Zhao et al. BMC Anesthesiology (2025) 25:115
https://doi.org/10.1186/s12871-025-02991-6

BMC Anesthesiology

SYSTEMATIC REVIEW Open Access

Local analgesia for the relief of pain in children undergoing venipuncture and intravenous cannulation: a systematic review and network meta-analysis

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Abstract

Background Venipuncture and intravenous cannulation are common procedures in hospitals that often cause pain, particularly in children. Despite the availability of various local analgesia methods to alleviate needle-associated pain, the most effective approach remains unknown. The objective of this study is to compare and rank the efficacy of different local analgesia methods in reducing pain in children undergoing venipuncture and intravenous cannulation.

Method Six databases including PubMed, Embase, CINAHL, Scopus, Web of Science, and the Cochrane Library were searched from January 1,1990 to December 1,2024. The primary outcome is the self-reported pain. We assessed the certainty of the body of evidence from the NMA for the primary outcome based on CINeMA.

Result 40 RCTs consisting of 4481 children and 9 local analgesia methods were included in the analysis. Results showed that vapocoolant spray was no more effective than placebo or routine care in reducing needle-associated pain in children. Other interventions including EMLA cream, lidocaine cream, lidocaine iontophoresis, amethocaine, needle-free lidocaine injection system, EMLA patch, lidocaine/tetracaine heating patch and Buzzy produced greater pain reduction in children compared to placebo and routine care. Amethocaine was the most effective local analgesia method with the probability of 57.6% being the best, followed by Buzzy and lidocaine iontophoresis with the probability of 17.0% and 8.4%, respectively.

Conclusion Most local analgesia methods were effective in relieving pain in children undergoing venipuncture and intravenous cannulation except vapocoolant spray which did not show greater pain reduction than placebo or routine care. Amethocaine, Buzzy and lidocaine iontophoresis are the top 3 local analgesia methods to relieve pain in children undergoing venipuncture and intravenous cannulation. However, due to the limited number of direct comparisons, interpretation of some results should be made with caution.

Keywords Local analgesia, Venipuncture, Intravenous cannulation, Children, Pain

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Background

Needle procedures, such as venipuncture and intravenous cannulation, are the most frequently performed procedures in hospitals and one of the most common painful sources for children [1, 2]. As reported, 71% of the hospitalized children and 57.1% of children visiting the emergency room underwent venipuncture or application of peripheral venous catheter. Procedure-induced pain was rated to be moderate and severe by 19.5-38.3% and 8.5-38.3% of children respectively, in different settings [3, 4]. Needle procedure-induced pain has short-term and long-term effects. In short term, pain can cause anxiety, fear and avoidance in children and distress in parents [1]. In terms of long-time effects, repeated nociceptive procedures in early stage of life may contribute to the alteration of sensation and pain pattern at older ages [5, 6]. In addition, procedure-induced pain may interfere with the procedures. An autonomic response triggered by needle pain and fear may result in vasoconstriction, which, in turn, makes venipuncture and cannulation more difficult or even failed [7]. Repeated procedures increase the suffering of children and may damage the relationship between nurses and parents. Due to the significant consequences of pain, pain has been highlighted as the fifth vital sign and gained more and more attention of nurses. Accordingly, some guidelines have been established to manage pain in children during venipuncture and intravenous cannulation [8–10].

It is a priority of nurses to manage pain in children through adequate and effective interventions. Pharmacological and non-pharmacological methods have been recommended for effective management of procedural pain in children [10]. In order to relieve pain during venipuncture and intravenous cannulation, there have existed multiple approaches, such as acupressure [11], distraction and hypnosis [12], sugar [13], local analgesia methods (topical anesthetics, vapocoolant spray and Buzzy), and so on.

Among the approaches, topical anesthetics play a vital role in reducing pain for children with needle procedures. There are several types of topical anesthetic agents, formulations and drug delivery systems in use. Traditional agents utilized as topical anesthetics include eutectic mixture of lidocaine and prilocaine (EMLA) and various lidocaine or amethocaine formulations. The EMLA contains 2.5% lidocaine and 2.5% prilocaine which is widely used and usually regarded as “golden standard” to relieve pain during venipuncture and intravenous cannulation [14]. The EMLA is available either in the form of cream or patch. The EMLA cream is an oil and water emulsion of lidocaine and prilocaine. The EMLA patch applies a small dressing to enhance the effect of cream. They are usually effective about 60 minutes’ application [15]. Lidocaine cream, including ELA-Max or Maxilene, commonly uses for pain control and recommends a 30-minute onset time [16, 17]. Another agent is amethocaine or Ametop which contains 4% gel of amethocaine and requires application time ranging from 30 min to 45 min [18].

Novel drug-delivery systems include lidocaine iontophoresis, lidocaine/tetracaine heating patch, pressurized lidocaine delivery system. Lidocaine iontophoresis is a transdermal drug delivery system that uses an electric current to carry ionized lidocaine across the intact skin and requires several minutes for anesthetic to take effects [19]. The lidocaine/tetracaine heating patch is a novel drug delivery system that uses controlled heat to enhance the delivery of a eutectic mixture of 70 mg lidocaine and 70 mg tetracaine through the skin [20, 21]. The pressurized lidocaine delivery system is a needle-free lidocaine injection device. It employs compressed gas to generate the pressure that delivers the stream or particles of lidocaine to penetrate into the skin and induces dermal analgesia within seconds [22, 23].

In addition, non-pharmacological methods including vapocoolant spray and Buzzy are widely used for local pain relief in children undergoing venipuncture and intravenous cannulation. Vapocoolant spray is a cold spray which produces rapid cooling of the skin via evaporation, decreases the speed of impulse conduction through sensory nerves, and thereby reduces pain. It is a rapid-acting alternative to traditional topical anesthetics [24]. Vibration and cold device (Buzzy) is a bee-shaped device applying a battery-operated vibration and ice to produce analgesia immediately [25].

