Supplemental Information

SEARCH STRATEGIES

Database: Ovid Medline Epub Ahead of Print, in-Process, and Other Nonindexed Citations. Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to August 2017

1 extremely low birth weight infant.mp. or Infant, Extremely Low Birth Weight/(1604)

2 infant*.tw. (349997)

3 exp Infant/ (1032254)

4 infant.mp. or Infant/ (1078011)

5 newborn*.tw. (143141)

6 newborn.mp. (678717)

7 Premature newborn.mp. (1088)

8 premature*.tw. (110729)

9 Preterm.mp. (57495)

10 Neonate.mp. (24897)

11 Neonates*.tw. (58462)

12 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (1352647)

13 exp Bloodletting/ (2594)

14 bloodletting.mp. (2813)

15 Phlebotom*.tw. (6994)

16 phlebotomy.mp. or exp Phlebotomy/ (7130)

17 Venipuncture*.tw. (2974)

18 Venipuncture.mp. (2841)

19 Venepuncture.mp. (875)

20 Blood test.mp. or exp Hematologic Tests/ (236026)

21 punctures/ or exp phlebotomy/ (17479)

22 Puncture*.tw. (38940)

23 Puncture.mp. (37578)

24 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (295247)

25 exp Infusions, Intravenous/ or exp Catheterization, Peripheral/ or exp Catheters, Indwelling/ or intravenous catheter.mp. (77457)

26 intravenous catheter*.tw. (1911)

27 Cannulation.mp. or exp Catheterization/ (187304)

28 injection.mp. or exp Injections/ (605915)

29 intravenous administration.mp. or exp Administration, Intravenous/ (153375)

30 exp Catheterization/or Catheters, Indwelling/or exp Central Venous Catheters/or Percutaneous venous catheter.mp. (190979)

31 central venous catheter.mp. or exp Central Venous Catheters/ (7042)

32 25 or 26 or 27 or 28 or 29 or 30 or 31 (862648)

33 24 or 32 (1133479)

34 EMLA.mp. (1136)

35 emla.tw. (911)

36 exp Prilocaine/or exp Anesthetics, Combined/or exp Lidocaine/or exp Anesthetics, Local/(98871)

37 local anesthetic*.tw. (6896)

38 exp Anesthetics, Local/(97605)

39 Topical anesthetic*.tw. (304)

40 Topical anesthetic.mp. (234)

41 Eutectic mixture of local anesthetics.mp. or exp Administration, Topical/ (77076)

42 exp Ointments/ (12180)

43 Lidocaine.tw. (19166)

44 Prilocaine.tw. (1435)

45 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 (190527)

46 Randomized controlled trial.pt. (448607)

47 exp Random Allocation/ or Random*.mp. (1126587)

48 controlled clinical trial.pt. (91938)

49 randomized.ab. (389503)

50 randomized.mp. or exp Clinical Trials as Topic/ (872753)

51 placebo.ab. (184002)

52 drug therapy.fs. (1938065)

53 randomly.ab. (271986)

54 trial.ab. (407943)

55 trial*.mp. (1451136)

56 groups.ab. (1677968)

57 placebo.mp. or exp Placebo Effect/ (189956)

58 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 (4531537)

59 12 and 33 and 45 and 58 (911)

60 extremely low birth weight infant.mp. or exp Infant, Extremely Low Birth Weight/ (1604)

61 Low Birth weight.mp. or exp Infant, Low Birth Weight/ (40626)

62 exp Infant, Small for Gestational Age/ or exp Birth Weight/ or Small for gestational age.mp. (45122)

63 12 or 60 or 61 or 62 (1361630)

64 33 and 45 and 58 and 63 (928)

Database: Embase, Before 1974 to August 23, 2017

1 infant*.tw. (405071)

2 exp Infant/ (1006716)

3 infant.mp. or Infant/ (707539)

newborn*.tw. (172313)

5 newborn.mp. (632098)

6 Premature newborn.mp. (1304)

7 premature*.tw. (141275)

8 Preterm.mp. (79540)

9 Neonate.mp. (36434)

10 Neonates*.tw. (76837)

11 Low Birth weight.mp. or exp low birth weight/ (58458)

12 extremely low birth weight infant.mp. or exp extremely low birth weight/ (3224)

13 Small for gestational age.mp. or exp small for date infant/ (14419)

14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (1317986)

15 exp Bloodletting/ (9628)

16 bloodletting.mp. (625)

17 Phlebotom*.tw. (8729)

18 phlebotomy.mp. or exp Phlebotomy/ (10531)

19 Venipuncture*.tw. (3969)

20 Venipuncture.mp. (3812)

21 Venepuncture.mp. (1199)

22 Blood test.mp. or exp Hematologic Tests/ (241685)

23 punctures/ or exp phlebotomy/ (37460)

24 Puncture*.tw. (56024)

25 Puncture.mp. (72351)

26 Vein puncture.mp. or exp vein puncture/ (6086)

27 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 (329362)

28 intravenous catheter.mp. or exp intravenous drug administration/ or exp catheter/ or exp vein catheterization/ or exp peripheral vascular system/ or exp catheterization/ or exp intravenous catheter/ or exp infusion/ (1526746)

29 intravenous catheter*.tw. (2433)

30 Cannulation.mp. or exp Catheterization/ (178883)

31 injection.mp. or exp Injections/ (628034)

32 intravenous administration.mp. (39794)

33 central venous catheter.mp. or exp central venous catheter/ (22212)

34 Percutaneous venous catheter.mp. (9)

35 indwelling catheter.mp. or exp indwelling catheter/ (14128)

36 injection.mp. or exp injection/ (628034)

37 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 (2083261)

38 27 or 37 (2358007)

39 EMLA.mp. (3178)

40 emla.tw. (1756)

41 exp Prilocaine/ or exp Anesthetics, Combined/ or exp Lidocaine/ or exp Anesthetics, Local/ (478845)

42 local anesthetic*.tw. (9879)

43 exp Anesthetics, Local/ (222064)

44 Topical anesthetic*.tw. (414)

45 Topical anesthetic.mp. (330)

46 Eutectic mixture of local anesthetics.mp. or exp Administration, Topical/ (116601)

47 exp Ointments/ (13929)

48 Lidocaine.tw. (25078)

49 Prilocaine.tw. (1882)

50 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 (600752)

51 Random*.mp. (1368521)

52 controlled clinical trial.mp. or exp controlled clinical trial/ (665219)

53 randomized controlled trial/ (480554)

54 exp placebo effect/ or exp placebo/ or placebo.mp. (394989)

55 crossover$.mp. (83639)

56 trial*.mp. or exp "clinical trial (topic)"/ or exp "randomized controlled trial (topic)"/ or exp "controlled clinical trial (topic)"/ (1970415)

57 exp factorial design/ or factorial$.mp. (66598)

58 group*.mp. (4283337)

59 randomly.mp. (347375)

60 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 (6077779)

61 14 and 38 and 50 and 60 (2422)

Search Name: EMLA and Neonates

Search Engine: Cochrane Central Register of Controlled Trials

Date Run: August 23, 2017

SUPPLEMENTAL TABLE 3 Description

Identification No.	Search	Hits
1	infant:ti,ab,kw (word variations have been searched)	43 800
2	MeSH descriptor: [Infant, Newborn] explode all trees	14 862
3	newborn:ti,ab,kw (word variations have been searched)	20 616
4	MeSH descriptor: [Infant, Premature] explode all trees	3274
5	preterm infant:ti,ab,kw (word variations have been searched)	5820
6	Neonate:ti,ab,kw (word variations have been searched)	4910
7	extremely low birth wt infant:ti,ab,kw (word variations have been searched)	369
8	MeSH descriptor: [Infant, Low Birth Wt] explode all trees	2058
9	MeSH descriptor: [Infant, Extremely Low Birth Wt] explode all trees	99
10	MeSH descriptor: [Infant, Very Low Birth Wt] explode all trees	861
11	Small for Gestational Age:ti,ab,kw (word variations have been searched)	1033
12	#1 or#2 or#3 or#4 or#5 or#6 or#7 or#8 or#9 or#10 or#11	47 438
13	bloodletting:ti,ab,kw (word variations have been searched)	154
14	phlebotomy:ti,ab,kw (word variations have been searched)	547
15	Venipuncture:ti,ab,kw (word variations have been searched)	400
16	Venepuncture:ti,ab,kw (word variations have been searched)	155
17	MeSH descriptor: [Hematologic Tests] explode all trees	11 317
18	Puncture:ti,ab,kw (word variations have been searched)	3408
19	#13 or#14 or#15 or#16 or#17 or#18	15 420
20	intravenous catheter:ti,ab,kw (word variations have been searched)	2109
21	cannulation:ti,ab,kw (word variations have been searched)	1134
22	MeSH descriptor: [Administration, Intravenous] explode all trees	17 172
23	MeSH descriptor: [Injections] explode all trees	20 605
24	MeSH descriptor: [Catheterization, Peripheral] explode all trees	830
25	MeSH descriptor: [Catheterization, Central Venous] explode all trees	861
26	percutaneous venous catheter:ti,ab,kw (word variations have been searched)	113
27	"indwelling catheter":ti,ab,kw (word variations have been searched)	396
28	#20 or#21 or#22 or#23 or#24 or#25 or#26 or#27	33 777
29	#19 or#28	47 538
30	EMLA:ti,ab,kw (word variations have been searched)	650
31	Lidocaine:ti,ab,kw (word variations have been searched)	8033
32	Prilocaine:ti,ab,kw (word variations have been searched)	969
33	Eutectic mixture of local anesthetics:ti,ab,kw (word variations have been searched)	215
34	MeSH descriptor: [Administration, Topical] explode all trees	14 099
35	"topical anaesthetics":ti,ab,kw (word variations have been searched)	158
36	"local anaesthetics":ti,ab,kw (word variations have been searched)	2054
37	combined anesthetics:ti,ab,kw (word variations have been searched)	620
38	#30 or#31 or#32 or#33 or#34 or#35 or#36 or#37	23 642
39	#12 and#29 and#38	242

