rate; RR, respiratory rate; BP, blood pressure; O₂, oxygen; SD, standard deviation; PIPP, Premature Infant Pain Profile; CI, confidence interval; MetHb, methemoglobin; NFCS, Neonatal Facial Coding System.

Hospitalized full-term and preterm neonates routinely undergo tissue-damaging interventions as part of their medical treatment. The skin is the site of noxious stimulation for many procedures, including heel lancing, venipuncture, arterial puncture, lumbar puncture (LP), and percutaneous venous catheter (PVC) placement. These cutaneous procedures are frequently repeated in many patients as necessitated by their clinical conditions. Analgesics are not routinely administered in clinical practice because of the relatively short duration of the intervention, perceived lack of importance of the pain, and concerns of toxicity from currently available agents. This practice is being questioned by recent evidence that neonates are capable of both perceiving and exhibiting reproducible responses to noxious stimulation. The immediate pain response is complex, involving behavioral changes such as facial grimacing and body movements, as well as physiologic, metabolic, and hormonal changes. Preliminary data suggest that pain may have long-term effects in neonates such as pain memories.^{1,2}

EMLA 5% cream (eutectic mixture of local anesthetics, lidocaine and prilocaine; Astra Pharma, Inc, Mississauga, Ontario, Canada) is a topical anesthetic used in children and adults to diminish pain from cutaneous procedures. EMLA represents a therapeutic breakthrough as it is the first topical anesthetic preparation that penetrates intact skin to provide reliable anesthesia. The usual dose for children and adults is 1 g to 2 g applied under an occlusive dressing for approximately 1 hour before the procedure.

The efficacy of EMLA for treatment of procedural pain in children and adults is well established. In neonates, however, there has been no systematic evaluation of its efficacy. There has been no evaluation of the risk of serious adverse effects. In children and adults, adverse effects are limited to transient local skin reactions such as blanching and redness. There is substantial apprehension about using EMLA in neonates because of the potential risk of methemoglobinemia from prilocaine metabolites that can oxidize hemoglobin. As compared with children and adults, neonates are believed to be at increased risk of methemoglobinemia. Neonates have a deficiency in the enzyme that reduces methemoglobin (MetHb), NADH cytochrome b₅ reductase.³ In addition, the higher body surface area to weight ratio in infants may result in higher systemic exposure from the same dose relative to adults. Preterm infants may be at even greater risk of toxicity because of immaturity in skin barrier properties⁴ that enhances percutaneous absorption of drugs.

The purpose of this review was to systematically

evaluate the efficacy and safety of EMLA as an analgesic for procedural pain in neonates, to provide evidence-based recommendations for clinical practice and to identify areas for future research.

METHODS

Literature Search

Medline was searched for relevant articles published from January 1, 1966 to December 31, 1996; EMBASE from 1993 to 1996; and Reference Update from January 1, 1995 to December 1, 1996 with the following MeSH terms or text words: "infant-newborn, pain, analgesia, anesthesia, EMLA, lidocaine-prilocaine, local anesthetics." In addition, manual searches of bibliographies, personal files, scientific meeting proceedings, and recent issues of key journals were performed. Language restrictions were not applied. Attempts were made to obtain additional data from investigators of published studies.

Inclusion Criteria

Only reports with information on neonates (for this study defined as up to 1 month of age) were included. All randomized controlled trials and cohort (nonrandomized) studies that included a placebo/unexposed group were included for the determination of efficacy. Trials of different designs, however, were handled separately. The efficacy of EMLA was reviewed for the following procedures: circumcision, heel lancing, PVC insertion, LP, and venous/arterial puncture. Because neonates respond to noxious stimuli with behavioral, physiologic, hormonal, and metabolic changes, all prospective studies that reported data on any of these variables were included. Experimental pain procedures, such as the measurement of pain thresholds using von Frey hairs, and case reports were excluded from the analysis. Two investigators (A.T., A.O.) agreed through a consensus process on the inclusion of a specific study. For the determination of safety, all prospective studies were included. Clinically important methemoglobinemia, defined as a MetHb concentration >5% and requiring medical intervention, was the main focus for adverse effects.

Data Abstraction

Data abstracted from each report included the procedure studied, study design, gestational age (GA), sample size, dosage regimen, control group treatment, and outcomes. Abstracted data were verified by two investigators (A.T., A.O.).