With so many methods available, nurses may be confronted with such a situation that they need choose the most effective one from two or more local analgesia measures. Under that situation, information on relative efficacy of these interventions is critical. There have been several meta-analyses comparing the efficacy of two local analgesia methods or one local analgesia with placebo/routine care to provide information for nurses when selecting pain relief methods for children [24, 26–30]. For instance, Lander et al. compared amethocaine with EMLA cream and found that amethocaine was more effective in preventing pain in children with venipuncture and intravenous cannulation. These meta-analyses synthesizing direct evidence of head-to-head trials provide valuable information to nurses on relative effects of some two local analgesia methods. However, the information is insufficient for nurses facing the selection between local analgesia methods which have not been directly compared in previous studies. Thus, this study aimed to use a network meta-analysis to compare multiple local analgesia methods simultaneously and produce estimates of the relative effects between any pair of them and find the most effective intervention in pain control. Child-reported pain was the primary outcome of the current study considering that pain is a subjective experience and the child-reported pain would be the most valid indicator for pain. In addition, indicators related to the selection of a local analgesia method were included as secondary outcomes, consisting of success rate at the first attempt, pain assessed by others, anxiety, fear, satisfaction, difficulty of procedure and skin adverse effects.

Methods

Literature search strategy

The following databases were searched for relevant studies: PubMed, Embase, CINAHL, Scopus, Web of Science, and The Cochrane Library. The published date was from January1, 1990 to December 1, 2024 and the language of publication was restricted to English. Initial search terms included "topical anesthetic", "local anesthetic", "EMLA", "lidocaine/prilocaine cream", "lidocaine, prilocaine drug combination", "lidocaine", "liposomal lidocaine", "ELA-Max", "Maxilene", "vapocoolants", "vapocoolant spray", "amethocaine", "Ametop", "tetracaine", "lidocaine iontophoresis", "lidocaine tetracaine patch", "RaPydan", "synera", "s-caine", "needle free system", "needleless system", "J-tip", "INJEX", "ALGRX", "Buzzy", "catheterization, peripheral", "phlebotomy", "blood specimen collection", "venipuncture", "intravenous cannula*", "intravenous puncture", "intravenous insert*", "intravenous placement", "intravenous catheter*", "intravenous access", "intravenous injection", "intravenous infusion", "blood draw*", "blood sampling" "venous cannula*", "venous puncture", "venous insert*", "venous placement", "venous catheter*", "venous access", "venous injection", "venous infusion", "child", "child*", and "adolescent". For each database, the search strategy was personalized. An example search in the PubMed database was shown in the Supplementary File 1. After eligible articles were identified, the reference lists of the eligible articles were manually searched. Included articles in conventional pairwise meta-analyses on this topic were screened as well to avoid possible missing of eligible studies.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) the study compared the analgesic effects of different local analgesia methods, local analgesia methods with placebo, or with routine care; (2) the local analgesia methods were noninvasive and applied on the skin surface; (3) the local analgesia methods were used for procedures of peripheral venipuncture and intravenous cannulation; (4) the study design was a randomized controlled trial; (5) participants were children aged between 2 and 19 years; (6) the language publication is limited to English.

Studies were excluded if (1) the local analgesia methods were applied for peripheral central venous catheter(PICC) or Totally implantable venous access port systems(Port) indewlling; (2) the intervention was a compound method, that is, the intervention integrated more than one pain management method (e.g. topical anesthetics plus virtual reality); (3) data or the full text was not available.

Study selection and data extraction

All records of literature search were imported to the Endnote to eliminate duplicates. Two researchers read the titles and abstracts to screen for potential eligible studies. Then the same researchers independently evaluated the qualification of studies and extracted data. Disagreements between them were resolved by a third researcher.

Information extracted from the included studies comprised the author, year of publication, country, participant age, sample size, local analgesia methods (name/ / dose/application duration), comparison intervention, needle gauge, study setting, cause for procedure, venipuncture site (dorsum of hand/antecubital area/others), pain measurement tool, pain measuring timing (during/after), primary outcome (child-reported pain), secondary outcome (success rate at the first attempt/pain assessed by others/anxiety/fear/satisfaction/difficulty of procedure /skin adverse effects). For studies with pain measured multiple times, only the values measured during or immediately after needle procedure were used. Results of a same intervention with different doses in one study were pooled if the analysis showed no difference in analgesic effect between doses. For studies only reporting median, interquartile range, median or full range, mean and standard deviation (SD) were calculated according to the estimating formulae of Wan [31]. If two types of scales were employed in the same objects in one study, the data with more information was used.

Quality assessment

The Cochrane handbook for systematic reviews of interventions 5.1.0 [32] was used to assess the quality of included studies. Potential sources of bias include random sequence generation, allocation concealment, blinding of participants and staff, blinding of outcome assessors, incomplete outcome data, and selective reporting. The risk of bias from each potential source is evaluated as high, low or unclear. Two researchers independently assessed the risks of bias, and discrepancies were resolved by the third researcher.

Data analysis

A frequentist network meta-analysis combining direct and indirect comparisons in a random-effects model was conducted using the "network" and "mvmeta" packages in the software Stata SE version15.1 (StataCorp LP. College Station, TX, USA). Effect sizes were standardized mean differences (SMDs) because included studies involved different pain rating scales. By combining both direct and indirect evidence across a network of studies, network meta-analysis can compare multiple interventions simultaneously in a single analysis and produce estimates of the relative effects between any pair of interventions in the network. In addition, it can provide estimation of the ranking of the interventions. To valid a network meta-analysis, a core assumption of transitivity should be fulfilled. Transitivity means that different sets of studies included in a network meta-analysis should be similar in important effect modifiers, which makes the estimates from indirect comparisons plausible and comparable to direct evidence. The statistical manifestation of transitivity is consistency. In the present study, we used both global (the global Wald test) and local approaches (node splitting method) to check the inconsistency. For the global approach, inconsistency is evaluated in the entire network by modifying the network meta-analysis model to account for potential inconsistency, whereas the local approach detects potential inconsistent loops of evidence in the network. If p values were greater than 0.05 in the global Wald test and node splitting analysis, it indicates that there was no significant inconsistency [33].

The comparisons of interventions were illustrated with a network map. Relative effects between two interventions were displayed with a league table or a forest plot. The ranking probabilities for all interventions were estimated using the probability of being best, mean rank, the surface under the cumulative ranking curve (SUCRA) [34]. The SUCRA is a numeric presentation of the overall ranking with a single number for each intervention. SUCRA values range from 0 to 100%. The greater the SUCRA value (closer to 100%), the higher the likelihood that the intervention is in the top rank; on the contrary, the smaller the SUCRA value (closer to 0), the more likely that the intervention is in the bottom rank. A funnel plot and Egger's test were used to detect the presence of any significant publication bias in the network meta-analysis.