SUPPLEMENTAL TABLE 4 RoB Assessment Tool

Domains	Criteria for Judgement of RoB
Random sequence generation (selection bias): the method used to generate the allocation sequence in enough detail to allow an assessment of whether it should produce comparable groups.	Low risk (any truly random process, eg, random No. table; computer random No. generator); high risk (any nonrandom process, eg, odd or even date of birth; hospital or clinic record No.); or unclear (no or unclear information provided to permit judgment)
Allocation concealment (selection bias): the method used to conceal the allocation sequence in sufficient detail and determined whether intervention allocation could have been foreseen in advance of, or during, recruitment, or changed after assignment.	Low risk (eg, telephone or central randomization; consecutively numbered, sealed, opaque envelopes); high risk (open random allocation; unsealed or nonopaque envelopes, alternation; date of birth); or unclear risk (no or unclear information provided to permit judgment)
Blinding (performance bias): the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We judged studies to be at low RoB if they were blinded, or if we judged that the lack of blinding could not have affected the results	Low risk (blinding of participants and key study personnel ensured, and it is unlikely that the blinding could have been broken or that no blinding or incomplete blinding occurred, but the review authors judge that the outcome is not likely to be influenced by lack of blinding); high risk (blinding of key study participants and personnel attempted, but it is likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding or no blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding); or unclear risk (no or unclear information provided to permit judgment)
Blinding of outcome assessment (detection bias): the methods used to blind outcome assessors from knowledge of which intervention a participant received and blinding should be assessed separately for each outcome	Low risk (blinding of outcome assessment ensured, and it is unlikely that the blinding could have been broken or that no blinding of outcome assessment occurred, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding); high risk (blinding of outcome assessment, but it is likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding or no blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding); or unclear risk (no or unclear information provided to permit judgment)
Incomplete outcome data (attrition bias): the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors	Low risk (no missing outcome data, reasons for missing outcome data are unlikely to be related to true outcome; missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups, and because pain is a continuous outcome, for continuous outcome data, plausible effect size [MD or SMD] among missing outcomes is not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods); high risk (reason for missing outcome data is likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for continuous outcome data, plausible effect size (MD or SMD) among missing outcomes is enough to induce clinically relevant bias in observed effect size; "as-treated" analysis done with substantial departure of the intervention received from that assigned at randomization; potentially inappropriate application of simple imputation); or unclear risk (insufficient reporting of attrition and exclusions to permit judgment)
Selective reporting: state how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Low risk (the study protocol is available and all of the study's prespecified outcomes that are of interest in the review have been reported in the prespecified way, or the study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were prespecified); high risk (not all of the study's prespecified primary outcomes have been reported; 1 or more primary outcomes is reported by using measurements, analysis methods, or subsets of the data that were not prespecified; 1 or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis); or unclear risk (no or unclear information provided to permit judgment)
Other sources of bias: any important concerns that could be the possible sources of bias	Low risk (study appears to be free of other sources of bias); high risk (there is at least 1 important RoB due to specific study design or early termination of trial or extreme baseline imbalance); or unclear risk (no or unclear information provided as to whether an important RoB exists)

SUPPLEMENTAL TABLE 5 Characteristics of Excluded Studies

Study	Reason for Exclusion
Abuelkheir	Population: children from 2 mo to 6 y for routine immunization
Anand	Design: it is systematic review
Anonymous	Design: it is narrative review
Anonymous	Did not meet the study eligibility criteria
Anonymous	Population: all children were older than 3 mo
Arendt-Nielsen	Population and design: patients were adult, and not RCT
Arendts	Population and comparator: children from 12 mo to 12 y of age, and comparator was Amethocaine
Arrowsmith	Population and comparator: patients were 1–15 y old, and comparator is Amethocaine
Ballantyne	Design: it is commentary or summary of evidence from an RCT
Ballantyne	Intervention: intervention was tetracaine gel, and comparator was EMLA cream
Basiri-Moghadam	Population: all infants 4 mo old
Batalha	Population: all children older than 3 mo
Baxter	Design and population: it is a prospective randomized trial with no control group, and population is 0–18 y of age
Bellieni	Design: it is not RCT (no control group), and procedure is IM injection
Bueno	Design and intervention: it is a review article, and intervention is sucrose
Chen	Intervention: intervention is lidocaine versus pacifier
Clarke	Population: all children older than 3 mo
Danek	Population: all children older than 3mo
Deshmukh	Intervention: comparing placebo with sucrose at different concentrations, no EMLA
Di Gioia	Design: it is not an RCT
Essink-Tjebbes	Design: it is a systematic review
Eun Kyung Choi	Population: all children older than 13 mo
Fabre	Design: it is not an RCT
Faghihi	It does not meet the study eligibility criteria
Fein	Population: all children older than 3 mo
Fry	Population: all patients older than 12 mo
Fukuda	It does not meet the study eligibility criteria
Garcia	Outcome measure presented in proportion, which made it difficult to extract the data
Gourrier	Design: it is a prospective clinical trial with no comparator
Gourrier	Design: it is a prospective clinical trial with no comparator
Gupta	Procedure was an IM injection (DPT)
Hui-Chen	Design: it is a prospective study and not RCT
Jain	Intervention: intervention is amethocaine
Jain	Intervention: intervention is amethocaine
Koren	Design: it is a narrative review
Kurien	Population: all children older than 3 mo
Lehr	Design: it is a narrative review
Lemyre	Intervention: tetracaine versus placebo
Lemyre	Intervention: tetracaine versus placebo
Lindh	Population: infants are having immunization as procedure
Long	Intervention: tetracaine versus placebo
Lunoe	Population and intervention: patient population was 1–6 y of age, and intervention is lidocaine
Meyer	Design: letter to editor, and procedure commented was heel lancing
Michiels	Design: it is a systematic review
Mjahed	Population: all children older than 3 mo of age
Moghadam	Population: it does not meet the population criteria and procedure
Moore	Intervention: amethocaine versus placebo
Muraca	Population: patients who required IM injection
Newbury	Population: all children older than 3 mo
Oliveira	Could not get the abstract as presented at a Pediatric Academic Societies Annual Meeting in 2005
Robertson	Design: it is not an RCT
Robieux	Population: all children older than 3 mo
Sabety	Intervention: lidocaine versus sucrose
Shah	Design: it is a systematic review
Taddio	Population: all children older than 3 mo, and procedure is pain
Taddio	Design: it is not an RCT
Taddio	Design: it is a systematic review
Taddio	Design: it is not an RCT
Taddio	Could not find the abstract that was presented in 2010; however, study was published in 2011
Taddio	Intervention: lidocaine liposomal versus sucrose versus lidocaine + sucrose
Taddio	Intervention: liposomal lidocaine procedure: vaccination, DPT
Taddio	Intervention: liposomal lidocaine procedure: vaccination, DPT
Weise	Design: it is not an RCT

TABLE 5 Continued

Study	Reason for Exclusion
Wig	Population: all children older than 3 mo
Wilson	Intervention: comparing placebo with sucrose
Young	Population: all children older than 3 mo

DPT, diphtheria, pertussis and polio; IM, intramuscular.

SUPPLEMENTAL TABLE 6 Characteristics of Study by Abad et al

	Description
Methods	Single-center RCT performed at neonatal unit of the University Hospital of the Canary Islands, Tenerife, Spain
Participants	51 term neonates in stable condition, with a GA between 37 and 42 wk and a postnatal age <4 d. 55 venipunctures were performed in 51 term neonates
Interventions	Group W: 2 mL of spring water Group S: 2 mL of sucrose 24% Group E: 1 g of EMLA cream Group E + S: 1 g of EMLA cream and 2 mL of sucrose water During data extraction, group E was used as intervention group and group S as comparator group
Outcomes	Total crying time, HR, respiratory rate, and arterial oxygen saturation were measured blindly at baseline, immediately postvenipuncture, and 2 and 4 min afterward
Notes	The physiologic response to venipuncture over time was measured as an indicator of distress and pain caused by the invasive procedure. HR and RR were assessed by a cardiorespirograph (Roche Patient Monitoring, mod. 107; Roche, Watford, UK), and SaO_2 was measured transcutaneously with a pulse oximeter (Nellcor, mod. N180; Hayward, CA)

HR, heart rate; SaO_2, oxygen saturation.