Statistical Methods

A priori, a decision was made that if there were at least 2 randomized controlled trials that evaluated the efficacy of EMLA for the same procedure and using the same outcome measures, study results would be pooled using a random effects model for weighted mean differences to obtain an overall estimate of effect size. The overall difference in MetHb concentration between groups would be combined using the same method. The risk of methemoglobinemia would be estimated by determining the incidence and 95% confidence interval (CI) from the data provided in each prospective report.

RESULTS

Efficacy Studies

Thirteen studies that assessed the efficacy of EMLA in reducing pain in a total of 662 neonates were retrieved.⁵⁻¹⁷ Two studies were excluded; 1 because an experimental procedure was used to measure pain threshold,⁵ and another because it did not include a control/no treatment group.⁶ Thus, 11 studies were used for the analysis. The characteristics of included studies are summarized in Table 1. The pain response of infants undergoing the following cutaneous procedures was investigated: circumcision, heel lancing, LP, PVC placement, venous puncture, and arterial puncture. Nine of the studies were randomized controlled trials with sample sizes

TABLE 1. Efficacy Studies of EMLA for Procedural Pain in Neonates

Reference	Procedure	Study* Design	Sample Size	Dosage Regimen	Gestational Age at Birth (wk)
Taddio ⁸	Circumcision	db, p, r, pc	59	1 g for 60–80 min	37–42
Benini ⁷	Circumcision	p, r, pc	27	0.5 g for 45–65 min	37–42
Lander ⁹	Circumcision†	p, r, c	52	2 g for 90 min	Full-term
Larsson ¹¹	Heel lancing	db, p, r, pc	110	0.5 g for 10–120 min	37–43
Ramaoli ¹⁰	Heel lancing†	p, r, pc	20	0.5 g (=1 cm) for 30 min	29–36
Stevens ¹²	Heel lancing†	p, r, pc	60	0.5 g for 30 min	30–36
McIntosh ¹³	Heel lancing	p, c	35	nr‡ for 60 min	26–34
Lindh ¹⁷	Venipuncture†	db, p, r, pc	60	nr‡ for 60 min	Full-term
Gourrier ¹⁶	Venipuncture	p, c	67§	≥2 kg; 1/4 tube (≈0.5 g)	26–41
Gourrier ¹⁶	Arterial puncture	p, c	90§	<2 kg; nr‡ for 60–180 min ≥2 kg; 1/4 tube (≈0.5 g)	26–41
Enad ¹⁴	Lumbar puncture†	p, r, pc	49	1 g for 60 min	≥34
Garcia ¹⁵	Percutaneous venous catheter placement†	p, r, pc	13	1.25 g for 60 min	Very low birth weight

* db, double-blind; p, prospective; r, random, pc, placebo controlled; c, controlled (no treatment group).

† Published in abstract form only.

‡ nr, not reported.

§ Number of procedures (not infants) tested.

ranging from 13 to 110 infants. GA at the time of delivery was provided in 8 reports, and ranged from 26 to 43 weeks. Two studies that included data from both neonates and older infants were included.^{13,16} The dose of EMLA used was 0.5 to 2 g in 9 studies, and was not specified in two studies. The duration of application ranged from 10 minutes to 3 hours. Outcome measures included behavioral (facial action, body action, cry) and physiologic [heart rate (HR), respiratory rate (RR), blood pressure (BP), and oxygen (O₂) saturation] parameters. Data from individual studies could not be combined using meta-analytic techniques because of a wide variability in procedures, dosage regimens, outcome measures, and reporting of results. There was only one exception: two studies of circumcision pain^{7,8} (see below) that used similar outcome measures were combined. Because of the diversity among studies, the results are reported according to procedure investigated.

Procedure 1. Circumcision

The efficacy of EMLA for the treatment of circumcision pain was investigated in three studies that included a total of 138 neonates (Table 1).

Double-blind Randomized Controlled Study

Taddio et al⁸ randomly assigned neonates to 1 g of EMLA or a cosmetically identical placebo cream on the outside of the prepuce for 60 to 80 minutes before circumcision. Infants pretreated with EMLA had lower ($P < .05$) facial action pain scores [assessed using the Neonatal Facial Coding System (NFCS)],¹⁸ percent crying time, and HR during surgery as compared with placebo. Facial activity scores were 12% to 49% lower during various stages of the procedure. The average difference in percentage crying and HR between the groups compared with baseline values, was 55% and 10 beats per minute, respectively. BP was lower in the EMLA group compared with con-

trols, but the difference did not reach statistical significance.