Assessment of the certainty of the evidence

Confidence of the evidence estimates from the network meta-analysis was assessed based on the CINeMA (Confidence in Network Meta-Analysis) approach. The CINeMA framework is implemented in a freely available, user-friendly web application aiming to facilitate the evaluation of confidence in the results from network meta-analysis. It covers 6 domains: within-study bias (referring to the impact of risk of bias in the included studies), reporting bias (referring to publication and other reporting bias), indirectness, imprecision, heterogeneity and incoherence. Each domain was judged at 3 levels (major concerns, no concerns, some concerns) to each domain. Judgments across domains can be summarised to obtain 4 levels of confidence for each relative treatment effect (very low, low, moderate, or high) [35].

Results

Identification of relevant studies and characteristics of included studies

Overall, 2565 records were identified through database search. After removing duplicates and reading titles and abstracts, 101 studies were left for full text reading. Finally, 40 studies met the inclusion criteria and were included in the meta-analysis. Of the 61 excluded studies, the reasons for exclusion were as follows: 6 studies had no accessible full text, 14 studies did not meet the age criteria, 18 studies did not meet the outcome criteria, 10 studies were not RCTs, 11 studies involved ineligible interventions and 2 studies were not published in English. Detailed screening and selection process are illustrated in Fig. 1.

In total, 4481 participants were included in the network meta-analysis. The mean trial sample size ranges from 22 to 339. The average age of participants reported in the included studies ranged from 5.3 to 14.0 years and male participants accounted for 50.9% of the total population. Two studies were crossover RCTs and the rest were parallel-group RCTs. Two studies were multicentric and the remaining articles were monocentric. There are 37 two-arm trials and 3 three-arm trials. Nine local analgesia methods were included (EMLA cream in 13 studies, Buzzy in 12 studies, lidocaine cream in 7 studies, needle-free lidocaine injection system in 7 studies, vapocoolant spray in 3 studies, lidocaine iontophoresis in 4 studies, amethocaine in 3 studies, lidocaine/tetracaine heating patch in 3 studies and EMLA patch in 2 studies) (see Supplementary File 2).

Eight pain measurement scales were used including the Visual Analog Scale (23 studies) [15, 18, 19, 21–23, 27, 36–51], the Facial Pain Scale-Revised (9 studies) [14, 17, 22, 50, 52–56], the Wong-Baker Faces Scale (9 studies) [21, 41, 46, 48, 57–61], the Oucher Scale (2 studies) [62, 63], the Numeric Rating Scale (2 study) [57, 59], the Color Analog Scale (1 study) [64], the Facial Affective Scale (1 study) [65] and the Poker Chip Tool (1 study) [66]. Eight studies used more than one scale for pain measurement [21, 22, 41, 46, 48, 50, 57, 59].

The most commonly used research setting was the emergency department (15 studies). The primary reasons for venipuncture and intravenous cannulation were blood tests (12 studies) and surgical procedures (7 studies), with other reasons including chemotherapy, blood transfusions, and fluid administration. The dorsum of the hand was the most frequently used site for needle procedures (21 studies), followed by the antecubital area (14 studies). Needle sizes ranged from 18G to 24G, with 22G being the most commonly used.

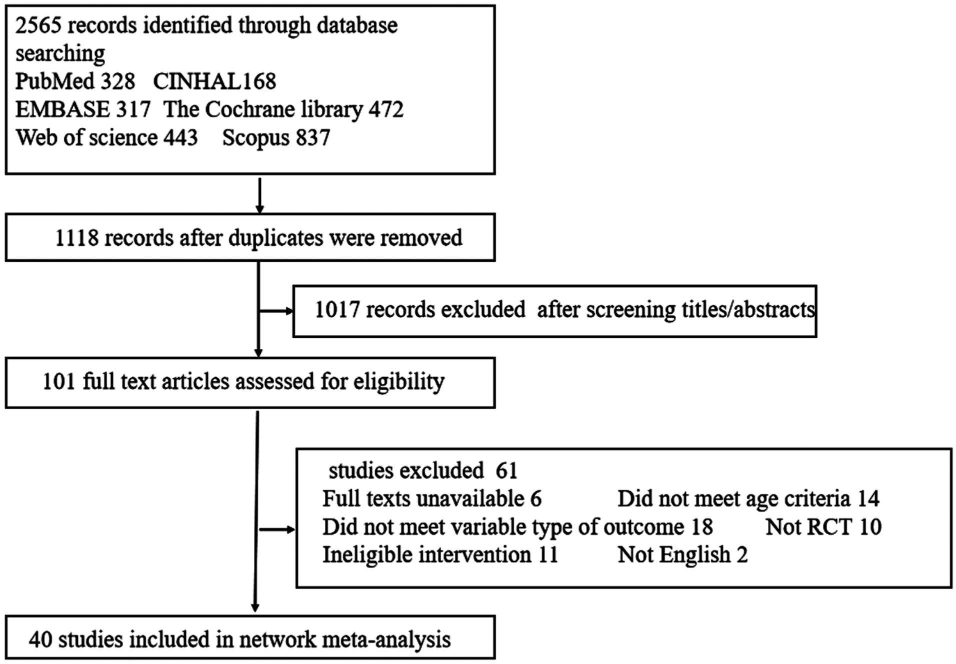

Fig. 1 Flowchart of study selection

Risk of bias assessment

Supplementary File 3 presents the risk of bias of the included studies. Twenty-two studies were evaluated as having a low risk of the methods of random sequence generation. More than half of the included studies did not report adequate information on their methods of allocation concealment (22 studies, 55.0%). Due to the different appearance of interventions, blinding for participants and personnel was not possible in some studies. Among them, 13 studies (32.5%) were evaluated as having a high risk of results being biased from non-blinding. The same 13 studies were considered to be high in the risk of bias from non-blinding of outcome assessment as well. The risk of bias from selective outcome reporting and others was low in all included studies. Briefly, the overall risk of bias was rated as high in 13 studies (32.5%), moderate in 4 studies (10.0%), and low in 23 studies (57.5%).

Primary outcome (child-reported pain)

The network map of available intervention comparisons in this study is shown in Fig. 2. Nodes in the network represent interventions and the size of the nodes is proportionate to the number of children receiving the intervention. Lines link direct comparisons of interventions and the thickness of the lines represents the number of trials included in each comparison. As shown in Fig. 2, the network of the studies included in the analysis is well connected. The most frequently compared intervention was EMLA cream, which was directly compared with all other interventions except vapocoolant spray and Buzzy. EMLA patch was the least compared intervention which was only directly compared with EMLA cream. Comparisons including needle-free lidocaine injection system versus placebo, vapocoolant spray versus placebo and Buzzy versus routine cares made large contributions to the network estimation. Neither the global Wald test nor the node splitting analysis (except lidocaine cream versus needle-free lidocaine injection system) was significant indicating that the whole network and loops were consistent and the prerequisite for network meta-analysis was satisfied.