SUPPLEMENTAL TABLE 7 Abad et al: RoB

Bias	Author's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	Neonates were randomly allocated, using a randomly numbered table, to 1 of the 4 treatments
Allocation concealment (selection bias)	High risk	No clear information provided regarding allocation concealment, such as telephone or central randomization; consecutively numbered, sealed, opaque envelopes; hence, considered as high risk
Blinding of participants and personnel (performance bias)	Low risk	Staff members not engaged in the study participated in the placement of monitors, treatment application, and skin preparation
Blinding of outcome assessment (detection bias)	Low risk	Different people, unaware of group assignment, performed the venipuncture and data recording, respectively
Incomplete outcome data (attrition bias)	Low risk	Data from 51 neonates (38 boys, 13 girls) were obtained. In total, 55 recordings of SaO_2, HR, and RR were performed. In total, 55 recordings of time spent crying were made
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were prespecified, such as total crying time, and all the physiologic variables
Other bias	Low risk	I did not identify other sources of bias

HR, heart rate; SaO_2, oxygen saturation.

SUPPLEMENTAL TABLE 8 Acharya et al

	Description
Methods	Single-center RCT performed at special care infant unit, Peterborough District Hospital
Participants	20 preterm infants with GAs between 26 and 36 wk were included in the study
Interventions	0.5 mL of EMLA or placebo cream over a prominent vein on the dorsum of the hand or foot, in a thick layer, and covered with occlusive dressing
Outcomes	Changes in physiologic variables (heart rate, blood pressure, oxygen saturation) and behavioral responses (NFCS score, crying time) before and after venipuncture. Toxicity was assessed by comparing methemoglobin concentrations at 1 and 8 h after application.
Notes	The procedure was divided into 3 phases. The preprocedure phase, from beginning of recordings to needle insertion, lasted 2.5 min. The procedure phase lasted from needle insertion to needle removal, and the postprocedure phase, from needle removal to end of recordings, lasted 2.5 min

SUPPLEMENTAL TABLE 9 Acharya et al: RoB

Bias	Author's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	Infants were randomly assigned to receive either EMLA or a placebo cream (aqueous cream) on the first occasion. The alternate cream was used on the second occasion. The creams were dispensed in 1-mL syringes in 0.5-mL aliquots
Allocation concealment (selection bias)	High risk	No clear information provided regarding allocation concealment, such as telephone or central randomization; consecutively numbered, sealed, opaque envelopes; hence, considered as high risk
Blinding of participants and personnel (performance bias)	Low risk	Randomization and blinding were done by 1 of the authors (J.P.) in the hospital pharmacy
Blinding of outcome assessment (detection bias)	Low risk	30 s of the tape before needle insertion and 30 s of the tape after needle insertion for all infants with each cream were analyzed by 2 of the authors (R.B.) and (P.B.) on separate occasions. Both were blinded to the type of creams used
Incomplete outcome data (attrition bias)	Low risk	19 patients completed the study (1 patient was discharged early and had venipuncture with only 1 cream)
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were prespecified, such as changes in physiologic variables (heart rate, blood pressure, oxygen saturation), behavioral responses (NFCS score, crying time), and methemoglobin concentrations at 1 and 8 h after the application
Other bias	Low risk	I did not identify other sources of bias

SUPPLEMENTAL TABLE 10 Aziznejad et al

	Description
Methods	Single-center RCT in neonatal ward of ward of Amirkola Pediatric Hospital, Babol, Iran 120 term neonates (GA of 37–42 wk) with neonatal hyperbilirubinemia needed venipuncture
Participants	120 term neonates (GA of 37–42 wk) with neonatal hyperbilirubinemia needed venipuncture
Interventions	120 neonates were divided into the following 4 groups: group 1: no treatment, group 2: 2 mL of 25% sucrose, group 3: 2 mL of breast milk, and group 4: 1 g of 2.5% EMLA cream
Outcomes	Pain is the outcome that was assessed by the DAN pain scale. The associated physiologic indices, including heart rate and respiratory rate in min and arterial blood oxygen saturation, were measured and recorded by pulse oximeter device at the beginning of and 5 min after venipuncture. Also, crying time in s was measured and recorded in 5 first min of venipuncture
Notes	Venipuncture of all samples was venously performed by one of the staff members of a neonatal ward previously coordinated with and by using Scalp Needle No. 23 (SUPA Co.) in the antecubital area

SUPPLEMENTAL TABLE 11 Aziznejad et al: RoB

Bias	Author's Judgment	Support for Judgment
Random sequence generation (selection bias)	High risk	Samples were allocated by nonrandom sampling methods in 4 randomly arranged block groups
Allocation concealment (selection bias)	High risk	No clear information provided regarding allocation concealment, such as telephone or central randomization; consecutively numbered, sealed, opaque envelopes; hence, considered as high risk
Blinding of participants and personnel (performance bias)	Low risk	It is a double-blind study, and it appears that blinding of participants and key study personnel ensured and is unlikely that the blinding could have been broken
Blinding of outcome assessment (detection bias)	Low risk	DAN score is observed by a specific and trained nurse (a person other than the sampler) through 3 separate parameters: facial movements, organ movement, and sound levels. The neonate was filmed to enhance the accuracy of those parameters, and finally the DAN score was measured and recorded
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data were reported
Selective reporting (reporting bias)		Although the study protocol is not available, it is clear that the published reports include all expected outcomes, including those that were prespecified in the trial
Other bias	Low risk	I did not identify other sources of bias

SUPPLEMENTAL TABLE 12 Biran et al

	Description
Methods	Multicenter, randomized, double-blind prospective study from the NICUs of 2 French hospitals (Hôpital Armand Trousseau and Centre Hospitalier de Meaux)
Participants	80 infants younger than 37 wk GA during 1 routine venipuncture for blood sampling
Interventions	Each child randomly received either sucrose and application of a placebo cream (S group) or sucrose and EMLA cream (SE group) before venipuncture
Outcomes	Pain outcome was assessed by using the DAN behavioral scale and PIPP
Notes	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

SUPPLEMENTAL TABLE 13 Biran et al

Bias	Author's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	An assistant not involved in the study performed the randomization in advance in blocks of 8, using a randomly numbered table
Allocation concealment (selection bias)	Low risk	40 infants were allocated to the sucrose group, and 40 infants were allocated to the sucrose and EMLA group. Placebo or EMLA cream syringes were covered with identical stickers. Treatment allocations were placed in opaque, sealed envelopes, and the syringes were numbered 1–80
Blinding of participants and personnel (performance bias)	Low risk	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.
Blinding of outcome assessment (detection bias)	Low risk	2 specially trained observer nurses independently assessed the recordings to assess the arousal state and the pain induced by the procedures by using the DAN scale, the 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
Incomplete outcome data (attrition bias)	Low risk	4 infants were excluded after random assignment (3 in the sucrose group and 1 in the sucrose and EMLA group) because of technical video problems; thus, the final analysis included 37 infants in the sucrose group and 39 in the sucrose and EMLA group
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes, such as pain
Other bias	Low risk	I did not identify other sources of bias

SUPPLEMENTAL TABLE 14 Brisman et al

	Description
Methods	Single-center, double-blind, randomized, and placebo-controlled study with parallel groups
Participants	47 neonates, aged 0–3 mo, with a postconceptual age of >37 wk and a body wt between 2.8 and 5.7 kg, were included in a double-blind, randomized, placebo-controlled study
Interventions	Total dose of 1.0 g EMLA or placebo was applied to 2 sites (0.5 g at each site) for 60–70 min
Outcomes	Venous methemoglobin levels were determined in each patient at baseline and at 3 randomly assigned times, 0.5–18 h after application
Notes	All infants had an indwelling venous catheter for other medical purposes. Blood samples for methemoglobin determinations were drawn from the indwelling venous catheter and determined by a spectrophotometric method using an OSM3 Hemoximeter

