Efficacy and Safety of EMLA Cream for Pain Control Due to Venipuncture in Infants: A Meta-analysis

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abstract

CONTEXT: The eutectic mixture of lidocaine (EMLA) cream has been used to reduce the pain during venipuncture in infants.

OBJECTIVE: To determine the efficacy and safety of EMLA in infants <3 months of age requiring venipuncture in comparison with nonpharmacological interventions in terms of pain reduction, change in physiologic variables, and methemoglobinemia.

DATA SOURCES: Medline, Embase, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature, Web of Science, and gray literature were searched from inception to August 2017, without language restrictions.

STUDY SELECTION: We selected randomized controlled trials in which researchers compared EMLA with nonpharmacological interventions.

DATA EXTRACTION: Two reviewers independently performed abstract screening and full-text review, and extracted the data and assessed the risk of bias.

RESULTS: Ten randomized controlled trials (907 infants) were included. EMLA revealed little or no effect in reduction of pain (standardized mean difference: 0.14; 95% confidence interval [CI]: −0.17 to 0.45; 6 trials, n = 742; moderate-quality evidence) when EMLA was compared with sucrose, breastfeeding, or placebo. In comparison with placebo, EMLA revealed a small-to-moderate effect on increasing methemoglobin levels (mean difference: 0.35; 95% CI: 0.04 to 0.66; 2 trials, n = 134; low-quality evidence). There was an increased risk of blanching of the skin in the EMLA group (relative risk: 2.63; 95% CI: 1.58 to 4.38; 2 trials, n = 123; I^2 = 84%, very low–quality evidence).

LIMITATIONS: Our results may not be applicable to older infants.

CONCLUSIONS: EMLA reveals minimal benefits in terms of reduction of pain due to venipuncture procedure in comparison with placebo and no benefit in comparison with sucrose and/or breastfeeding. Moreover, it produced an elevation in methemoglobin levels and skin blanching.

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Drs Shahid and Florez conceptualized and designed the systematic review and search strategy, screened the title and abstract, reviewed the full-text articles, collected and extracted the data, conducted the statistical analysis, drafted the initial manuscript, and reviewed and revised the final manuscript; Dr Mbuagbaw coordinated and supervised data collection and critically reviewed the methodology and manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Hospitalized infants, including preterm and term infants, undergo many routine painful procedures such as venipuncture.[1] Venipuncture is one of many invasive procedures used in neonates.[2] Venipuncture is performed either for blood sampling or the insertion of venous catheters.[3,4] In a large multicenter study, venipuncture was reported as the second-most common skin-breaking procedure in the NICU and often required multiple attempts to complete.[4]

Both term and preterm infants have the physiologic and anatomic capacity to experience pain.[5] In infants, acute response to pain is evaluated by physiologic, behavioral, and biochemical changes in their body.[5–7] Earlier studies have revealed that if pain is managed poorly, it could lead to alterations in reaction, perception, coping strategies, and emotional changes to subsequent painful stimuli.[8] There is growing evidence that untreated pain in infants could lead to hyperanalgesia, sleep disturbances, and decreased mother and infant bonding.[9,10] Both the Canadian Pediatrics Society and American Academy of Pediatrics have endorsed guidelines for effective use of pharmacologic and nonpharmacologic therapies for the prevention and management of pain associated with routine neonatal procedures.[11]

The eutectic mixture of lidocaine (EMLA) is a mixture of lidocaine (25 mg/g) and prilocaine (25 mg/g) in a cream base, which provides dermal anesthesia and/or analgesia.[12,13] Lidocaine and prilocaine are both amide-type local anesthetic agents. EMLA cream acts by diffusing through intact skin to block neuronal transmission from dermal receptors.[14] EMLA stabilizes neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of nerve impulses, thereby effecting local anesthetic action.[13]

The use of EMLA in infants and children has been studied in the last 2 decades, and there is evidence that EMLA is an effective topical anesthetic for venipuncture in infants >3 months of age and in children.[15–19] However, its use in infants <3 months of age, for venipuncture, has led to conflicting conclusions.[20–22] Young infants have shown lower levels of capacity for nicotinamide adenine dinucleotide reductase, which reduces methemoglobin to hemoglobin,[1,23,24] and therefore EMLA could potentially lead to methemoglobinemia in this group.[23]

According to the US Food and Drug Administration and the manufacturer,[13,25] EMLA is not recommended to be used in preterm infants; moreover, no more than 1 application site at a time is recommended for infants <3 months. Systematic reviews have been published on the use of EMLA cream for pain for all of the neonatal procedures.[1,26] However, assessment of the efficacy and safety of EMLA in comparison with nonpharmacological interventions for pain, particularly pain due to venipuncture procedure in infants <3 months, has not been systematically summarized yet.

Our aim was to determine the anesthetic efficacy and safety of EMLA cream in term and preterm infants aged <3 months requiring venipuncture in comparison with standard nonpharmacological interventions.

METHODS

This systematic review and meta-analysis protocol was registered in PROSPERO (registration number: CRD42017065445). This report follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA).[27]

Eligibility Criteria

Criteria included all types of randomized controlled trials (RCTs) in which researchers examined the effectiveness of EMLA cream (lidocaine 2.5% and prilocaine 2.5%), at any dose, location of the body, or length of time before venipuncture. The population of interest was infants who are term (37–42 weeks' gestational age [GA]) and preterm (25–36 weeks' GA) up to a postnatal age of 3 months who required venipuncture for blood drawing or venous catheter insertion, from both inpatient and outpatient settings. The nonpharmacological comparators were placebo, no EMLA (no treatment at all), sucrose, breastfeeding, and skin-to-skin care.

Outcomes

The primary outcomes were pain and methemoglobinemia. Pain was measured during the venipuncture and up to 1 hour postprocedure by either one of the following pain scales or other validated measures: Premature Infant Pain Profile (PIPP),[28] Neonatal Facial Coding System (NFCS),[29] Douleur Aigue Nouveau-ne behavioral scale (DAN),[30] or Neonatal Infant Pain Scale (NIPS).[31] The safety outcome was determined by the proportion of infants with methemoglobinemia measured after venipuncture. The threshold of >5% of methemoglobin was considered as positive methemoglobinemia in infants without clinical signs and symptoms.[32] The secondary outcomes were total duration of crying (duration of crying measured in seconds from the beginning of the venipuncture until its cessation), heart rate and desaturation (during and after venipuncture), number of venipuncture attempts, and number of skin-blanching events (white or pale skin due to vasoconstriction).