When compared with routine care and placebo, all the local analgesia methods except vapocoolant spray produced significant pain reduction (see Figs. 3 and 4).

The relative effects of two interventions combining direct and indirect evidence are presented in a league table (Fig. 5). The analysis revealed that amethocaine, Buzzy and lidocaine iontophoresis were better in relieving pain compared to vapocoolant spray. There were no significant differences in pain relief between the remaining interventions.

The probability of being the best, mean rank and the SUCRA are presented in Supplementary File 4. According to the results, amethocaine ranked the highest with the probability of being the best (57.6%), mean rank (1.9) and SUCRA (90.8%). Followed by Buzzy and lidocaine iontophoresis with the probability of being the best (17.0% and 9.3%), mean rank (2.8 and 3.8) and SUCRA (81.7% and 71.7%), respectively. Vapocoolant spray was the least efficacious intervention with the probability of being the best (0%), mean rank (9.2) and SUCRA (18.4%).

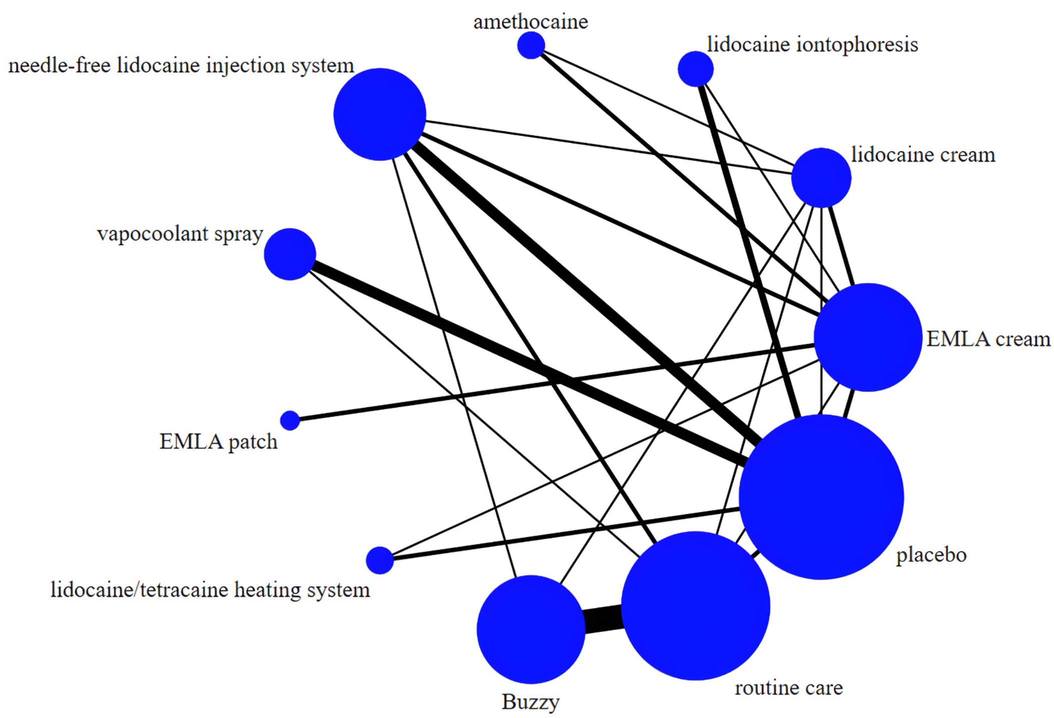

Fig. 2 Network map of local analgesia methods

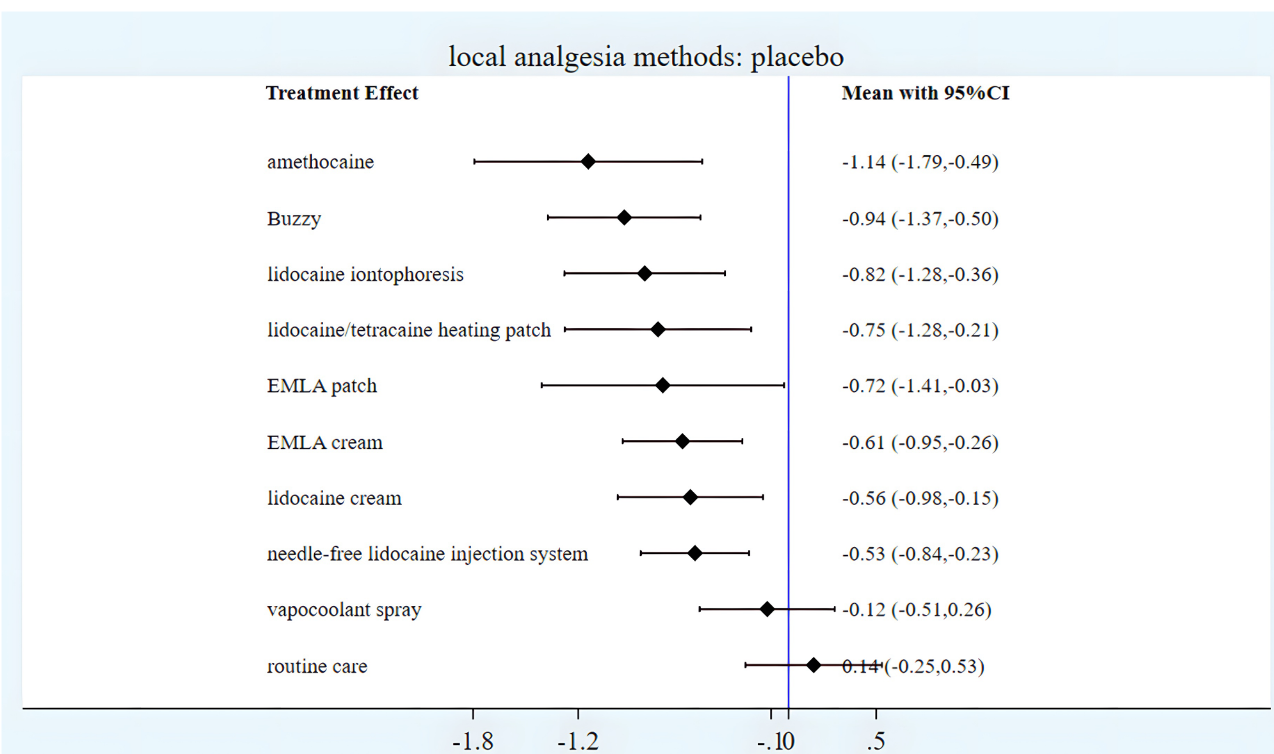

Fig. 3 Forest plot of local analgesia methods versus placebo

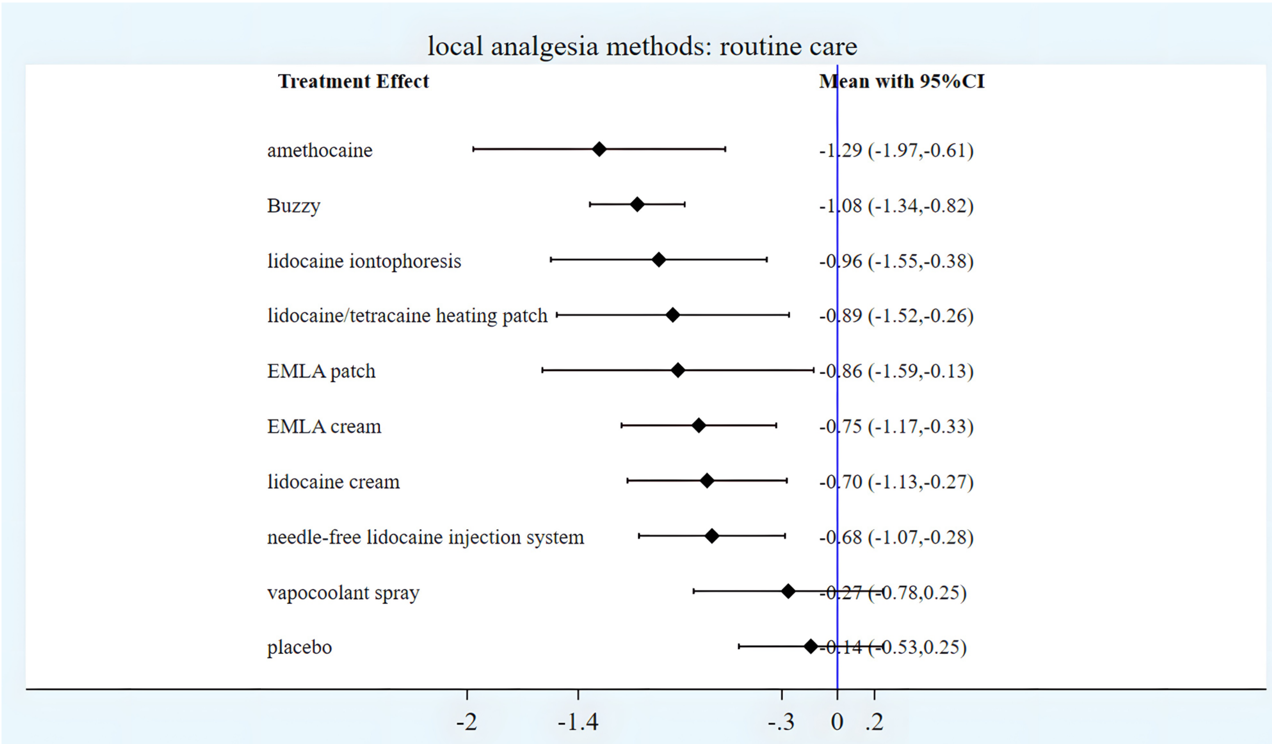

Fig. 4 Forest plot of local analgesia methods versus routine care

amethocaine										
-0.21 (-0.91,0.50)	**Buzzy**									
-0.32 (-1.09,0.44)	-0.12 (-0.73,0.50)	**lidocaine iontophoresis**								
-0.40 (-1.19,0.39)	-0.19 (-0.85,0.46)	-0.08 (-0.76,0.61)	**lidocaine/tetracaine heating patch**							
-0.43 (-1.26,0.41)	-0.22 (-0.98,0.54)	-0.10 (-0.90,0.69)	-0.03 (-0.84,0.78)	**EMLA patch**						