SUPPLEMENTAL TABLE 15 Brisman et al: RoB

Bias	Author's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	Each eligible infant was randomly assigned to EMLA or placebo treatment. Patients were treated with 1 g of EMLA or placebo cream (0.5 g at 2 different sites), either on the back of the hand or on the cubital area, each site covering an area of 4–5 cm^2
Allocation concealment (selection bias)	High risk	No clear information provided regarding allocation concealment, such as telephone or central randomization; consecutively numbered, sealed, opaque envelopes; hence, considered as high RoB.
Blinding of participants and personnel (performance bias)	Low risk	The study was double blind, randomized, and placebo controlled with parallel groups
Blinding of outcome assessment (detection bias)	Low risk	Because the outcome measure is methemoglobin level, which was assessed by spectrophotometric method that I believe will not be affected by whether the blinding of outcome assessors was done or not, it is considered as low RoB
Incomplete outcome data (attrition bias)	Low risk	47 infants (36 boys, 11 girls) were treated with active cream or placebo. 10 patients in the EMLA group and 8 in the placebo group had received paracetamol. 4 patients in the EMLA group and 3 in the placebo group had surgery during the study period
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that the published reports include all expected outcomes, such as methemoglobin level
Other bias	Low risk	I did not identify other sources of bias

SUPPLEMENTAL TABLE 16 Gradin et al

	Description
Methods	Multicenter RCT performed in Sweden
Participants	201 newborn infants undergoing venipuncture for clinical purpose Inclusion criteria: GA ≥36 wk; >24 h postnatal age to <30 d of life
Interventions	Group 1: EMLA on the skin and placebo (sterile water) orally Group 2: glucose 30% orally and placebo on the skin 0.5 g of EMLA or placebo on the dorsal aspect of the hand and covered with an occlusive dressing, and after 60 min, the dressing and test substance were removed. A 1-mL dose of 30% glucose or water was given by syringe into the infant's mouth
Outcomes	Pain was measured by the duration of crying after the skin puncture and by the PIPP scale PIPP: the PIPP was used to assign points for changes in 5 parameters during the first 30 s after the painful events: 3 for different facial actions, 1 for heart rate, and 1 for oxygen saturation. The higher the score, the greater the pain response. A total of 6 or less indicates minimal or no pain, and the maximum score is 18 Other outcomes were total time taken for blood sampling, any local effect of the cream on skin, presence of parents, use of pacifier or finger for sucking, and frequency of successful sampling
Notes	Data from an earlier study was used to estimate the sample size with 80% power and $P < .1$

SUPPLEMENTAL TABLE 17 Gradin et al: RoB

Bias	Author's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	On inclusion in the study, the infants were randomly allocated to 1 of 2 groups by use of a table of random numbers
Allocation concealment (selection bias)	Low risk	Treatments were received in identical packages marked only with a No. The Pharmacy of Orebro Medical Center Hospital, Sweden, performed the packing and randomization procedure in batches of 20
Blinding of participants and personnel (performance bias)	Low risk	It is a double-blind study, and it appears that blinding of participants and key study personnel ensured, and it is unlikely that the blinding could have been broken. One assistant nurse placed 0.5 g of EMLA or placebo on the dorsal aspect of the hand and covered it with an occlusive dressing, and a 1-mL dose of 30% glucose or water was given by syringe into the infant's mouth
Blinding of outcome assessment (detection bias)	Low Risk	Blinding of outcome assessment was ensured. 4 independent observers, trained in the PIPP method and familiar with the observation protocol (2 in Orebro, 2 in Huddinge), made the observations. Interobserver reliability was 0.81% by using the ICC
Incomplete outcome data (attrition bias)	Low risk	There were 99 infants in the EMLA group and 102 infants in the glucose group. 5 infants were excluded after the random assignment (1 in the EMLA group and 4 in the glucose group): 2 of them were <36 wk, 1 infant had antibiotic treatment, 1 developed seizures during the procedure, and in 1 case, the parents did not want to proceed. After exclusion of these 5 infants, there were equal numbers of infants in each group (98 infants in the EMLA group and 98 infants in the glucose group). Moreover, pain is the continuous outcome, and plausible effect size (MD) among missing outcomes was not enough to have a clinically relevant impact on observed effect size
Selective reporting (reporting bias)	Low risk	Although the study protocol is not available, it is clear that the published reports include all expected outcomes, including those that were prespecified in the trial
Other bias	Low risk	I did not identify other sources of bias

ICC, intraclass coefficient.

SUPPLEMENTAL TABLE 18 Larsson et al

	Description
Methods	Single-center RCT performed at the Karolinska Hospital in Sweden
Participants	120 term infants in the maternity ward who were to be tested for phenylketonuria were included in the study
Interventions	500 mg of EMLA or placebo was placed on the dorsum of the hand, covered with an occlusive dressing, and left in place for 60 min. 1 g of EMLA cream or placebo cream corresponded to ∼1 mL
Outcomes	Outcomes include pain, which was assessed by NFCS, total time needed to complete the phenylketonuria test, and the No. skin punctures required to complete venipuncture
Notes	The cream consists of the following: lignocaine 25 mg, prilocaine 25 mg, arlatone 289.19 mg, carboxy-polymethylene 10 mg, NAOH pH 8.7–9.7 q.s., and H_2O 1 g. The composition of the placebo consists of fractionated coconut oil 50 mg and arlatone

NAOH, sodium hydroxide.

SUPPLEMENTAL TABLE 19 Larsson et al: RoB

Bias	Author's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	Astra La "kemedel," So "derta" Ije, Sweden, performed the randomization procedure
Allocation concealment (selection bias)	Low risk	EMLA and placebo were supplied in identical tubes marked only with a No.
Blinding of participants and personnel (performance bias)	Low risk	Because EMLA and placebo were supplied in identical tubes marked only with a No., it was considered as blinding participants and personnel
Blinding of outcome assessment (detection bias)	Low risk	2 blinded observers analyzed the results from a video or audiotape. Each observer assessed the data independently and could not communicate findings to the other
Incomplete outcome data (attrition bias)	Low risk	5 patients in the EMLA group and 4 patients in the placebo group were excluded. These patients were not replaced
Selective reporting (reporting bias)	Low risk	Although the study protocol is not available, it is clear that the published reports include all expected outcomes, including those that were prespecified in the trial
Other bias	Low risk	I did not identify other sources of bias

SUPPLEMENTAL TABLE 20 Lindh et al

	Description
Methods	Single-center, randomized, double-blind, placebo-controlled trial performed in Sweden
Participants	60 term newborn infants from the maternity ward were enrolled
Interventions	1 g (1 mL of cream measured with a syringe) of EMLA or placebo (supplied by Astra, Sweden) was applied to a 4-cm^2 area on the dorsal side of the infant's left hand
Outcomes	Outcomes that were measured include incidence of crying, HR, and spectral analysis of HR variability
Notes	ECG electrodes (blue sensor, Medico test w) were used, and the ECG signal was sampled via a Hewlett Packard cardioscope and stored in a computer. The recording was divided into 3 different sequences starting with (1) a baseline period of 5 min, (2) 2 min of warming (37.8°C) the hand, and (3) venipuncture and blood sampling (80 s). Crying was recorded with a tape recorder and simultaneously stored in the computer (sampled at 1000 Hz) to allow for synchronization with the ECG signal

ECG, electrocardiogram; HR, heart rate.

SUPPLEMENTAL TABLE 21 Lindh et al: RoB

Bias	Author's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	Randomization was done by Astra, Sweden
Allocation concealment (selection bias)	Low risk	1 g (1 mL of cream measured with a syringe) of EMLA or placebo (supplied by Astra, Sweden) was applied to a 4-cm^2 area on the dorsal side of the infant's left hand, following a randomized double-blind procedure
Blinding of participants and personnel (performance bias)	Low risk	This is a double-blind RCT, and it appears that blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken
Blinding of outcome assessment (detection bias)	Low risk	This is a double-blind RCT, and outcomes are objective outcomes. It appears that outcome measurement is not likely to be influenced by lack of blinding of outcome assessor
Incomplete outcome data (attrition bias)	Low risk	2 tape recordings of crying were excluded, both in the EMLA group. 3 ECG recordings were excluded because of frequent artifacts (2 in the placebo group and 1 in the EMLA group)
Selective reporting (reporting bias)	Low risk	Although the study protocol is not available, it is clear that the published reports include all expected outcomes, including those that were prespecified in the trial
Other bias	Low risk	I did not identify other sources of bias

ECG, electrocardiogram.

SUPPLEMENTAL TABLE 22 Marcatto Jde et al

	Description
Methods	A randomized, triple-masked controlled trial was conducted at 2 tertiary NICUs in the city of Belo Horizonte, Brazil
Participants	Participants included 30 preterm neonates (≥28 and <37 wk of GA) during the first wk of life, with a clinical indication for PICC placement
Interventions	Group 1: EMLA plus placebo Group 2: glucose plus placebo cream Group 3: EMLA plus glucose The cream to be applied was outlined before the procedure by using a template (4 cm^2 corresponding to 0.6 g). Glucose or water was administered in amounts of 2 mL on the tongue with a pacifier 2 min before the skin preparation
Outcomes	Pain experienced was evaluated by using the NIPS, and pain was assumed when the score was ≥4. For pain, 6 observation periods were established: T1, baseline, lasting at least 15 min without any kind of handling of the neonate; T2, cream application; T3, application of antiseptic sterile drapes and tourniquet; T4, puncture; T5, progression of the catheter and dressing application; and T6, recovery phase, lasting 15 min after completing the procedure. As secondary outcomes, changes in HR, Sp02, and MAP were measured
Notes	A sample size of 9 patients in each group was determined to have 90% of power to detect this clinical effect, with a significance level (α) of .05 (2 tailed)

HR, heart rate; MAP, mean arterial pressure; Spo_2, O^2 saturation.