Data Sources

We searched Medline and Embase via Ovid, the Cochrane Central

Register of Controlled Trials, and the Cumulative Index to Nursing and Allied Health Literature from inception to August 2017. We did not apply any language restrictions. In Medline, a subject-specific search strategy was combined with the sensitivity-maximizing version of the Cochrane highly sensitive strategy and was modified for use in other databases (see Supplemental Information). We identified ongoing trials using Clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform. In addition, we contacted experts and searched bibliographies for additional references. We also searched the Web of Science and Open SIGLE (System for information on Grey Literature in Europe) databases for conference proceedings. We used the standard systematic review methods recommended by Cochrane.[33]

Study Selection

One author (S.S.) performed the search. The results were merged, and duplicate records were removed by using Endnote ×8 software.[34] Two reviewers (S.S. and I.D.F.) independently and in duplicate screened the identified titles and abstracts to assess their eligibility. Full texts were reviewed by 2 authors (S.S. and I.D.F.) independently and in duplicate. We included studies for which both reviewers agreed about the eligibility. Disagreements were resolved by discussion.

Data Abstraction

For each eligible study, 2 reviewers (S.S. and I.D.F.) independently and in duplicate extracted data into a pilot-tested Microsoft Excel spreadsheet. We extracted the following data: participants' characteristics, risk of bias (RoB) assessment, number of events, number of patients per arm (dichotomous outcomes), and mean, SD, and number of patients per arm (continuous outcomes) for all outcomes of interest.

For some studies, the results were presented only in graphs or figures without any numerical data, and we could not obtain the raw data from authors. For these studies, we extracted the data by using Plotdigitilizer software version 2.6.8.[35] In some of the studies, the measures of variance were not reported for continuous data; hence, following the approach by Furukawa et al,[36] we imputed the values, borrowing them from other studies similar in sample sizes and means.

RoB

Two reviewers (S.S. and I.D.F.) independently assessed RoB using the Cochrane RoB tool.[33] The following domains were assessed: sequence generation, allocation concealment, blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), completeness of follow-up, and selective reporting bias or any other biases (Supplemental Table 4). The reviewers made judgments on every criterion toward high or low RoB and avoiding the use of unclear risk as much as possible, unless no judgment could be made on the basis of the information provided in the study.

Data Synthesis and Analysis

Effect estimates were reported as risk ratios (RRs) and 95% confidence intervals (CIs) for dichotomous outcomes and as means and SDs for continuous outcomes. For the pain outcome, we used the standardized mean difference (SMD) because researchers used different scales, such as the NFCS, NIPS, PIPP, and DAN. We standardized the results to a uniform scale before they were combined,[37] using the NIPS pain scale, which is considered a reliable and widely used tool for pain assessment in infants.[38]

We performed meta-analysis using the statistical package Review Manager version 5.3[39] and applied the generic inverse variance method.[40] We used random effect models because we assumed that there was heterogeneity among studies, and heterogeneity can be better incorporated in random-effects models.[33]

When studies had more than 2 arms and more than 1 comparator,[41–43] data were extracted from each comparator and compared with the EMLA group. In these cases, the information from 2 non-EMLA groups (eg, sucrose and placebo groups) were compared separately with the EMLA group, creating 2 comparisons from 1 single study (eg, sucrose versus EMLA and placebo versus EMLA), but the information from the common EMLA (sample size and events, when applicable) group was divided out evenly among the 2 comparisons to avoid double counting patients.

We assessed heterogeneity with the χ^2 test ($P < .10$) and the I^2 statistic.[44] The I^2 value was assessed as "might not be important" (0%–40%), "moderate" (30%–60%), "substantial" (50%–90%), or "considerable" (75%–100%), as recommended by Cochrane.[40,45] Publication bias was assessed by evaluating the degree of asymmetry of funnel plot.[46]

Assessment of Quality of Evidence

We assessed the quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation approach,[47] using the online Guidelines Developmental Tool.[48]

RESULTS

Study Selection

We identified 3707 records from databases and 15 additional records through other sources.

After removing duplicates, 2988 titles and abstracts were screened. Seventy-eight studies were identified for full-text screening. In Fig 1, we show the PRISMA flow diagram of study selection. In Table 1, we show the characteristics of included studies. After full-text review, we excluded 68 studies (Supplemental Table 5). Additional information on each included study is presented in Supplemental Tables 6 through 24. In total, 907 patients were randomly assigned: 412 patients received EMLA, and 495 received either placebo, sucrose, water, or breast milk. Most of these trials were performed in Sweden. A dose of 0.5 to 1 g of EMLA was used in all studies.

RoB

The RoB assessment is shown in Supplemental Tables 7 through 25. In Supplemental Figure 6A, we show the RoB assessment for each study, and in Supplemental Fig 6B, we display a summary of the RoB by domain. The domains judged to have lowest RoB were blinding of participants and personnel, incomplete outcome data, and selective reporting of the outcome. Randomization was judged to have low RoB, except for in 2 studies.[42,52] Six studies had high RoB[20,41–43,50,52] for concealment of allocation because there was no clear information provided regarding allocation concealment. Blinding of outcome assessors was judged to be at high RoB in 1 study.[52]

Primary Effectiveness Outcome: Pain

In 6 studies, researchers reported pain during the venipuncture.[21,42,43,49,51,52] There was little to no reduction in pain when EMLA cream was compared with placebo, sucrose, and breastfeeding. Heterogeneity was substantial (SMD: 0.14; 95% CI: −0.17 to 0.45; 6 trials, $n = 742$; $I^2 = 71\%$; moderate-quality evidence; Fig 2). In 4 studies, researchers reported pain at the end of the venipuncture.[20,21,43,49] We found minimal-to-moderate reduction in pain score at the end of the venipuncture (SMD: −0.26; 95% CI: −0.59 to 0.07; 4 trials, $n = 226$; $I^2 = 25\%$; moderate-quality evidence; Fig 3). Overall, the quality of evidence for reduction of pain with