-0.54 (-1.12,0.05)	-0.33 (-0.79,0.12)	-0.22 (-0.74,0.31)	-0.14 (-0.69,0.41)	-0.11 (-0.71,0.49)	**EMLA cream**					
-0.58 (-1.20,0.03)	-0.38 (-0.83,0.08)	-0.26 (-0.85,0.33)	-0.18 (-0.81,0.44)	-0.16 (-0.87,0.56)	-0.04 (-0.43,0.35)	**lidocaine cream**				
-0.61 (-1.27,0.05)	-0.40 (-0.84,0.03)	-0.29 (-0.82,0.25)	-0.21 (-0.80,0.37)	-0.18 (-0.89,0.52)	-0.07 (-0.43,0.29)	-0.03 (-0.45,0.40)	**needle-free lidocaine injection system**			
-1.02 (-1.77,-0.28)	**-0.82 (-1.37,-0.27)**	**-0.70 (-1.30,-0.10)**	-0.62 (-1.28,0.03)	-0.60 (-1.38,0.19)	-0.48 (-0.99,0.02)	-0.44 (-0.99,0.11)	-0.41 (-0.89,0.07)	**vapocoolant spray**		
-1.14 (-1.79,-0.49)	**-0.94 (-1.37,-0.50)**	**-0.82 (-1.28,-0.36)**	**-0.75 (-1.28,-0.21)**	**-0.72 (-1.41,-0.03)**	**-0.61 (-0.95,-0.26)**	**-0.56 (-0.98,-0.15)**	**-0.53 (-0.84,-0.23)**	-0.12 (-0.51,0.26)	**placebo**	
-1.29 (-1.97,-0.61)	**-1.08 (-1.34,-0.82)**	**-0.96 (-1.55,-0.38)**	**-0.89 (-1.52,-0.26)**	**-0.86 (-1.59,-0.13)**	**-0.75 (-1.17,-0.33)**	**-0.70 (-1.13,-0.27)**	**-0.68 (-1.07,-0.28)**	-0.27 (-0.78,0.25)	-0.14 (-0.53,0.25)	**routine care**

Fig. 5 Relative effects of different local analgesia methods

Secondary outcomes

Success rate at the first attempt

Fifteen studies reported success rate at the first attempt. Among them, 11 studies did not find difference in success rate at the first attempt between interventions and controls. Four studies reported higher success rate when using lidocaine/tetracaine heating patch (compared with EMLA cream), vapocoolant spray (compared with placebo), lidocaine cream (compared with placebo) and lidocaine iontophoresis (compared with placebo) (Supplementary File 2).