SUPPLEMENTAL TABLE 23 Marcatto Jde et al: RoB

Bias	Author's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	The infants were randomly assigned sequentially to 1 of 3 treatment groups by using a randomly numbered table
Allocation concealment (selection bias)	High risk	No clear information provided regarding allocation concealment, such as telephone or central randomization; consecutively numbered, sealed, opaque envelopes; hence, considered as high RoB
Blinding of participants and personnel (performance bias)	Low risk	This is a triple-blind RCT, and it appears that blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken
Blinding of outcome assessment (detection bias)	Low risk	The procedures were videotaped, and the NIPS scores were determined by another researcher who was blinded to the treatment
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data were reported
Selective reporting (reporting bias)	Low risk	Although the study protocol is not available, it is clear that the published reports include all expected outcomes, including those that were prespecified in the trial
Other bias	Low risk	I did not identify other sources of bias

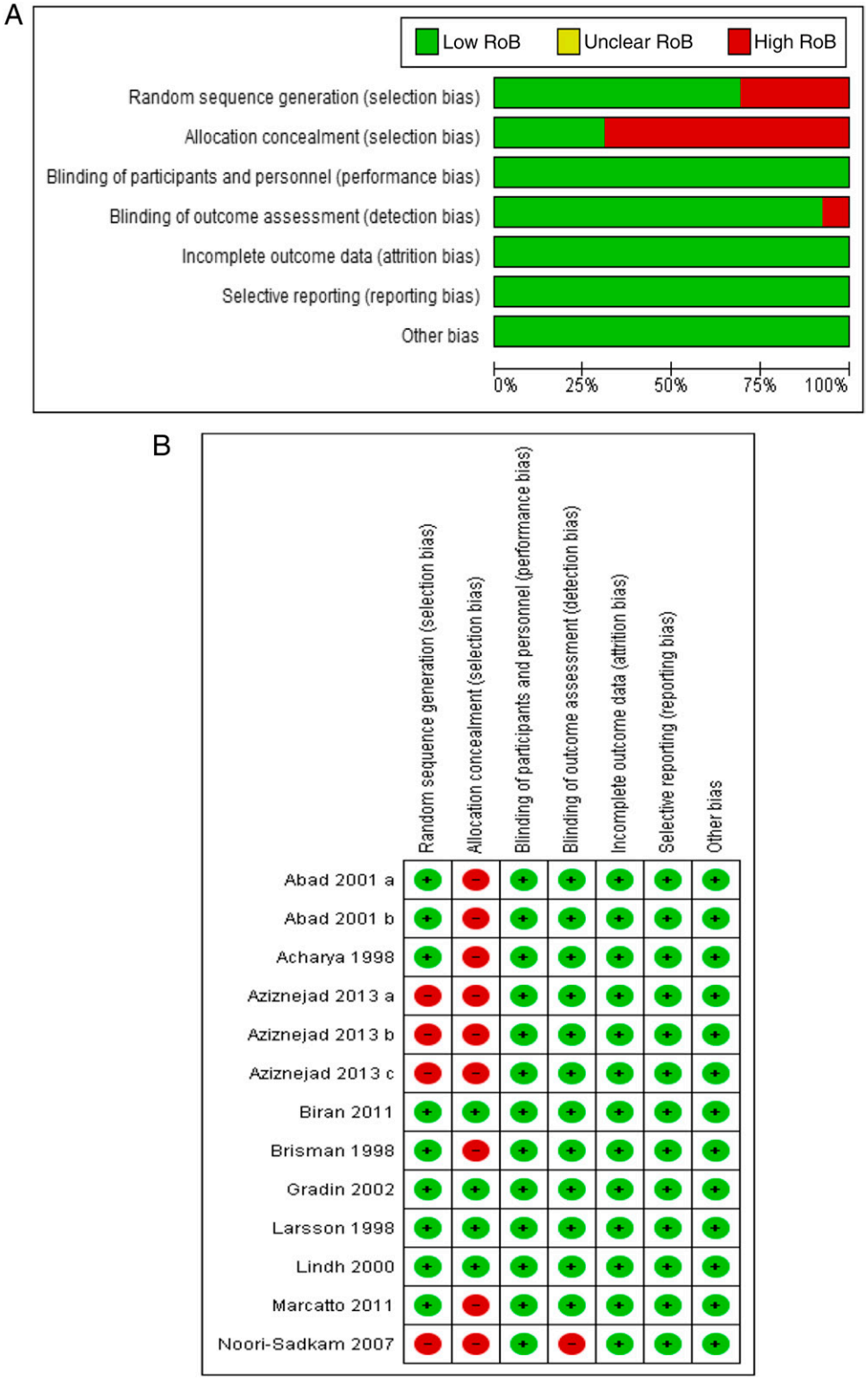
SUPPLEMENTAL TABLE 24 Noori-Sadkam

	Description
Methods	Single-center, double-blind, RCCT was conducted in Shahid Sadoughi Hospital situated in Yazd city, Yazd Province
Participants	220 term neonates (≥38 wk), aged more than 1 and <15 d, who underwent venipuncture for bilirubin measurement
Interventions	Group 1 received 0.5 g of EMLA cream, which was applied to the skin of the newborns, along with 1 mL of orally administered sterile water as placebo. Group 2 received 1 mL of 30% solution of glucose, which was administered orally to the neonates whose skin was treated with 0.5 g of vitamin A and D cream as placebo
Outcomes	Symptoms associated with pain while venipuncturing was measured by NIPS, and crying time was compared between the 2 groups
Notes	Data from an earlier study were used to estimate the sample size by considering $\sigma 1 = 7.5$ (SD of crying time in EMLA group) and $\sigma 2 = 6.7$ (SD of crying time in glucose group)

RCCT, randomized clinical trial.

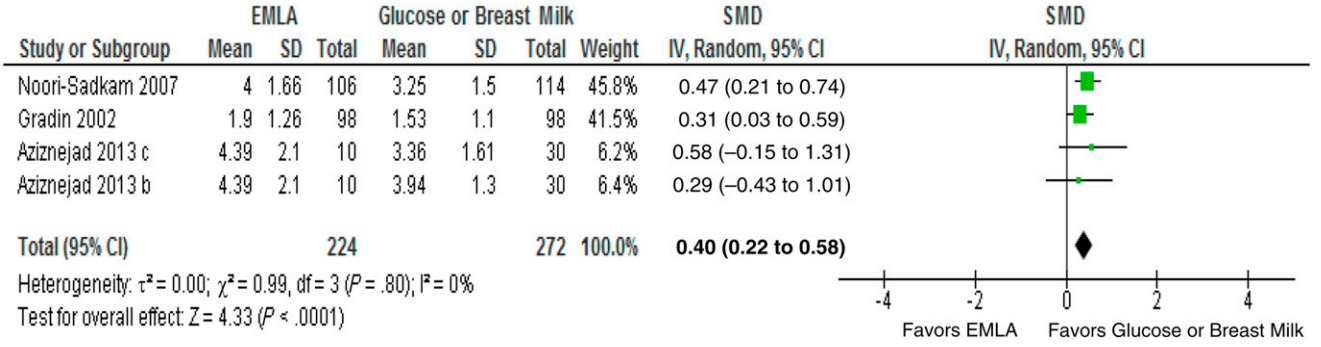
SUPPLEMENTAL TABLE 25 Noori-Sadkam: RoB

Bias	Author's Judgment	Support for Judgment
Random sequence generation (selection bias)	High risk	Although it is reported as a double-blind randomized clinical trial, no explanation was provided regarding how randomization was done
Allocation concealment (selection bias)	High risk	No clear information provided regarding allocation concealment, such as telephone or central randomization; consecutively numbered, sealed, opaque envelopes; hence, considered as high RoB
Blinding of participants and personnel (performance bias)	Low risk	This is a double-blind trial, and it appears that blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken
Blinding of outcome assessment (detection bias)	High risk	Although it is reported as double-blind randomized trial, no information was provided regarding blinding of outcomes assessors. The NIPS scores were done at the time of venipuncture, which could likely be influenced by the lack of blinding
Incomplete outcome data (attrition bias)	Low risk	A total of 10 neonates, 9 subjects in group I and 1 in group 2, did not meet research criteria because of unsuccessful venipuncture and were therefore excluded
Selective reporting (reporting bias)	Low risk	Although the study protocol is not available, it is clear that the published reports include all expected outcomes, including those that were prespecified in the trial
Other bias	Low risk	I did not identify other sources of bias