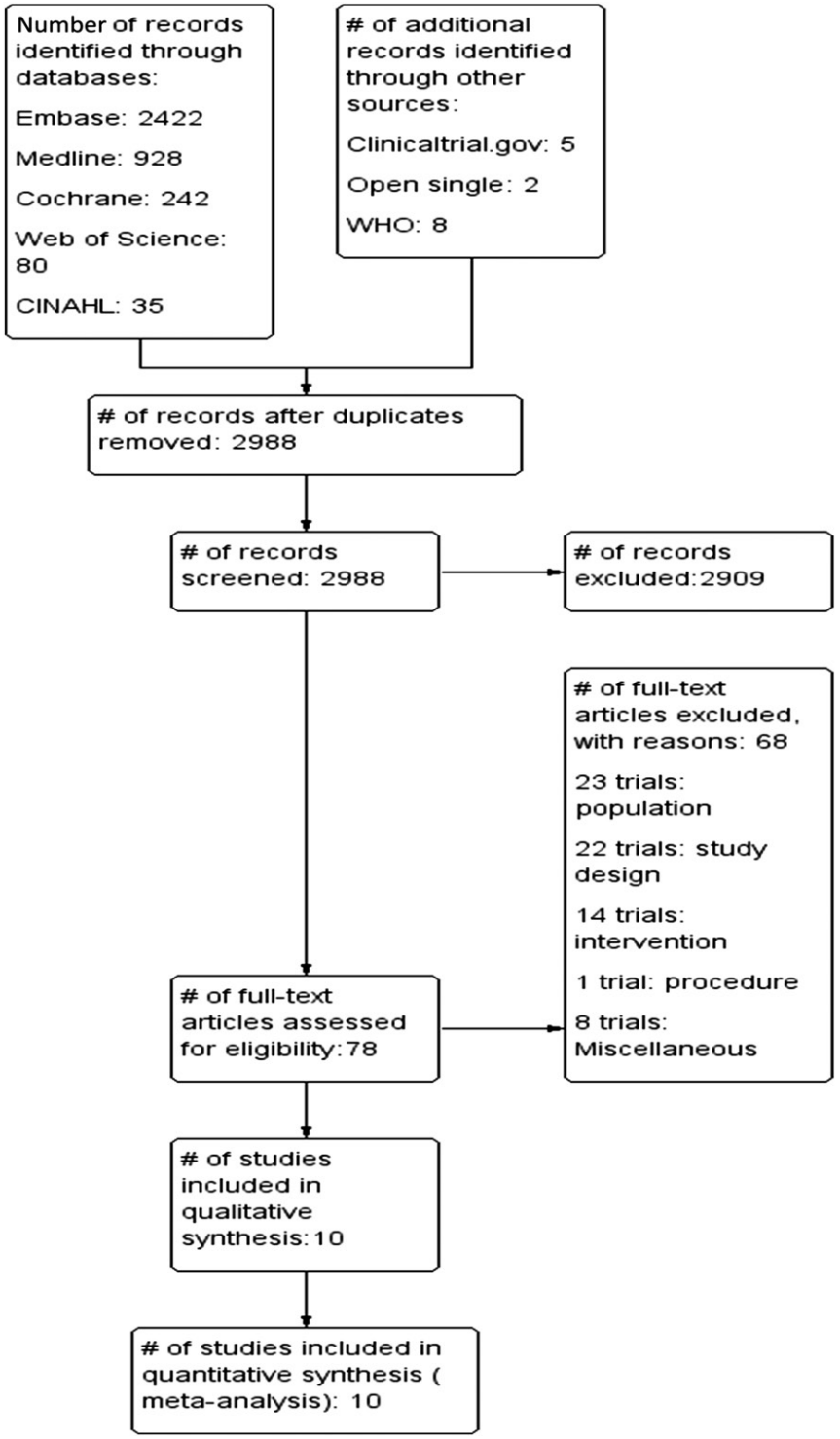

FIGURE 1
PRISMA study flow diagram. CINAHL, Cumulative Index to Nursing and Allied Health Literature; WHO, World Health Organization.

TABLE 1 Summary of Included Studies

No.	Study	Location	Total No. Patients	Included in Review	Patient Characteristics	Intervention	Details of Comparators	Outcomes
1	Abad et al[41]	Spain	51	51	GA: 37–42 wk BW: 2.8–3.7 kg PNA: <4 d	1 g of EMLA	2 mL of spring water, 2 mL of sucrose 24%, and 1 g of EMLA + 2 mL of sucrose	Total crying duration, RR, O_2 sat, HR
2	Acharya et al[20]	United Kingdom	20	19	GA: 26–33 wk BW: 0.916–2.246 kg PNA: 3–65 d	0.5 mL of EMLA	0.5 mL of placebo cream	HR, BP, O_2 sat, NFCS score, methemoglobin level
3	Aziznejad et al[42]	Iran	120	120	GA: 37–42 wk BW: 2.6–3.5 kg PNA: 2–18 d	1 g of EMLA	No treatment, sucrose, breast milk	HR, RR, O_2 sat, DAN score, and crying time
4	Biran et al[49]	France	80	76	GA: 25–36 wk BW: 0.810–3.0 kg PNA: 1–68 d	0.5 g of EMLA and 0.5 mL of sucrose	0.5 mL of sucrose + placebo cream (0.5 g)	DAN and PIPP score
5	Brisman et al[50]	Sweden	47	47	GA: 37–42 wk BW: 2.8–5.5 kg PNA: 1–74 d	1 g of EMLA	1 g of placebo cream	Venous met-hemoglobin levels
6	Gradin et al[51]	Sweden	201	196	GA: 32–42.3 wk BW: 1.1–5.5 PNA: 1–30 d	0.5 g of EMLA cream and 1 mL of water	0.5 g of placebo cream and 1 mL of sucrose	PIPP score, HR, crying time, local skin changes, and time needed to complete the venipuncture
7	Larsson et al[21]	Sweden	120	111	GA: 37–43 wk BW: 2.3–4.9 kg PNA: 3–8 d	0.5 mL of EMLA	0.5 mL of placebo	NFCS score, first cry latency, first cry duration, total cry time, and total time to complete venipuncture
8	Lindh et al[22]	Sweden	60	46	GA: 37–42 wk BW: 3.1–4.1 kg PNA: 3–4 d	1 g of EMLA	1 g of placebo	Incidence of crying, heart rate, and heart rate variability
9	Marcatto Jde et al[43]	Brazil	30	21	GA: >28 to <37 wk BW: NR PNA: <7 d	0.6 g of EMLA and 2 mL of water	0.6 g of placebo and 2 mL of sucrose	NIPS score, HR, O_2 sat, and BP
10	Noori-Sadkam[52]	Iran	220	220	GA: ≥38 wk BW: 2.3–4.5 kg PNA: 1–15 d	0.5 g of EMLA cream with 1 mL of water	0.5 g of placebo cream and 1 mL of sucrose	NIPS and crying time

BP, blood pressure; BW, birth weight; HR, heart rate; O_2 sat, oxygen saturation; PNA, postnatal age; RR, respiratory ra.