Randomized Controlled Studies

Benini et al⁷ administered 0.5 g of EMLA or petrolatum jelly placebo for 45 to 65 minutes before circumcision. For all outcome measures [HR, transcutaneous O₂ saturation, cry duration, facial action (scored using NFCS)],¹⁸ EMLA was associated with a significantly ($P < .05$) reduced response compared with placebo during the painful phases of the procedure (eg, clamping, incision of foreskin, lysis, and application of Gomco [Gomco, St Louis, MO] clamp). The average HR for the EMLA group compared with the control group was 25 beats per minute less and the average O₂ saturation was 5% higher. Twenty percent less facial activity and 15% less crying was also observed in the EMLA-treated infants. Cry features such as maximum fundamental frequency, peak spectral energy, and dysphonation, however, were not significantly different between groups.

Lander et al⁹ studied the efficacy of 2 g of EMLA applied for 90 minutes before circumcision. Infants were randomized to four groups: no treatment, EMLA, dorsal penile nerve block, or penile ring block. Although the EMLA group had a lower mean HR during foreskin retraction than did the no treatment group (169 vs 200 beats per minute), HR values were even lower for the two block groups (151 beats per minute). Investigators did not report the standard deviation (SD) and P values among treatment groups. Infants in all three intervention groups cried significantly less than those in the no treatment group (data and P values were not provided).

Meta-analysis of Efficacy of EMLA for Circumcision

Meta-analytic techniques were used to summarize the HR outcome data for two studies of circumcision pain.^{7,8} The mean increase in HR (ie, compared with

baseline values) was 12 to 27 beats per minute less for the EMLA group compared with placebo during various stages of the surgical procedure ($P < .05$) (Table 2).

Procedure 2. Heel Lancing

Pain from heel lancing was investigated in 4 studies involving a total of 225 neonates (Table 1).

Double-blind Randomized Controlled Study

Larsson et al¹¹ used a randomized double-blind design and allocated 112 3-day-old, full-term neonates to eight different application time groups (10, 20, 30, 40, 50, 60, 90, 120 minutes) after 0.5 g of EMLA or a cosmetically identical placebo cream. Each randomization group included 7 infants treated with EMLA and 7 infants treated with placebo. The primary outcome measure was the occurrence of crying during the procedure. Fifty-four of the 56 neonates (96%) that received EMLA cried compared with 52 out of 54 neonates (96%) that received placebo, which was not significantly different.

Randomized Controlled Study

Ramaoli et al¹⁰ randomly assigned preterm neonates to 1 cm (=0.5 g) of EMLA or placebo (glycerin) to the heel for 30 minutes before heel lancing. Pain was assessed using changes in HR, BP, RR, and behavior (on the Prechtl scale). Five serial assessments were made for each subject. These assessments were made 3 minutes before the heel lance, at the start of sampling, at the end of sampling, and at 3 minutes and 8 minutes after sampling. Investigators did not report any statistically significant differences between groups for any of the outcome measures. Within groups, systolic BP was higher at the end of sampling when compared with 3 and 8 minutes after sampling ($P = .01$).

In a study by Stevens et al¹² involving 60 preterm neonates 30 to 36 weeks GA, neonates randomly received 0.5 g of EMLA or Glaxal base placebo for 30 minutes before heel lancing. Pain was assessed by a blinded observer from a videotape and computerized physiologic data using the Premature Infant Pain Profile (PIPP).¹⁹ The PIPP score is derived by summing the pain scores obtained from seven indi-

cators: brow bulge, eye squeezed shut, nasolabial furrow, O₂ saturation, HR, GA, and infant behavioral state. No statistically significant differences between groups were reported; the mean (SD) PIPP score was 10.2 (4.1) in the EMLA group and 9.5 (4.0) in the placebo group ($P = .48$).

Nonrandomized Controlled Study

McIntosh et al¹³ used a prospective, nonrandomized, nonblinded study design to evaluate the effect of EMLA in pain from heel lance. EMLA was administered to 21 preterm neonates (7 to 35 days old) for 1 hour before heel lancing. The dose of EMLA, however, was not specified. A dummy period preceded the administration of EMLA in all cases that mimicked the procedure in all aspects except that the heel was not lanced. Neonatal response to the real heel lancing with EMLA was then compared with the dummy period. The outcome measures included HR, RR, transcutaneous O₂ tension, and carbon dioxide tension. Pretreatment with EMLA was associated with a significant increase in HR (mean difference, 8; CI, 2 to 14), HR variability (mean difference, 9; CI, 4 to 12), and transcutaneous O₂ tension variability (mean difference, 0.3; CI, 0.1 to 0.6). There also was a trend toward an increase in carbon dioxide tension variability ($P = .053$). Other interventions that were tested in the same trial included use of a spring-loaded heel lancing device and nursing comfort measures (stroking and vocal reassurance during the procedure). Unlike EMLA, both of these nonpharmacologic interventions did not significantly alter physiologic changes during heel lancing when compared with the dummy period. This study suggests that EMLA did not diminish the pain from heel lancing. Taken together, none of the studies evaluating EMLA for heel lancing pain showed a significant benefit from the drug on infant pain.