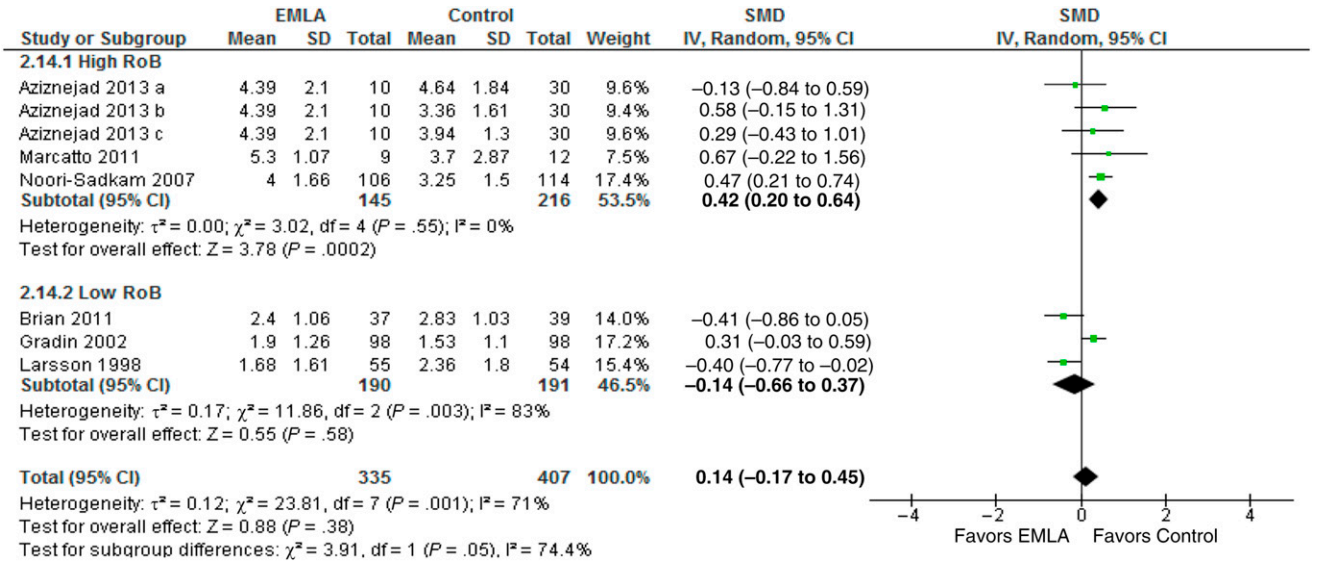


SUPPLEMENTAL FIGURE 6

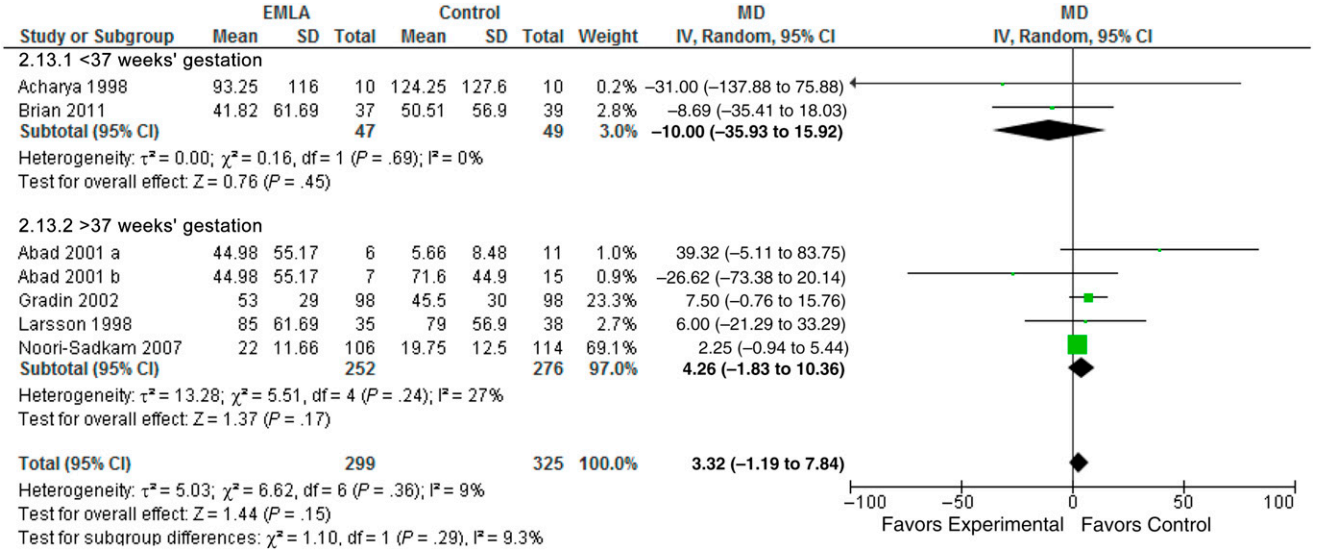
A, RoB graph: review authors' judgments about each RoB item presented as percentages across all included studies. B, RoB summary: review authors' judgments about each RoB item for each included study.



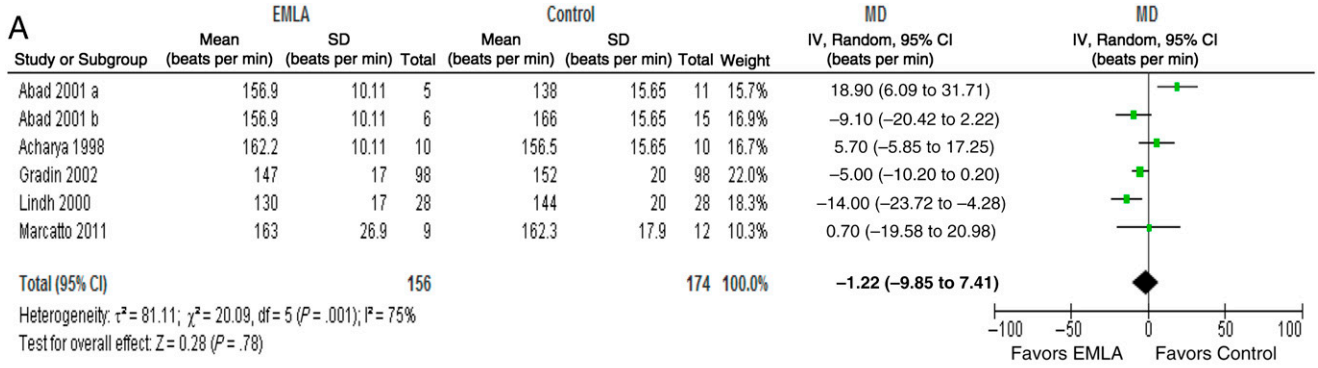
SUPPLEMENTAL FIGURE 7
Forest plot of the comparison of EMLA versus control. The outcome was pain during the venipuncture in term infant. df, degrees of freedom; IV, intravenous.

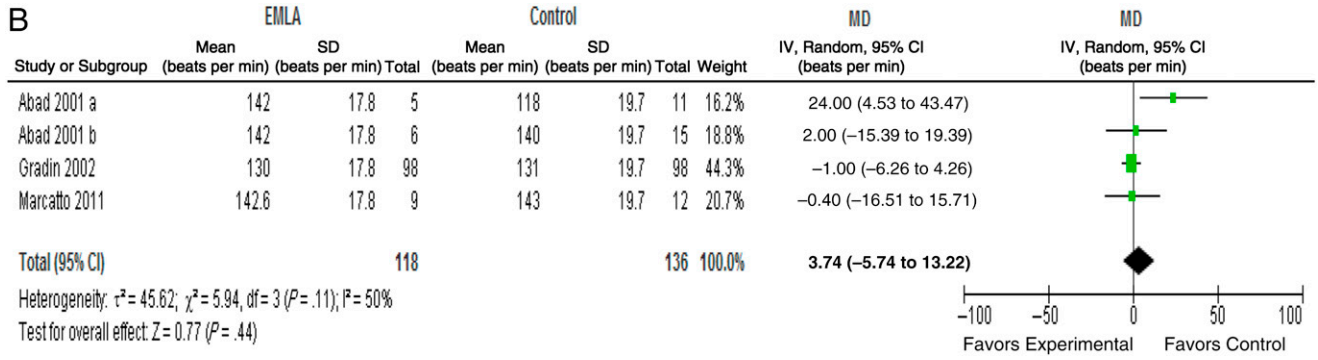


SUPPLEMENTAL FIGURE 8
Forest plot of comparison of EMLA versus control. The outcome was a sensitivity analysis for pain. df, degrees of freedom; IV, intravenous.