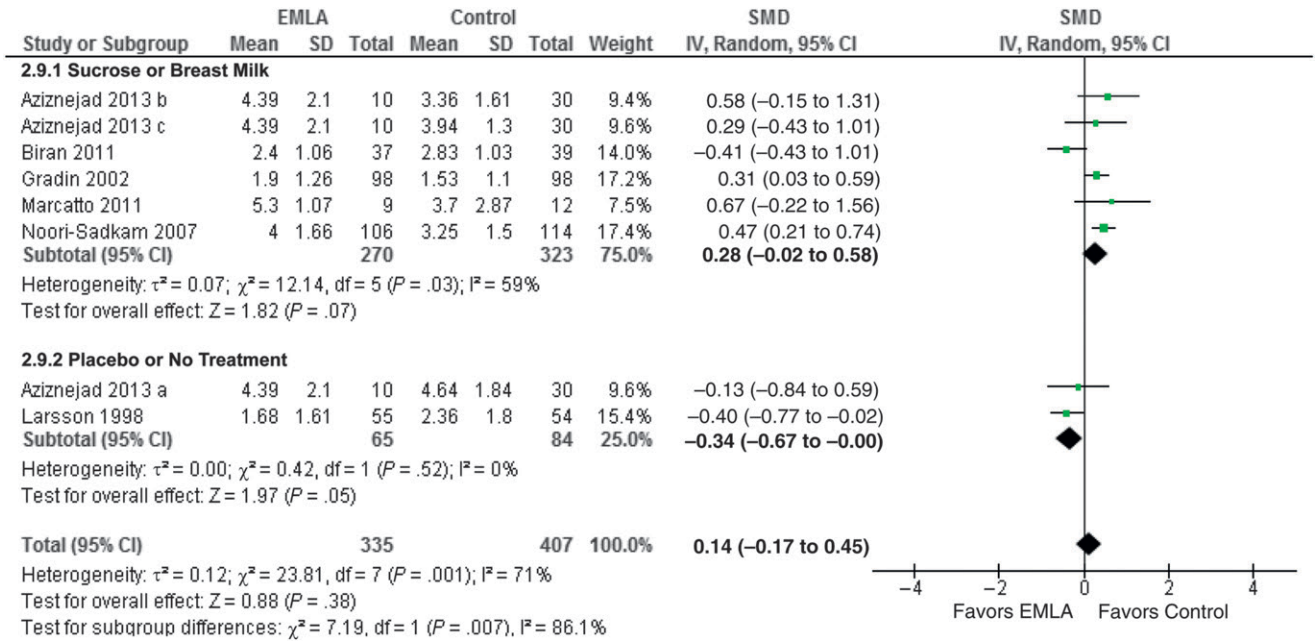

FIGURE 2
Forest plot of the comparison of EMLA versus control. The outcome was pain during venipuncture. df, degree of freedom; IV, inverse variance method.

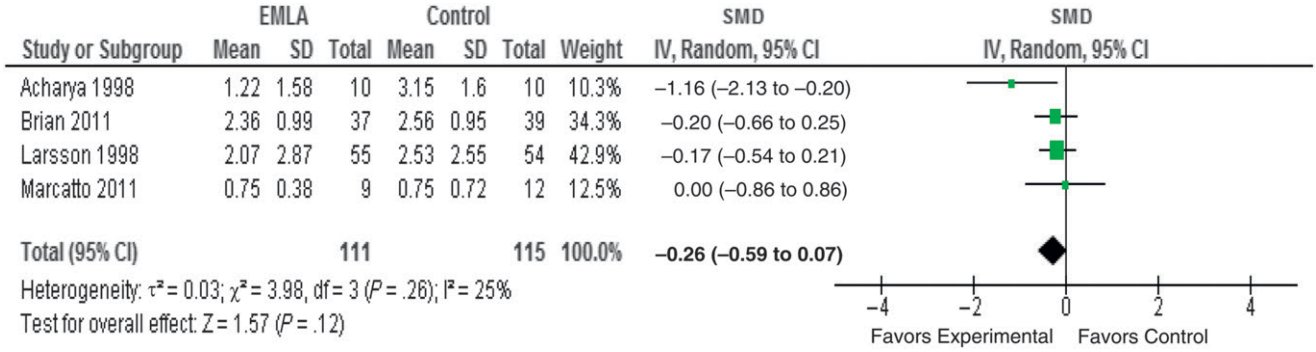

FIGURE 3
Forest plot of the comparison of EMLA versus control. The outcome was pain at the end of venipuncture. df, degrees of freedom; IV, intravenous.

EMLA cream is moderate quality because of inconsistency and imprecision (Table 2).

Primary Safety Outcome: Methemoglobinemia

There was a moderate effect size in elevation of methemoglobin levels between 2 groups at 2 different time periods (mean difference [MD]: 0.35%; 95% CI: 0.04% to 0.66%, 2 trials, $n = 134$; $I^2 = 58\%$; low-quality evidence) favoring the placebo over EMLA[20,52] (Table 2, Fig 4). In none of these studies did authors report methemoglobin levels of >5% or any clinical symptom.

Secondary Outcomes

Total Duration of Crying

In 6 studies, authors reported total duration of crying during venipuncture in 624 patients.[20,21,41,49,51,52] EMLA was compared with placebo or sucrose, and subgroup analysis was performed based on GA at birth. The duration of crying was comparable in both groups (MD: 3.32; 95% CI: −1.19 to 7.84, 6 trials, $n = 624$; $I^2 = 9\%$; moderate-quality evidence; Supplemental Fig 9, Table 2).

Heart Rate

Heart rate was assessed in 5 studies[20,22,41,43,51] in which researchers compared EMLA versus placebo or sucrose and showed there was no difference in reduction in heart rate during the venipuncture (MD: −1.22; 95% CI: −9.85 to 7.41; 5 trials, $n = 330$; $I^2 = 75\%$; low-quality evidence; Supplemental Fig 10, Table 2) and after (MD: 3.74; 95% CI: −5.74 to 13.22; 3 trials, $n = 254$; $I^2 = 50\%$, very low–quality evidence; Supplemental Fig 10, Table 2).