Procedure 3. Venipuncture

The efficacy of EMLA for decreasing pain from venipuncture was assessed in two studies involving 127 procedures (Table 1).

Double-blind Randomized Controlled Study

Lindh et al¹⁷ used a double-blind design to assess the efficacy of EMLA for decreasing pain during venipuncture in healthy 3-day-old neonates. Sixty neonates were administered either EMLA or a placebo (constituents not identified) for 1 hour before venipuncture. Investigators reported that HR and cry duration favored the EMLA-treated group, however, no data (or significance levels) were provided. In addition, the dose of EMLA was not specified.

Nonrandomized Controlled Study

Gourrier et al¹⁶ used a cohort design to evaluate the effectiveness of EMLA for venous and arterial puncture in preterm neonates aged 1 to 64 days (Table 1). Neonates ≥ 2 kg received one quarter of a tube of EMLA (equivalent to ≈ 0.5 g); neonates < 2 kg received less, although the exact dose was not specified. EMLA was applied for 1 to 3 hours before the procedure. The median duration of application was

TABLE 2. Meta-analysis Results for Heart Rate Changes During Circumcision*

Stage of Procedure	Weighted Mean Difference in Heart Rate† (95% CI)
Forceps application	-12.27 (-38.63, 14.09)
Lysis of adhesions	-12.42 (-20.34, -4.49)
Dorsal incision	-26.92 (-37.78, -16.07)
Application of clamp	-27.21 (-35.98, -18.45)
Foreskin cutting	-12.05 (-20.84, -3.26)
Removal of clamp	-11.67 (-19.93, -3.42)

* Based on data from Benini et al⁷ and Taddio et al.⁸

† The mean increase in heart rate (\pm SD) from baseline was calculated for each treatment group. Then the weighted mean difference in heart rate between EMLA and placebo groups with 95% confidence intervals (CI) was calculated for each of the stages of the circumcision using the statistical program included in Revman 3.0 using a random effects model. A CI that does not include the value 0 indicates a significant finding at the $< .05$ level.

105 minutes. Pain was assessed using a behavioral pain scale developed by the investigators. The variables on the scale were infant arousal, expression, and agitation; the total score ranges from 0 to 5. Pain scores were graded by a blinded observer and compared when EMLA was used and when it was not. Altogether, 116 infants who received 157 skin punctures were included. EMLA was utilized for 120 punctures. In 54 cases, EMLA was applied before venipuncture. No intervention was administered for the remaining 37 punctures, 13 of which were venipunctures.

Although it may have been preferable to analyze data using a rank test, investigators divided pain scores into two categories for analysis according to severity: mild, 0 to 2 and severe, 3 to 5. Ninety-four neonates (72 in the EMLA group) who had baseline pain scores of 0 or 1 were included in the analysis. Of these, 33 were treated with EMLA and 6 received no treatment before venipuncture. The remainder (39 in the EMLA group and 16 in the control group) underwent arterial puncture. When all 74 cases were included in the analysis, pretreatment with EMLA was associated with a higher frequency of low pain scores (57%) than the controls (18%) ($P < .001$). The frequency of low pain scores when venous stabs were administered was 78.8% in the EMLA group. The frequency of low pain scores in the control group was not provided. Application times of >90 minutes were more efficacious than shorter duration times ($P < .001$).¹⁶

Unpublished data obtained by the investigators revealed a mean (\pm SD) behavioral pain score of 2.43 (0.46) in the EMLA-treated group ($n = 51$) compared with 3.58 (0.82) in the control group ($n = 12$) ($P < .05$). Infant HR was analyzed in 49 infants: 39 were treated with EMLA. The HR was 158.5 (6.5) in the EMLA group versus 163.8 (12.1) in the control group ($P > .05$).

Together, these data suggest that EMLA decreases the pain from venipuncture.

Procedure 4. Arterial Puncture

Nonrandomized Controlled Study

In the study by Gourrier et al¹⁶ (described above), the frequency of low pain scores when arterial stabs were administered was 41% compared with 12.5% in the control group ($P < .05$).