Pain assessed by others

Pain was assessed by parents in 12 studies, by operators in 5 studies, and by observers in 10 studies. All the comparisons, except one comparing lidocaine/tetracaine heating patch with EMLA cream and one comparing needle-free lidocaine injection system with Buzzy, were local analgesia methods versus placebo or routine care. There was no difference in pain assessed by operators between lidocaine/tetracaine heating patch and EMLA cream. Needle-free lidocaine injection system and Buzzy showed no difference in pain reduction evaluated by parents. All the comparisons with placebo or routine care, except one comparing Buzzy with routine care [60], reported significant less pain in local analgesia group when assessed by observers (Supplementary File 2).

Anxiety

Anxiety was assessed in 8 studies. Two studies showed significantly lower anxiety in the Buzzy group than the routine care group and three studies did not. Other studies did not find difference in anxiety in comparisons (EMLA cream versus routine care, lidocaine cream versus needle-free lidocaine injection system, and lidocaine cream versus Buzzy) (Supplementary File 2).

Fear

Fear was assessed in 4 studies. Three studies showed less fear with local analgesia (needle-free lidocaine injection system and Buzzy) than routine care. No difference was found when needle-free lidocaine injection system was compared with EMLA cream and Buzzy (Supplementary File 2).

Satisfaction

Satisfaction was assessed in 7 studies. Two studies reported greater satisfaction with lidocaine iontophoresis and vapocoolant spray when compared with placebo. Other studies did not show difference in satisfaction between comparisons (lidocaine iontophoresis versus EMLA cream, needle-free lidocaine injection system versus Placebo, lidocaine/tetracaine heating patch versus Placebo, lidocaine cream versus needle-free lidocaine injection system and Buzzy versus lidocaine cream) (Supplementary File 2).

Difficulty of procedure

Eleven studies evaluated the difficulty of needle procedure (or ease of procedure) using different interventions. Nine studies did not find difference in the difficulty of procedure between interventions and controls. Two studies were in favor of needle-free lidocaine injection system (versus EMLA cream) and vapocoolant spray (versus placebo) (Supplementary File 2).

Adverse skin reactions

Sixteen studies reported side effects of the skin including erythema, pallor, pruritus, discomfort, burning, tingling, and edema. Overall, the occurrence of skin reactions of local analgesia was common (0 to 90%), but the reactions were mild. Among the 16 studies, 13 did not find difference in the side effects of the skin between interventions and controls. Two studies showed that EMLA cream had more blanching than lidocaine cream and placebo. And one study reported more erythema with needle-free lidocaine injection system than placebo (Supplementary File 2).

Publication bias

The funnel plot is displayed in Fig. 6. No substantial asymmetry was found through visually estimating the funnel plot and Egger's test ($P = 0.348$) indicated that there was no evidence of publication bias.

Certainty of the evidence

Certainty of evidence for each comparison was assessed using CINeMA. It showed that 89.1% (49) and 5.5% (3) of all the comparisons were judged "low" and "moderate" in confidence rating, respectively. Only 3.6% (2) comparisons (lidocaine iontophoresis versus routine care and amethocaine versus placebo) between two interventions were judged "high" in confidence rating (see Supplementary File 5).

Discussion

The study comprehensively integrated data on 9 local analgesia methods from 40 randomized controlled trials and performed a network meta-analysis to provide information on effectiveness and relative efficacy of these interventions in children undergoing venipuncture and intravenous cannulation. Results showed that amethocaine, Buzzy, lidocaine iontophoresis, lidocaine/tetracaine heating patch, EMLA patch, EMLA cream, lidocaine cream and needle-free lidocaine injection system were effective in relieving pain of needle procedures in children, whereas vapocoolant spray was not better than placebo and routine care. Moreover, amethocaine, Buzzy and lidocaine iontophoresis were of the highest probability to be the most effective interventions.

Amethocaine was found to be the most effective intervention in the network meta-analysis. In the network meta-analysis combining direct and indirect evidence, amethocaine was not superior than EMLA cream in pain control. This result is inconsistent with a previous meta-analysis which found amethocaine to be more efficacious than EMLA cream in pain relief [27]. Considering that

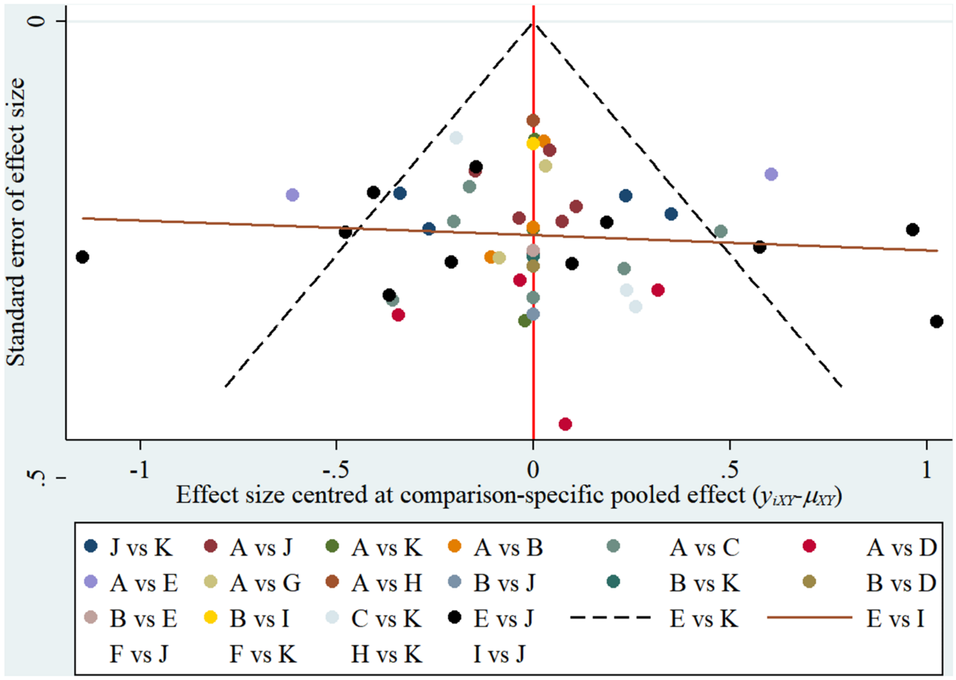

Fig. 6 Funnel plot of local analgesia methods. Note: A: EMLA cream; B: lidocaine cream; C: lidocaine iontophoresis; D: amethocaine; E: needle-free lidocaine injection system; F: vapocoolant spray; G: EMLA patch; H: lidocaine/tetracaine heating patch; I: Buzzy; J: routine care; K: placebo

the meta-analysis in 2006 involved only two studies, the relative efficacy of amethocaine versus EMLA cream is inconclusive. More research is required to confirm the result.