TABLE 2 Grading of Recommendations Assessment, Development, and Evaluation Evidence Profile and Summary of Findings

Certainty Assessment							No. Patients		Effect		Certainty	Importance
No. Studies	Study Design	RoB	Inconsistency	Indirectness	Imprecision	Other Considerations	EMLA	No EMLA	RR (95% CI)	Absolute (95% CI)		
Pain during the venipuncture 6	Randomized trials	Not serious[a]	Serious[b]	Not serious	Not serious[c]	None	335	407	—	SMD: 0.14, SD higher (0.17 lower to 0.45 higher)	⨁⨁⨁◯ Moderate	Critical
Pain at the end of the venipuncture 4	Randomized trials	Not serious[d]	Not serious[e]	Not serious	Serious[f]	None	111	115	—	SMD: 0.26, SD lower (0.59 lower to 0.07 higher)	⨁⨁⨁◯ Moderate	Critical
Methemoglobinemia 2	Randomized trials	Serious[g]	Not serious[h]	Not serious	Serious[i]	None	68	66	—	MD: 0.35% higher (0.04 higher to 0.66 higher)	⨁⨁◯◯ Low	Critical
Total duration of crying 7	Randomized trials	Serious[j]	Not serious[k]	Not serious	Not serious[l]	None	299	325	—	MD: 3.32 s higher (1.19 lower to 7.86 higher)	⨁⨁⨁◯ Moderate	Critical
Heart rate during the procedure 6	Randomized trials	Serious[m]	Serious[n]	Not serious	Not serious[o]	None	150	174	—	MD: 1.22 beats per min lower (9.85 lower to 7.41 higher)	⨁⨁◯◯ Low	Important

TABLE 2 Continued

Certainty Assessment							No. Patients		Effect		Certainty	Importance
No. Studies	Study Design	RoB	Inconsistency	Indirectness	Imprecision	Other Considerations	EMLA	No EMLA	RR (95% CI)	Absolute (95% CI)		
Heart rate after the procedure 4	Randomized trials	Serious[p]	Not serious[q]	Not serious	Serious[r]	None	118	136	—	MD: 3.74 beats per min higher (5.74 lower to 13.22 higher)	⨁⨁◯◯ Low	Important
Oxygen saturation 3	Randomized trials	Serious[s]	Not serious[t]	Not serious	Very serious[u]	None	21	36	—	MD: 0.35% higher (0.77 lower to 1.47 higher)	⨁◯◯◯ Very Low	Important
Skin blanching 2	Randomized trials	Serious[v]	Serious[w]	Not serious	Very serious[x]	None	47 out of 63 (74.6%)	11 out of 60 (18.3%)	2.63 (1.58 to 4.38)	299 more per 1000 (from 106 more to 620 more)	⨁◯◯◯ Very Low	Important

—, not applicable.

[a] Of the 6 included studies, 2 studies were at high RoB for random sequence generation (Aziznejad et al,[42] Noori-Sadkam [52]), and 3 studies were at high RoB for allocation concealment (Aziznejad et al,[42] Marcatto Jde et al,[43] and Noori-Sadkam[52]); moreover, Noori-Sadkam[52] was at high RoB for blinding of outcome assessor and randomization. Three studies were at low RoB for all the items (Biran et al,[49] Gradin et al,[51] and Larsson et al[21]). In sensitivity analysis, excluding the studies with high RoB does not change the results (point estimate and 95% CI), as such, we did not rate down for RoB.

[b] The point estimate and 95% CI overlap in the sucrose or breast milk group; however, the *P* value is .03, and the I^2 is 59%. For the placebo or no treatment group, point estimate and 95% CI overlap with a *P* value of .52, and I^2 is 0%. When both groups were pooled together, the point estimates vary, and 95% CIs do not overlap, and there is a *P* value of .001, with I^2 of 71%. As such, it was rated down, and likely heterogeneity is explained by the subgroup.

[c] Most of the clinicians would consider 20% reduction in pain as minimal clinically important difference. The point estimate is 0.14 with the 95% CI of −0.17 to 0.45, which does not overlap the threshold line (effect size of 0.2) and crosses the no difference line; therefore, this precisely shows no effect, which would not change the decision about the use of EMLA for pain (we would be recommending against the use of EMLA). Moreover, the sample size appears adequate; hence, it was not rated down for imprecision.

[d] Of the 4 included studies, 2 studies were at high RoB for allocation concealment (Acharya et al[20] and Marcatto Jde et al[43]), and 2 studies (Biran et al[49] and Larsson et al[21]) were at low RoB for all the items; however, both Biran et al[49] and Larsson et al[21] together have a weight of over 70%, and, excluding the high-risk studies, this does not change the results. As such, it was not rated down for RoB.

[e] For pain at the end of procedure outcome, visually both point estimate and 95% CI overlap. Moreover, the *P* value is .20, and I^2 is 25% (low). Hence, this outcome was not rated down for inconsistency.

[f] The point estimate reveals the effect size of 0.26, which exceeds the MCID (minimal clinically important difference). However, the 95% CI (−0.59 to 0.07) overlaps the threshold and also crosses the no difference line; hence, it would change the decision regarding the use of EMLA. Moreover, the sample size does not meet the criteria of OIS (optimal information size) of at least 400; as such, this outcome was rated down for imprecision.

[g] Both the trials (Acharya et al[20] and Brisman et al[50]) were at high RoB for allocation concealment.

[h] For this outcome, the point estimate of both studies does not overlap, but there is some overlap of 95% CI. The pooled *P* value was .07, and there was moderate heterogeneity on I^2 (58%), although there is some heterogeneity between the studies, which is not explained by the time of methemoglobin measurement (<8 vs 8–24 h test of subgroup difference revealed a *P* value of .70 and an I^2 of 0%); however, this inconsistency would not change the judgment regarding the safety concerns with the use of EMLA because point estimates from both studies are on the same side of harm. A likely explanation of this heterogeneity is the difference in patient and intervention. In Acharya et al's[20] trial, patient population was only preterm infants (26–33 wk gestation), and intervention was 0.5 mL of EMLA, whereas in Brisman et al's[50] trial, patient population was term infants (>37 wk gestation), and 1 g of EMLA was used.

[i] Because OIS is <400, this outcome was rated down for imprecision.

[j] Of the 7 trials, 4 of them were at high RoB for allocation concealment (Acharya et al,[20] Abad et al,[41] and Noori-Sadkam), and one of them (Noori-Sadkam) was at high risk for the blinding of outcome assessor and randomization. Three studies were at low RoB (Biran et al,[49] Graddin and Larsson et al,[21] and Noori-Sadkam). Noori-Sadkam had a weight of 69.1% and was a large trial with high RoB, and it appears that excluding high-RoB studies does not necessarily change the result; as such, it was rated down for RoB.