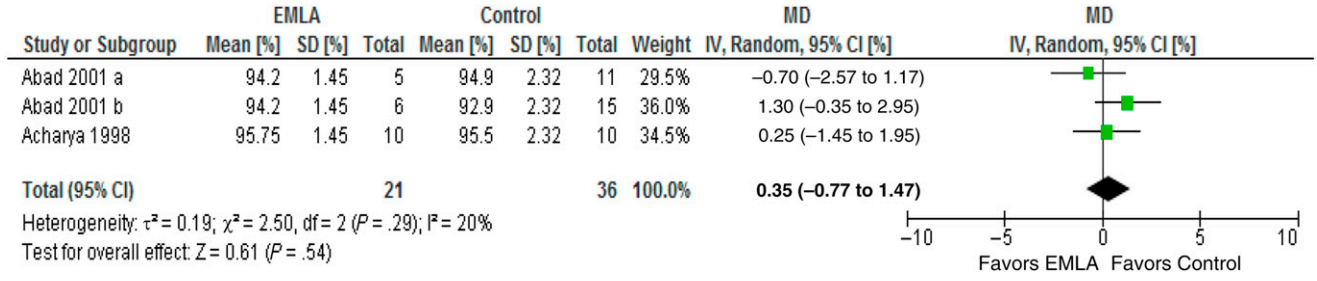
SUPPLEMENTAL FIGURE 9
Forest plot of comparison of EMLA versus control. The outcome was total duration of crying. df, degrees of freedom; IV, intravenous.





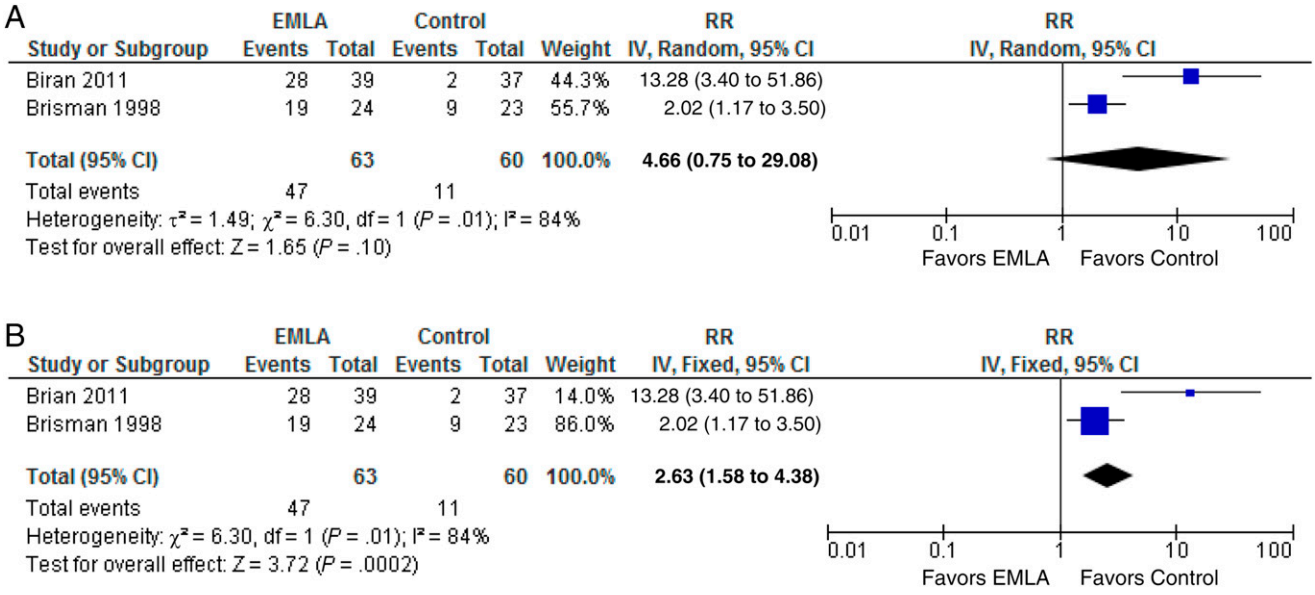
SUPPLEMENTAL FIGURE 10

A, Forest plot of comparison of EMLA versus control. The outcome was heart rate during venipuncture (beats per minute). B, Forest plot of comparison of EMLA versus control. The outcome was heart rate after venipuncture (beats per minute). df, degrees of freedom; IV, intravenous.



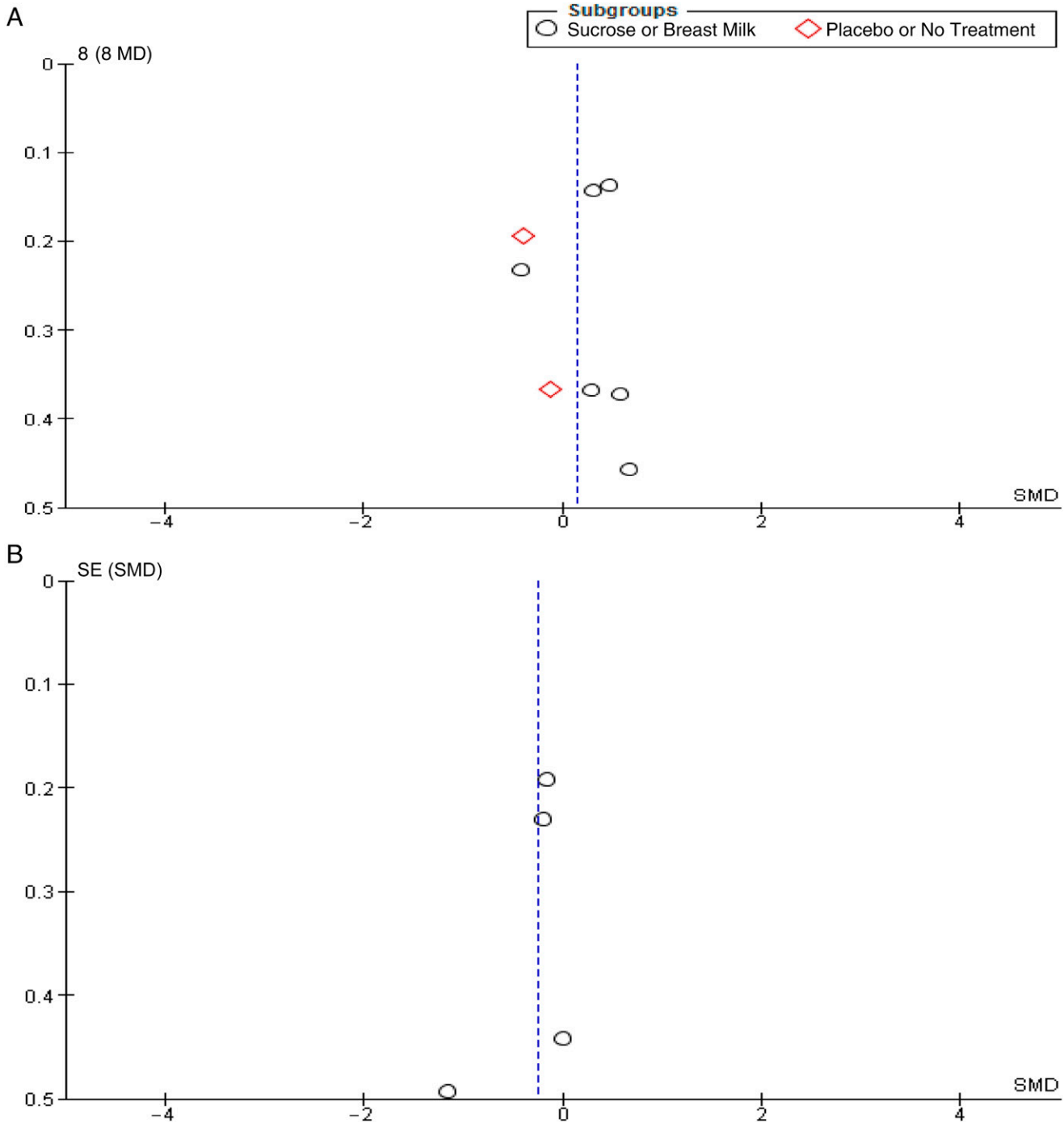
SUPPLEMENTAL FIGURE 11

Forest plot of comparison of EMLA versus control. The outcome was oxygen saturation percentage. df, degrees of freedom; IV, intravenous.