Unpublished data obtained by the investigators revealed a mean (\pm SD) behavioral pain score of 3.13 (0.42) in the EMLA-treated group ($n = 63$) compared with 3.96 (0.45) in the control group ($n = 23$) ($P < .05$). Mean HR was 166 (4.6) in the EMLA group ($n = 59$) versus 164.8 (6.4) in the control group ($n = 21$) ($P > .05$). O₂ saturation was evaluated in a total of 25 infants: 19 received EMLA. The O₂ saturation was 92.8% (1.9) in the EMLA group versus 94% (2.5) in the control group ($P > .05$).

The lower pain scores observed in the group who received EMLA before venipuncture suggests that EMLA is more successful for venous stabs than arterial stabs and that venous stabs are not as painful as arterial stabs.

Procedure 5. Lumbar Puncture

Randomized Controlled Study

The efficacy of EMLA in alleviating the pain from LP was investigated in one study (Table 1). Enad et al¹⁴ randomly assigned neonates to 1 g of EMLA or placebo (identity not provided) for 1 hour before LP. Physiologic parameters (BP, HR, O₂ saturation) and behavioral response (scored from 0 to 3) were assessed by a blinded observer before, during, and 5 minutes after LP. Percent change from baseline values during and after LP did not differ between groups for physiologic parameters ($P > .09$) and behavioral scores ($P > .25$). The results suggest that EMLA is ineffective for the treatment of pain from LP. Of note, the nature of the behavioral pain measure and the observed values were not provided in the report.

Procedure 6. PVC Placement

Randomized Controlled Study

EMLA was tested for decreasing the pain from PVC placement in one study (Table 1). Garcia et al¹⁵ randomly assigned very low birth weight infants to 1.25 g of EMLA or zinc oxide placebo for 1 hour before PVC placement. Pain response was measured by a blinded observer using serial HR, RR, BP, and O₂ saturation measurements obtained before and 3, 5, and 60 minutes after skin puncture. HR was significantly lower for the EMLA-treated neonates compared with controls at all times during the procedure ($P < .05$). RR response was attenuated in the EMLA group during skin puncture only. BP and O₂ saturation were not significantly altered in either group during the procedure. EMLA was therefore shown to attenuate HR and RR increases during PVC placement but not BP and O₂ saturation. Investigators did not provide values for HR, RR, BP, and O₂ saturation values for the two treatment groups.

Safety Studies

MetHb concentrations were measured in 12 studies.^{6,8-10,14,15,20-25} One study that included data from infants aged 0 to 3 months was included.²⁰ The characteristics of each study including sample size, GA of infants, dose of EMLA, duration of exposure, timing of samples, and MetHb concentrations is provided in Table 3. MetHb concentrations were compared in infants before and after exposure to EMLA, or between infants exposed to EMLA and placebo or no treatment with no statistically significant differences in 7 studies.^{8,10,14,15,20-23} Meta-analytic techniques could be used to combine the data from 4 randomized controlled studies.^{8,10,21,23} The results revealed that mean MetHb concentrations did not differ between EMLA-treated and placebo-treated infants (weighted mean difference, -0.11% ; 95% CI, -0.31% to 0.10%).

The lack of clinically important methemoglobinemia after administration of repeated doses of EMLA was reported in two studies. During a 2-year study period, Gourrier and colleagues^{25,26} administered a mean of 3.2 doses of EMLA to 500 infants (GA, 26 to 41 weeks; postnatal age, ≤ 3 months). One hundred

TABLE 3. Safety Studies With EMLA in Neonates

Reference	Procedure	Gestational Age at Birth (wk)	Number Exposed	Dosage Regimen	Sampling Time (h)	% MetHb* (mean, SD)
Law ²⁴	Circumcision	35–41	10	1.0 g for 60–80 min	8	0.44 (0.53)
Taddio ⁸	Circumcision	37–42	38	1.0 g for 60 min	1–18	1.3 (0.6)
Lander ⁹	Circumcision†	Full-term	13	2.0 g for 90 min	nr‡	(range, 0–4.5)
Ramaoli ¹⁰	Heel lancing†	29–36	10	0.5 g (=1 cm) for 30 min	0.5	0.6 (0.2)
Ramaoli ²⁰	Heel lancing†	Full-term	15	1 g for 30 min	0.5	0.85 (0.2)
Taddio ²³	Heel lancing†	30–37	26	0.5 g for 30 min	8	1.3 (0.5)
Taddio ²²	Heel lancing	30–37	30	0.5 g for 60 min	4–12	1.3 (0.3)
Enad ¹⁴	Lumbar puncture†	≥34	nr‡	1.0 g for 60 min	4	0.85 (0.84)
Garcia ¹⁵	Percutaneous venous catheter placement†	Very low birth weight	7	1.25 g for 60 min	nr‡	(range, 0.3–2.0)
Andreasson ²⁰	Venipuncture†	Full-term (0–3 months)	nr‡	1 g for 60–70 min	0.5–18	(range, 0.5–2.5)
Rubio ⁶	Needle insertion†	29 ± 2.5	48	0.5–1 g for 30–40 min	8	0.68 (0.55)
Gourrier ^{25,26}	nr‡	26–41	158	≥2 kg: 1/4 tube (≈0.5 g) <2 kg: nr‡ for 60–180 min	nr‡	(range, 0.4–6.2)