[k] This outcome was presented in a subgroup of infants <37 wk versus infants >37 wk. Visually, point estimate and 95% CI overlap with a *P* value of .69 and an I^2 of 0% in infants <37 wk gestation, whereas in infants >37 wk gestation, both point estimate and 95% CI overlap with a *P* value of .24 and an I^2 of 27%. Overall, the pooled *P* value was .36, and I^2 was 9%; as such, this outcome was not rated down for inconsistency.

[l] For duration of crying, we do not have MCID from literature. The point estimate was 3.32 (increase in the duration of crying), and the 95% CI of −1.19 to 7.84 overlaps the no difference line; however, the sample size was ~600, and as such, it was not rated down for precision.

TABLE 2 Continued

[m] There were 3 studies with high RoB for allocation concealment (Abad et al,[41] Acharya et al,[20] and Marcatto Jde et al[45]), and only 2 of them (Gradin et al[51] and Lidh) were at low RoB for all the items.

[n] There is variability in point estimates across studies, and some overlap of 95% CI; however, the *P* value of a χ^2 test was .001, and I^2 was 75%; as such, this outcome is rated down.

[o] We do not have literature to guide the MID (minimal important difference). The 95% CI is wide and overlaps the no difference line; however, the OIS is almost 400, and as such, it was not rated down for imprecision.

[p] Two studies were at high RoB for allocation concealment (Abad et al[41] and Marcatto Jde et al[45]), and only 1 study was at low RoB for all the items (Gradin et al[51]). Separating high-risk studies from low-risk studies (Gradin et al[51]) does not significantly change the point estimate and 95% CI; as such, it was not rated down for RoB.

[q] For this outcome, there is little variability in point estimates across studies, and for most studies, 95% CIs overlap; moreover, the *P* value of a χ^2 test was .11, with moderate heterogeneity of 50% (I^2). As such, it was not rated down for inconsistency.

[r] Because the 95% CI (−5.74 to 13.22) is wide and overlaps the no difference line, the upper boundary of CI suggests an increase in heart rate, whereas the lower boundary of CI reveals reduction in heart rate. As such, it would change our decision and recommendation. Moreover, sample size is not large; therefore, this outcome was rated down for imprecision.

[s] All the studies were at high RoB for allocation concealment (Abad et al[41] and Acharya et al[20]).

[t] For this outcome, point estimates varied; however, 95% CIs overlap across studies with a *P* value of .29 and minimal heterogeneity of 20% (I^2); hence, there are no major concerns related to inconsistency, and as such, it was not rated down.

[u] The point estimate is 0.35, and 95% CI is −0.77 to 1.47, which crosses the no difference line. The sample size is small, and as such, this outcome was rated down by 2 levels.

[v] One of the trials (Brisman et al[50]) was at high RoB for allocation concealment, and another trial was at low RoB for all the items (Biran et al[49]). The weight of Brisman et al's[50] study was more (55%) than Biran et al's[49] study (44%), and as such, it was rated down for RoB.

[w] Point estimates vary widely across studies with no overlap of 95% CI; moreover, the *P* value of a χ^2 test was .01 with a substantial heterogeneity of 84% (I^2). As such, this outcome was rated down by 2 levels.

[x] Sample size does not meet the criteria for OIS for binary outcome.

Oxygen Saturation

In 2 studies,[20,41] authors reported degree of oxygen saturation during venipuncture and revealed no difference in oxygen saturation when EMLA was compared to placebo or sucrose (MD: 0.35; 95% CI: −0.77 to 1.47; 2 trials, $n = 57$; $I^2 = 20\%$; very low–quality evidence; Supplemental Fig 11, Table 2).

Skin Blanching

In 2 studies, researchers reported skin blanching as an adverse effect of EMLA application.[49,50] The meta-analysis under the random effects model revealed no statistical difference between EMLA and placebo (see Supplemental Fig 12A). However, we ran a post hoc sensitivity analysis with a fixed-effects model because the initial analysis revealed counterintuitive results (ie, both studies separately revealed statistical difference between EMLA and placebo, and when pooled together, they showed no statistically significant differences), and we found that EMLA increased the risk of skin blanching (RR: 2.63; 95% CI: 1.58 to 4.38; 2 trials, $n = 123$; $I^2 = 84\%$, very low–quality evidence; Supplemental Fig 12B, Table 2).

Subgroup Analyses

A priori, we intended to perform subgroup analysis on the basis of GA at birth (37–42 and <37 weeks) and birth weight (< or > 2500 g). However, we only performed the analysis based on GA because of limited data.[20–22,41] Additional post hoc subgroup analyses were performed on the different pain scales used for pain measurement and the type of comparators (placebo or sucrose or breast milk) and were based on 2 different time periods of serum methemoglobin levels (<8 hours or 8–24 hours after the EMLA application).

Pain

Subgroup analyses were performed to assess the effect of EMLA compared with placebo or no treatment and sucrose or breastfeeding and were also based on different pain scales. There was small-to-moderate effect size in reduction in pain favoring EMLA in comparison with placebo or no treatment (SMD: −0.34; 95% CI: −0.67 to −0.00; 2 trials, $n = 149$; $I^2 = 0\%$). There was no effect in reduction of pain with sucrose or breastfeeding when compared with EMLA in both preterm and term infants (SMD: 0.28; 95% CI: −0.02 to 0.58; 5 trials, $n = 593$; $I^2 = 59\%$; Fig 2). Interestingly, when subgroup analysis was done only for term infants, EMLA was inferior to sucrose or breast milk (SMD: 0.44; 95% CI: 0.22 to 0.58; 3 trials, 5 trials, $n = 496$; $I^2 = 0\%$; Supplemental Fig 7). Subgroup analysis by pain scale revealed no effect when using the DAN and PIPP scale, but when using NIPS, EMLA was inferior to control (MD: 0.80; 95% CI: 0.39 to 1.20; $n = 241$; $I^2 = 0\%$; Fig 5).

Methemoglobinemia

Subgroup analysis was based on 2 different time periods of serum methemoglobin levels (<8 hours or 8–24 hours after EMLA application) and favored placebo over EMLA, with low-quality evidence.