Buzzy is the secondly best intervention. The studies comparing Buzzy with routine care were published since the year of 2010 and mainly from Turkey. There were no direct comparisons between Buzzy and other interventions except one study with lidocaine cream and one with needle-free lidocaine injection system. Buzzy was superior than vapocoolant spray and showed equal effectiveness with other interventions. The results just relied on indirect comparisons only. Direct comparisons between each intervention are needed to confirm these findings. One study [25] compared Buzzy combining the application of lidocaine cream with vapocoolant spray combining the use of lidocaine cream and showed that Buzzy was more effective in pain control, which in favor of the result of network analysis to some extent.

Lidocaine iontophoresis uses an external current of the same charge as lidocaine to deliver lidocaine into the dermis and provide topical anesthesia of the skin and underlying tissue [67]. Although it ranked 3 in the efficacy of pain relief in children undergoing venipuncture or intravenous cannulation, it has been relatively less used in children for venipuncture and intravenous cannulation compared with other local analgesia methods these years. Reasons for its limited application may include the availability of the delivery system and habits of nurses. In addition, many studies have reported intolerance of participants to the tingling and burning sensations associated with the application of iontophoresis, which may inhibit its use in practice as well [19, 68, 69]. The incidence of tingling and burning was found to be 60% and 10%, respectively [68]. However, compared with EMLA cream, lidocaine iontophoresis takes less time to establish analgesia in skin (13 min versus 60 min) [68], which is a major advantage for use in the current busy health care system.

It is noteworthy that, among the 9 interventions, vapocoolant spray is the only ineffective intervention compared with both placebo and routine care. The result is consistent with previous traditional meta-analysis [28]. The lack of benefit in children has been considered to be due to the cooling and/or burning sensation, caused by vapocoolant spray, which might be perceived by children as painful [70]. The explanation was supported by the evidence that application of vapocoolant spray was evaluated to be more painful than application of placebo, which might offset its anesthetic effect on pain during venipuncture and intravenous cannulation [28]. In this analysis, amethocaine, Buzzy, and lidocaine iontophoresis were more efficacious than vapocoolant spray. But the explanation of this result should be with caution for its effect relied on indirect evidence only.

However, lidocaine/tetracaine heating patch, EMLA patch, EMLA cream, lidocaine cream and needle-free lidocaine injection system were not different in pain relief compared with vapocoolant spray. In addition, there were no differences in degree of pain reduction between the remaining interventions. One study [71] showed that EMLA cream is equally effective as vapocoolant spray in reducing immunization pain in school-aged children. A study [72] found that lidocaine cream was not different from vapocoolant spray in relieving puncture pain in children aged from 0 to 18, which supported the result of this study. However, Lunoe et al. [73] revealed that needle-free lidocaine injection system was better than vapocoolant spray in pain relief for children aged from 1 to 6. Bourdier et al. [74] confirmed that EMLA patch was more effective than Buzzy in pain control in children of 18 months to 6 years old. It is worth mentioning that pain assessment in the studies of Lunoe and Bourdier was performed by nurses other than by children themselves. Therefore, interpretation of the results of this network meta-analysis needs caution, and high-quality studies are still needed to verify the relevant results in the future.

The findings provided evidence for the efficacy/inefficacy of lidocaine iontophoresis, lidocaine/tetracaine heating patch, EMLA cream, needle-free lidocaine injection system and vapocoolant spray in pain relief compared with placebo, and needle-free lidocaine injection system and Buzzy compared with routine care. Moreover, results of comparison of EMLA cream versus lidocaine cream, EMLA cream versus needle-free lidocaine injection system and EMLA cream versus EMLA patch also proved persuasive. The results of pairwise and network meta-analyses were consistent (see Supplementary File 6).

As reported, the absolute minimum clinically important difference for pain reduction was 8–40 mm (based on a 100-mm scale) [75]. Since the results of our network meta-analysis are standardized, we used the smallest standard deviation (15.1) and the largest standard deviation (35.1) reported in the included studies for the VAS 0–100 scale to convert the standardized network meta-analysis results in Fig. 5 into absolute values. We found that, compared to vapocoolant spray, amethocaine, Buzzy, and lidocaine iontophoresis reduced pain levels by 15.4–35.8, 12.4–28.8, and 10.5–24.6, respectively. This indicates that using 8 mm as the minimally clinically significant effect size, the reductions in pain levels for amethocaine, Buzzy, and lidocaine iontophoresis are all clinically meaningful. Compared to routine care, all interventions with statistically significant effects in Fig. 5 showed pain reductions exceeding 8 mm after conversion. Similarly, compared to placebo, all statistically significant interventions achieved the minimally clinically significant effect size. However, if 40 mm is used as the threshold, only amethocaine demonstrated a clinically meaningful reduction in pain levels compared to both routine care and placebo. This suggests that selection of local analgesia should consider the child's sensitivity to pain. For example, in routine settings, where moderate pain relief is sufficient, interventions such as Buzzy and lidocaine iontophoresis can be practical and effective alternatives. For high-stress or high-pain scenarios (e.g., children with needle phobia or previous traumatic experiences), amethocaine is the preferred choice due to its greater effect size.

Limitations

The main limitation of the study is the inconsistency between direct and indirect estimates of lidocaine cream versus needle-free lidocaine injection system. Although the global test showed no significant inconsistency treating the network as a whole, loop specific approach was performed in order to further evaluate the extent of inconsistency in the network. Loops refer to 'evidence cycles' formed by different pairwise comparisons in a network. Results showed that there was inconsistency in 2 out of 17 loops (11.8%) in our network in Fig. 7. The percentage of inconsistent loops is similar to 14% in previous studies [76, 77]. Both the inconsistent loops identified shared the same comparison (lidocaine cream versus needle-free lidocaine injection system) including only one study [49]. Veroniki and colleagues considered that, in such cases, inconsistency is possibly introduced by this particular study [78]. The only article that directly compared the needle-free lidocaine injection system with lidocaine cream was analyzed. It was not found that age of participants, needle gauge, venipuncture site, and venipuncture reasons included in this study were significantly different from others. However, it was found that some studies involving needle-free lidocaine injection system may rule out the discomfort caused by the application of the system itself, while some studies may not, which may be the source of inconsistency. Thus, future studies are needed to clearly distinguish between discomfort caused by the drug delivery system and venipuncture pain. Interpretation of results related with the comparison should be made with caution, for the presence of inconsistency may make the results more uncertain.