* MetHb levels were reported as a percentage of hemoglobin in all studies. The mean (SD) or range, is reported.

† Published in abstract form only.

‡ nr, not reported.

fifty-eight follow-up MetHb concentrations were obtained. In 119 cases, the sample was obtained any time after a delay of 24 hours from the first dose, and in the remaining 39 cases, the sample was obtained 2 hours after the first dose of EMLA. The maximum daily dose of EMLA was reported to be one application of 0.5 g for 1.5 to 3 hours in full-term newborns and a smaller quantity (unspecified) in preterm infants. Earlier reports by the same investigators¹⁶ indicate that one quarter of a tube of EMLA cream (equivalent to 1.25 g) was used per dose in full-term infants. Clarification of the dose with investigators revealed that 0.5 g is closer to the actual dose used. The MetHb concentrations were ≤5% for 97.5% of cases. Concentrations were >5% on 3 occasions; the maximum observed concentration was 6.2%. No clinically important cases of methemoglobinemia were observed, that is, none required medical intervention. Elevated MetHb concentrations were believed to have been attributable to the influence of repeated administration of EMLA, although the interval between doses was not provided, and/or the influence of anemia as MetHb concentrations were expressed as a percentage of hemoglobin. In the cases in which anemia was present, MetHb concentrations decreased after administration of blood transfusions.

Fitzgerald et al⁵ studied 7 neonates 27- to 32-weeks postmenstrual age. An unspecified small amount of cream was rubbed onto the heel (without an occlusive dressing) 4-hourly for a period of 1 to 4 weeks. Although the dose used was not specified, the tube of cream (5 g) was reported to last 2 weeks. Thus, a daily dose of approximately 0.36 g was used, or 0.06 g per dose. No clinical observations of methemoglobinemia or other adverse effects were reported, although MetHb concentrations were not measured.

The ratio of cases of clinically important methemoglobinemia (MetHb >5% and clinical signs requiring treatment with methylene blue) to total number of exposures from all published reports (including mul-

iple exposures) was computed to calculate the overall incidence of clinically important methemoglobinemia from EMLA. For the study by Fitzgerald,⁵ each neonate was included only once even though repeated applications of EMLA were administered because the number of applications was not specified. In the studies by Enad¹⁴ and Lindh,¹⁷ the number of infants treated with EMLA was not provided and it was assumed that 50% were treated with EMLA. The study by Andreasson²⁰ could not be included because neither the total or group sample sizes were specified. The incidence of clinically significant methemoglobinemia from all exposures to EMLA, whether single dose or multiple dose, was 0% (95% CI, 0% to 0.2%). If the analysis was repeated including only those cases in which MetHb concentrations were measured and found to be >5% and clinical signs of methemoglobinemia were present, then the incidence was still 0% (95% CI, 0% to 1.00%).

The analysis was repeated using MetHb concentration >5% to define methemoglobinemia. The calculated overall incidence was 0.79% (95% CI, 0.27% to 2.30%) for all neonates. The risk was 0% (95% CI, 0% to 3.21%) for full-term neonates and 1.14% (95% CI, 0.39% to 3.29%) for preterm neonates. There was insufficient data to calculate the risk of methemoglobinemia after repeated administration.

Two case reports of methemoglobinemia after application of EMLA in neonates were retrieved. In the first case, a 34-week GA, 1385 g, 5-day-old neonate with sepsis had been treated with two simultaneous applications of EMLA, one for central line placement and one for LP.²⁷ The total application time was 3 hours. The amount of cream applied was not provided in the report. The observed MetHb concentration was 12.6%. Methemoglobinemia was reversed with methylene blue and no long-term sequelae were reported. In the second case, a full-term, 2-day-old neonate received 3.5 g of EMLA for 60 minutes on the outside of the prepuce before circumcision.²⁸ The infant was noted to be cyanotic and a MetHb con-

centration obtained after circumcision was 16%. The infant was treated with 100% O₂ until the following day. A follow-up MetHb concentration was <2.1%.