Sensitivity Analysis

We conducted a sensitivity analysis for pain outcome to explore the impact of bias by excluding studies at high risk for allocation concealment. We found a small-to-moderate reduction in pain with placebo, sucrose, or breast milk (SMD: 0.42; 95% CI: 0.20 to 0.64; 3 trials, $n = 361$; $I^2 = 0\%$), whereas low-risk bias studies revealed no reduction to moderate reduction in pain with EMLA cream when compared with placebo or sucrose (SMD: −0.14; 95%

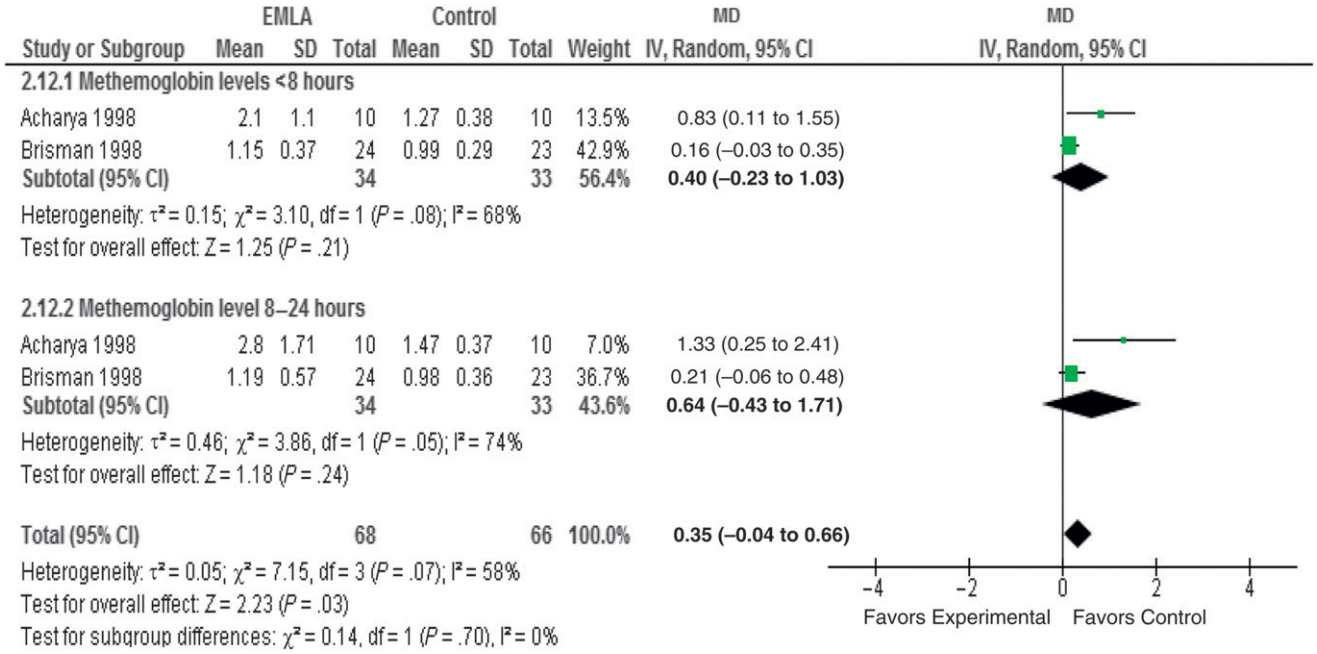

FIGURE 4
Forest plot of the comparison of EMLA versus control. The outcome was methemoglobinemia. IV, intravenous.

CI: −0.66 to 0.37; 3 trials, *n* = 381; I^2 = 83%; Supplemental Fig 8).

We conducted post hoc sensitivity analysis for skin blanching with a fixed effects model and found that there was an increased risk of skin blanching with use of EMLA cream during venipuncture procedure (RR: 2.63; 95% CI: 1.58 to 4.38; 2 trials, *n* = 123; I^2 = 84%; Supplemental Fig 12B).

DISCUSSION

Topical anesthetics may provide relief in pain during neonatal procedures in the hospital. EMLA is one of the topical agents that has been most frequently studied in the last decades for neonatal pain management during venipuncture.[53] In our review, we made an effort to synthesize all the evidence on EMLA efficacy for pain control in infants up to 3 months of age. We found that EMLA was similar to no treatment or placebo in most efficacy outcomes and inferior in safety outcomes.

EMLA revealed no reduction in pain scores (pooled effect) during and after venipuncture in comparison with all comparators (placebo, no treatment, sucrose, or breastfeeding); however, when EMLA was only compared with placebo or no treatment, it had a small effect on pain scores during the venipuncture. Hence, EMLA is better than placebo or no treatment. We found that pain scores were lower in the sucrose or breast milk intervention group when compared with EMLA; hence, clinicians can interpret this finding that in most of the cases, sucrose or breast milk will likely reduce the pain due to venipuncture as compared with EMLA. However, there is a possibility in some cases that sucrose or breast milk might not able to reduce the pain due to venipuncture procedure at all. Interestingly, it was noted that sucrose and breast milk were superior to EMLA for pain management when analysis was performed only in term infants.

We found no significant improvement in physiologic and behavioral changes. Furthermore, we found considerable clinical heterogeneity between studies in terms of variability of timing of assessments (during, at the end of the procedure, and a few minutes postprocedure). It is suggested that EMLA needs to be applied 60 minutes before venipuncture, which could be impractical in certain clinical settings such as acute care; however, it is suggested that in neonates, EMLA should be applied no longer than 30 minutes before skin puncture because of its faster clearance from immature skin.[54]

Regarding concerns related to the safety of EMLA application in term and preterm infants during venipuncture procedure, such as methemoglobinemia, in a few studies, researchers reported this important outcome.[20,50] Taddio et al[1] have reported 12 safety studies with EMLA in neonates for different procedures, such as heel lancing, circumcision, lumber puncture, venipuncture, and other needle-insertion procedures. The meta-analysis of 4 studies in that review revealed that methemoglobin concentrations did not differ between EMLA-treated and placebo-treated