The quality of the evidence was typically high risks of bias due to the differences of appearances of the treatment devices which were not available for blinding. In addition, the placebo in this analysis included placebo cream, jet placebo, saline and isopropyl alcohol. We assumed that the effects of the placebos were non-specific and similar across all interventions, but variations may in fact be present and result in uncertainty in the results.

When deciding which local analgesia method to be used, not only the effectiveness but also the price of the interventions need to be considered. In addition, other factors such as the length of time to take effects, the

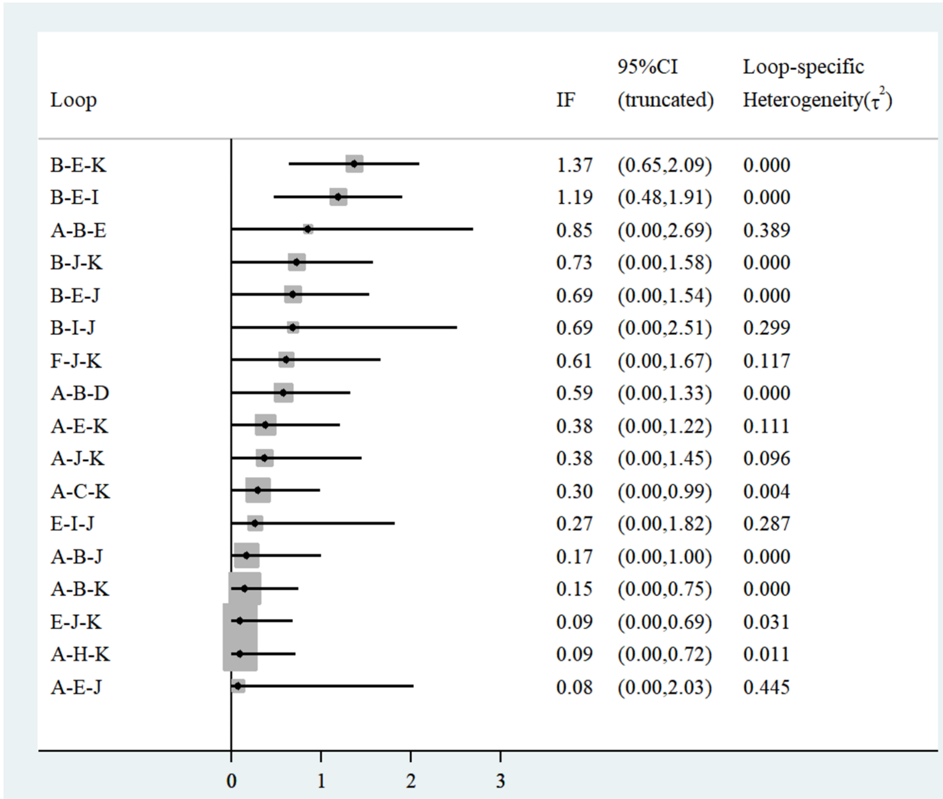

Fig. 7 Loop plot of local analgesia methods. Note: A: EMLA cream; B: lidocaine cream; C: lidocaine iontophoresis; D: amethocaine; E: needle-free lidocaine injection system; F: vapocoolant spray; G: EMLA patch; H: lidocaine/tetracaine heating patch; I: Buzzy; J: routine care; K: placebo

clinical availability and the difficulty of procedure are also taken into account. For example, the cost-effectiveness analyses [79, 80] showed that the application of needle-free lidocaine injection system is the best choice during venipuncture in pediatric emergency department, and amethocaine has an advantage in reducing cost and time compared with EMLA cream. Moreover, in practice, factors such as the preferences of children and families, as well as non-pharmacological techniques like distraction, are often integral to the selection and application of local analgesia methods. However, these elements were not incorporated into the current analysis, which therefore constitutes a limitation of this study, as it provides a 'stand-alone' analysis that may not fully capture the complexities of real-world clinical environment.

In addition, unpublished literature was not included, which may have introduced publication bias. Studies with non-significant or unfavorable results are less likely to be published, potentially skewing the findings towards more favorable outcomes.

Conclusion

Our research provides comprehensive information on the efficacy of currently used local analgesia methods in children undergoing venipuncture or intravenous cannulation. Results showed that amethocaine, Buzzy, lidocaine iontophoresis, lidocaine/tetracaine heating patch, EMLA patch, EMLA cream, lidocaine cream, and needle-free lidocaine injection system were more effective in relieving pain compared to placebo and routine care. Amethocaine, Buzzy and lidocaine iontophoresis are most likely to be the most effective interventions. However, the evidence body from the results of network meta analysis was judged "low" on a whole. Due to the limited number of direct comparisons, interpretation of some results should be made with caution.

This study highlights the need for direct comparisons between interventions, as many findings rely on indirect evidence. Specifically, further research is needed to directly compare lidocaine cream and needle-free lidocaine injection systems, as the results of this comparison introduce significant uncertainty. Future studies should also integrate factors such as patient preferences and non-pharmacological techniques which are commonly used alongside with local analgesia in clinical practice to better reflect the complexity of real-world clinical environment.

Abbreviations

EMLA	Eutectic mixture of lidocaine and prilocaine
SD	Standard deviation

SMDs	Standardized mean differences
SUCRA	The surface under the cumulative ranking curve
MCID	Minimum clinically important difference

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-025-02991-6.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Acknowledgements

Not applicable.

Author contributions

LML helped design the study, interpreted data, modified the manuscript and provided critical insights. LPZ and PQ were responsible for conceiving the idea, strategy searching, data extraction and analysis, and manuscript writing. (LPZ and PQ made same contribution to the work). XW and XLS participated in manuscript writing and reviewing. All authors have read and approved the final version of the manuscript.

Funding

There was no funding source in this study.

Data availability

The data extracted and analysed in this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 8 March 2024 / Accepted: 26 February 2025

Published online: 07 March 2025

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