The incidence of minor skin reactions after EMLA was reported in 5 studies. Taddio et al²² reported blanching in 20% (6/30) of neonates who received EMLA on the heel, and 30% of those who received it on the penis and abdomen.⁸ Larsson et al¹¹ observed blanching and redness on the heels in 70% and 5% of infants, respectively. Ramaioli et al²¹ reported no local adverse effects in 15 full-term neonates who also received EMLA on the heel. Gourrier et al¹⁶ encountered erythema in 3% (3/116) of neonates because of the occlusive (Tegaderm, 3M, Minneapolis, MN) dressing. After 2 years of clinical use of EMLA, Gourrier et al^{25,29} reported the occurrence of purpuric lesions on the site of application in 5 instances. Four neonates <32 weeks gestation and <3-days postnatal age experienced five episodes of rash (1 neonate had a second reaction when exposed to EMLA at a different skin site) after receiving doses of one eighth to one sixth of a 5 g tube of EMLA for 90 to 120 minutes. In all cases, the rash resolved without sequelae. Rechallenge some weeks later on 2 infants revealed no complications.

Four groups measured concentrations of local anesthetics in neonatal blood. Taddio et al²² measured lidocaine, prilocaine, and o-toluidine (the toxic metabolite believed to lead to methemoglobinemia) concentrations at 4, 8, or 12 hours after the dose in preterm neonates. In all cases, the observed concentrations were <0.3 µg/mL, <0.1 µg/mL, and <0.02 µg/mL for lidocaine, prilocaine, and o-toluidine, respectively. Of note, the limit of detection was 0.02 µg/mL for all drugs. Enad et al¹⁴ measured lidocaine concentrations 4 hours after administration of EMLA in neonates ≥34 weeks GA. The mean concentration was 0.07 µg/mL (range, 0.0 µg/mL to 0.1 µg/mL).

In full-term neonates, Taddio et al⁸ measured lidocaine, prilocaine, and o-toluidine concentrations 1 to 18 hours after administration of EMLA for circumcision. The highest observed concentrations of lidocaine and prilocaine were 0.14 and 0.11 µg/mL, respectively. o-Toluidine concentrations were below the limit of detection (<0.02 µg/mL) in all cases. Ramaioli et al²¹ measured lidocaine and prilocaine 0.5 hours after EMLA application on the heel. In all cases, concentrations were below the limit of detection (<0.04 µg/mL).

DISCUSSION

There are currently few therapeutic classes of drugs available for the treatment of acute procedural pain in neonates. The severity of potential adverse effects from opioid analgesics have discouraged clinicians from using them in neonates, and until recently, no commercially available local anesthetic preparation has been available that was suitable for use on intact skin. EMLA cream is considered a breakthrough in topical analgesia. This systematic review shows that EMLA's efficacy may be related to the type of cutaneous procedure. Three randomized controlled studies, including one double-blind study,

demonstrated that EMLA diminishes pain response during circumcision. Two studies, one of which was a double blind randomized controlled trial, demonstrated efficacy for decreasing venipuncture pain. EMLA was not shown to diminish pain from heel lancing in randomized and nonrandomized designs. A single randomized controlled study demonstrated some efficacy for PVC placement but not LP. A non-randomized controlled study showed that EMLA decreases the pain from arterial puncture.

The observed inconsistency in EMLA's efficacy may be attributable to study design issues including the sample size, procedure site, dosage regimen and administration techniques, outcome measures, and co-interventions. Studies in adults have revealed that the onset and duration of action of EMLA is related to the skin thickness at the site of application and local blood flow. Characteristics of the stratum corneum, epidermis, dermis, and local blood flow determine both the rate and the extent of absorption into tissues and systemic circulation. The length of analgesia depends on redistribution of the local anesthetic into the systemic circulation, and seems to be shortest for mucous membranes, the face, and diseased skin.^{30,31} The analgesic effect of EMLA also varies with duration of application and duration between time of cream removal and the initiation of the procedure. For the dorsum of the forearm, the sensory and pain thresholds have been found to increase linearly for increased application times (from 30 to 120 minutes). Thresholds are significantly increased for up to 240 minutes after cream removal.³² There are currently insufficient data in neonates to compare with adult data, but it seems likely that differences in either procedure site or dosage regimen can significantly impact on the time-efficacy response of EMLA.