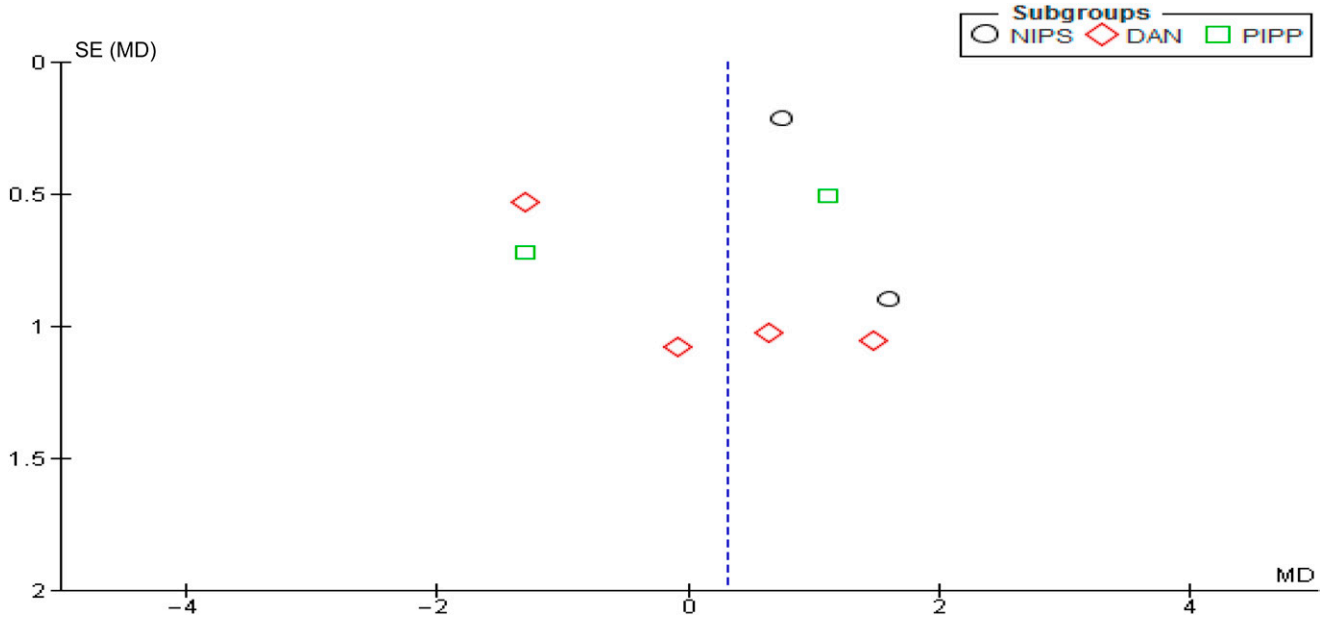
SUPPLEMENTAL FIGURE 12

A, Forest plot of the comparison of a random effects model: EMLA versus control. The outcome was skin blanching. B, Forest plot of the comparison of a fixed effects model: EMLA versus control. The outcome was skin blanching. df, degrees of freedom; IV, intravenous.

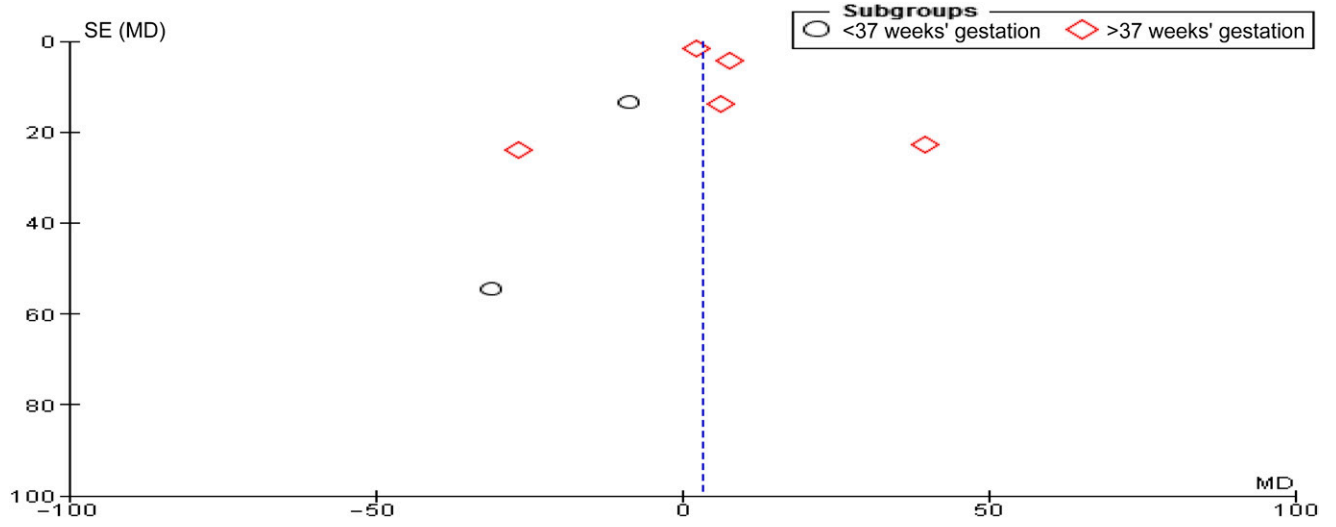


SUPPLEMENTAL FIGURE 13

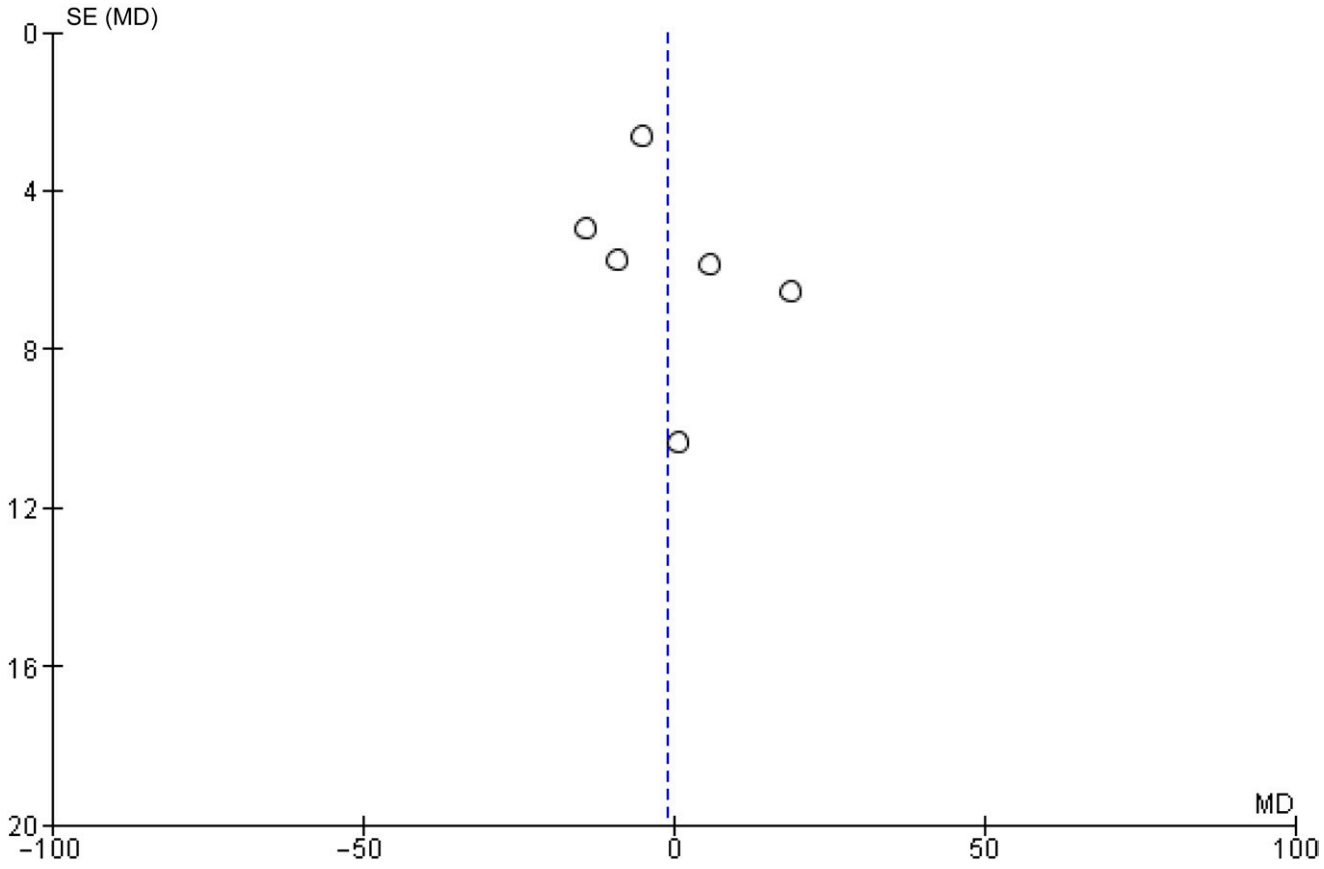
Funnel plots. A, Funnel plot of the comparison of EMLA versus control. The outcome was pain during venipuncture. B, Funnel plot of the comparison of EMLA versus control. The outcome was pain at the end of venipuncture.



SUPPLEMENTAL FIGURE 14
Funnel plot of the comparison of EMLA versus control. The outcome was pain during venipuncture based on pain scales.



SUPPLEMENTAL FIGURE 15
Funnel plot of the comparison of EMLA versus control. The outcome was total duration of crying.



SUPPLEMENTAL FIGURE 16
Funnel plot of the comparison of EMLA versus control. The outcome was heart rate during venipuncture (beats per minute).