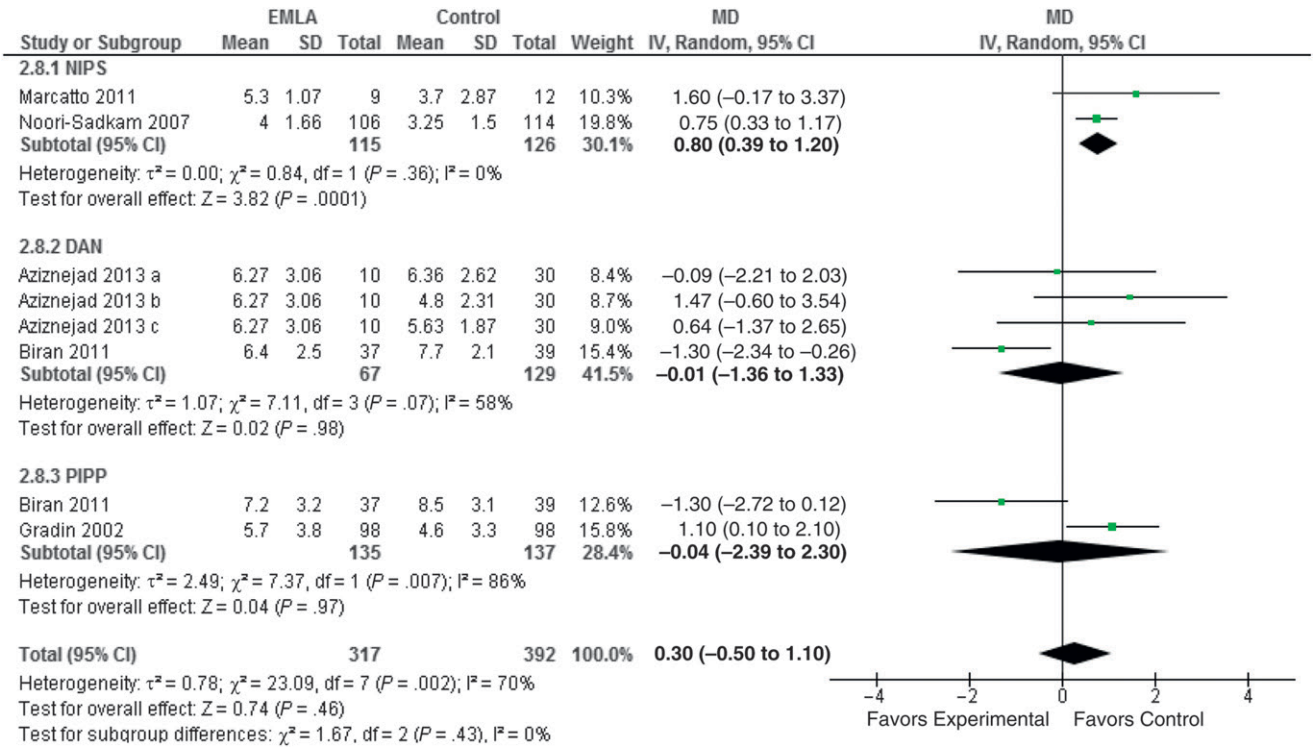

FIGURE 5

Forest plot of the comparison of EMLA versus control. The outcome was pain during venipuncture based on pain scales. df, degrees of freedom; IV, intravenous.

infants (MD: −0.11%; 95% CI: −0.31% to 0.10%). These results were different from our findings. In Taddio et al's review, the procedures for which EMLA was compared with placebo were heel lancing and circumcision, whereas we only analyzed venipuncture. Moreover, 3 of the trials combined measured the methemoglobin levels at <8 hours from EMLA application, which could explain the difference in findings.

The risk of methemoglobinemia with a single application of 0.5 g to 1 g of EMLA is low. However, there is no evidence in which it is suggested that applications of EMLA could lead to methemoglobinemia in neonates. Local skin reactions have been reported in the literature after application of EMLA.[55] We also found a significant increase in the event rate of skin blanching with EMLA when compared with placebo. An updated policy statement by the American Academy of Pediatrics reported that EMLA has been shown to decrease measures of pain during venipuncture, percutaneous central venous catheter insertion, and peripheral arterial puncture; however, methemoglobinemia, skin irritation, and toxicity are the major concerns.[53] With our findings, we support this statement.

Recently, Foster et al[26] published a Cochrane review in which they evaluated the efficacy and safety of 2 commonly used topical anesthetic creams, including EMLA, for any needle-related procedures, including venipuncture. However, the authors were not able to pool the results for the pain outcome because of differing outcome measures and methods of reporting. We believe that these authors conducted a review based on a broad research question: all the needle-related procedures in neonates. In this review, we focused on one intervention, EMLA, in a specific population (venipuncture procedure in infants younger than 3 months).

Our study has several strengths. First, we performed a meta-analysis for patient-important outcomes such as pain, crying duration, physiologic variables, and methemoglobin levels. Also, we conducted a comprehensive literature search through 4 databases, gray literature, and manual searches, reducing risk of publication bias. Additionally, we performed subgroup (term versus preterm, methemoglobin levels [<8 vs 8–24 hours] and pain scales) and sensitivity analyses to explore the robustness of the results and effect of assumption about RoB. Lastly, we applied high methodological standards in the searches and analyses, following the recommendations by Cochrane.[33]

There are a few potential limitations to describe. We included all the trials in which researchers compared EMLA with any nonpharmacological comparators. We were able to compare EMLA with sucrose and breast milk; however, we could

not compare EMLA with other nonpharmacological interventions such as skin-to-skin care. Our study results are applicable to a specific patient population because we included studies limited to term and preterm infants with a postconceptional age of 3 months; however, we found that the mean age of patients for most of the studies in this review was <1 month of age, except for 3 studies in which infants >1 month of age were included.[20,49,50]

CONCLUSIONS

We found that EMLA cream might help to reduce the pain in neonates during and at the end of venipuncture when compared with a placebo, with moderate-quality evidence. In addition, EMLA was inferior to sucrose or breastfeeding to control the pain. Lastly, in this review, we support the concerns on the elevation of methemoglobin levels and increased risk of skin blanching with EMLA use. On the basis of our assessment, we think clinicians may want to avoid the routine use of EMLA before venipuncture in both term and preterm infants and consider nonpharmacological interventions such as sucrose or breastfeeding. Future high-quality, blinded, randomized, and well-powered trials are needed in both term and preterm infants to address several important questions relating to different dosing of EMLA in term infants and other pharmacological and nonpharmacological strategies for pain management and their long-term effects, particularly in preterm infants.

ABBREVIATIONS

CI: confidence interval
DAN: Douleur Aigue Nouveau-ne behavioral scale
EMLA: eutectic mixture of lidocaine
GA: gestational age
MD: mean difference
NFCS: Neonatal Facial Coding System
NIPS: Neonatal Infant Pain Scale
PIPP: Premature Infant Pain Profile
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines
RCT: randomized controlled trial
RoB: risk of bias
RR: risk ratio
SMD: standardized mean difference

This trial has been registered with PROSPERO (https://www.crd.york.ac.uk/prospero/) (identifier CRD42017065445).

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