The lack of clinical efficacy of EMLA in heel lancing pain for preterm and full-term infants may be attributable to differences in the skin and blood perfusion in the heel compared with other cutaneous sites, and differences in the depth of tissue damage. In a study comparing skin thickness and skin blood perfusion in full-term infants, Larsson et al³³ found that skin perfusion was significantly enhanced in the heel compared with the other cutaneous regions (forehead, dorsum of hand). Although investigators did not investigate qualitative differences in the skin of different regions, they speculated that the lack of efficacy of EMLA is attributable to rapid clearance from the site of action.

Another factor that may influence the observed efficacy of EMLA is the outcome measure used to assess pain. Although there is no consensus regarding the most suitable way to measure neonatal pain, there are many accepted methods. Validated behavioral pain scales such as the NFCS¹⁸ and cry duration have been used. In addition to behavioral approaches, physiologic indicators such as HR, BP, and RR, and biochemical markers such as stress hormone concentrations have also been used. Finally, composite pain measures are also currently available. The most commonly used composite measures are the PIPP,¹⁹ Barrier et al³⁴ postoperative clinical scoring

system, the Neonatal Infant Pain Scale³⁵ and the Crying, Requires Oxygen, Increased Vital Signs, Expression and Sleepless Tool (CRIES).³⁶

With the abundance of choice in outcome measures, it is no wonder that investigators who have evaluated the efficacy of EMLA in neonates have utilized very diverse pain indicators in their studies. These differences prevent direct comparisons between studies and the use of meta-analytic techniques. Moreover, the sensitivity and specificity of these measures as indicators of neonatal pain are not clear. Neonatal pain response may vary with age,^{37,38} state,^{18,39} severity of illness,³⁹ repeated painful procedures,⁴⁰ and use of concomitant medications such as opioid analgesics or neuromuscular blockers. Preterm neonates may also respond to nonpainful stimuli in a similar way as they do to painful stimuli³⁷ because of a limited repertoire of responses or conditioning. The use of developmentally insensitive pain indicators such as presence or absence of infant crying¹¹ may have obscured differences between groups.

Cointerventions may have also contributed to the variability in the results. For example, heel warming before heel lancing may have increased blood flow to the region and increased uptake of EMLA into the bloodstream. Details regarding cointerventions such as heel warming were not consistently described by investigators. In addition, information about other comfort measures that were used were not consistently described.

The contribution of blinding, randomization, and choice of outcome measures on the observed efficacy of EMLA for different procedures could not be determined because of the limited number of studies. In general, however, studies of different methodologies yielded consistent results. EMLA was shown to decrease the pain from circumcision in 3 separate randomized controlled studies, in which only one of these studies used a double-blind design. EMLA was shown to be ineffective for decreasing pain from heel lancing pain in 4 studies that used vastly different designs (ie, randomized and nonrandomized) and different outcome measures. Finally, EMLA was shown to decrease the pain from venipuncture in a double-blind randomized controlled study and a nonrandomized controlled study, which is consistent with results of studies performed in other patient populations.

This systematic review demonstrated that the risk of methemoglobinemia is low after single dose application of EMLA. In full-term neonates, single doses ranging from 0.5 to 2 g applied for 10 to 180 minutes have not been reported to cause methemoglobinemia. 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. Concentrations of lidocaine and prilocaine are considerably lower than those considered toxic ($>5 \mu\text{g}/\text{mL}$)⁴¹ using these dosage regimens. There are currently insufficient data to determine the safety of repeated EMLA administration.

CONCLUSION

In summary, the current data provide sufficient evidence to recommend routine use of EMLA for neonatal circumcision pain treatment in settings where no analgesics are routinely administered. EMLA cannot be recommended more than other analgesic techniques with proven efficacy, such as regional nerve block with lidocaine. Further research is necessary to determine the relative and combined efficacy of different analgesic techniques and the most appropriate dosage regimens.

There may be some benefit from EMLA for neonates undergoing venous or arterial puncture and PVC placement; however, efficacy data for these procedures are limited. EMLA seems to be ineffective for treatment of heel lancing pain.

Single doses of EMLA are safe for application to the skin of neonates of GA >26 weeks. Additional research is needed before EMLA can be recommended for repeated administration. To facilitate systematic evaluations, investigators are encouraged to devise their research studies with similar outcomes, and to provide results in a consistent fashion (as described by The Standards of Reporting Trials Group).⁴²

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A Systematic Review of Lidocaine-Prilocaine Cream (EMLA) in the Treatment of Acute Pain in Neonates

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