Randomized controlled trial of topical EMLA and vapocoolant spray for reducing pain during wDPT vaccination

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Original article

Background: **Intramuscular vaccination is among the most common source of iatrogenic pain in infants. Vapocoolant sprays are rapid-acting alternative to topical anesthetics. They provide transient anesthesia via evaporation induced skin cooling, and reduce pain due to vaccine injection in children and adults. The objective was to compare the synergistic analgesic effect of eutectic mixture of local anesthetics (EMLA) with breastfeeding (EB group) and vapocoolant spay with breastfeeding (VB group) to that of only breastfeeding (BO group) during whole cell diptheria, pertussis and tetanus (wDPT) vaccination.**

Methods: **A double blind randomized controlled trial was done to include infants up to 3 months of age who came for their first wDPT vaccination. The primary outcome variable was the duration of cry after vaccination. Secondary outcome variables were Modified Facial Coding Score, Neonatal Infant Pain Scale and latency of onset of cry.**

Results: **Of the 201 eligible participants, 111 babies were excluded and remaining 90 babies were randomized into three groups of thirty each. The groups did not differ significantly in baseline characteristics. Median (interquartile range, IQR) of duration of cry was lesser [35.86 (21.07-107.75) seconds] in babies receiving EMLA cream with breast feeding (EB group) and in babies receiving vapocoolant spray with breast feeding (VB group) [32.58 (21.25-106.21) seconds] as compared to babies receiving only breast feeding (BO group) [67.5 (27.6-180) seconds] (P=0.147). Difference in median (IQR) of latency of cry was not statistically significant. Modified Facial Coding Score and Neonatal Infant Pain Scale at 1 minute and 3 minutes was significantly lower in the EB and VB group, as compared to the BO group (P<0.05).**

Conclusions: **Addition of topical EMLA application or vapocoolant spray to breastfeeding during wDPT vaccination does not reduce duration of cry in infants up to 3 months of age. However, they are able to show reduction in pain score and further studies are warranted to assess their efficacy as pain relief measures in infants and children.**

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Key words: **diptheria, pertussis and tetanus vaccine; eutectic mixture of local anesthetics; Modified Facial Coding Score; Neonatal Infant Pain Scale**

Introduction

Intramuscular vaccination is among the most common source of iatrogenic pain in infants and children which cause considerable stress and anxiety for infants and their parents.[1] Failure to alleviate the pain may result in drop out of infants from completing immunization schedule. Breast feeding has also been demonstrated to be effective analgesic in painful outpatient department procedures like heel prick,[2] venipuncture,[3] and immunization[4] in neonates and infants. The Cochrane review had concluded that breastfeeding or breast milk, if available, should be used to alleviate procedural pain in neonates undergoing a single painful procedure compared with placebo, positioning or no intervention.[5] EMLA (eutectic mixture of lidocaine 2.5% and prilocaine 2.5%) cream has been shown in trials on children to reduce pain due to painful procedures.[6-8] However, many parents decline it as they have to wait for 45 to 60 minutes extra for preparation time. Vapocoolant sprays are rapid-acting alternative to topical anesthetics. They provide transient

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anesthesia via evaporation induced skin cooling, and reduce pain due to vaccine injection in children and adults.[9-11] We therefore planned a study with the objective to evaluate if vapocoolant spray is comparable to EMLA cream and whether they have synergistic or additive analgesic effect to breastfeeding in alleviating pain due to first intramuscular injection of whole cell diptheria, pertussis and tetanus (wDPT) vaccine in term infants of up to 3 months of age.

Methods

Subject and study design

Setting

This study was carried out in the immunization clinic of Lala Lajpat Rai Memorial (LLRM) Medical College, Meerut (India) from October, 2010 to September, 2011.

Inclusion criteria

Healthy term infants of up to 3 months of age, who were on exclusive or partial breastfeeding and attended the immunization clinic for the first wDPT vaccination. They should also be willing to wait for 60 minutes preparation for analgesia. Written informed consent was taken from all the parents in local language.

Exclusion criteria

Infants who have required hospital admission for more than 48 hours, had perinatal asphyxia (5-min Apgar score <5) or history of delayed cry if born at home, preterm deliveries (delivery before <37 weeks of gestation), intra-uterine growth retardation (weight <10th percentile for gestational age), obvious neurological abnormality and previous surgery.

Design

This study was designed as a double blind, randomized controlled trial. This trial was approved by the ethical committee of LLRM Medical College, Meerut (UP) (India) and registered in clinical trial registry of India.

Randomisation and allocation concealment

Details of name, age, sex, weight, height, and head circumference were recorded on a prestructured proforma. Prior painful procedures experienced by the infants were noted. The subjects were randomized into three groups of 30 infants each through computer-generated random numbers. The numbers were written on paper slips, and these slips were put in serially numbered opaque sealed envelopes. The three groups were: 1) babies receiving EMLA cream with breast feeding (EB group); 2) babies receiving vapocoolant spray with breast feeding (VB group); and 3) babies receiving only breast feeding (BO group).

Procedure, intervention, observation and blinding

Babies were brought to the room where recruitment and vaccination was to be done. All the babies received intervention from one person only (AD). AD opened the sealed envelope and administered the intervention. The three groups were as follows: 1) EB group: 1 g of EMLA cream was applied at the site of injection which was then covered with an occlusive dressing (Tegaderm) for 60 minutes. Then cream was wiped from the skin by using tissue paper. At the same time infant was allowed to be breastfed and wDPT vaccine was given; 2) VB group: vapocoolant spray was applied at the site of injection from a distance of about 12 cm for two seconds and allowed to evaporate for up to 10 seconds. This technique avoided "frosting up" of vapocoolant on the skin. The area was then wiped with an alcohol swab and intramuscular wDPT was administered as baby was allowed to be breastfed. Vaccination was carried out within 20 seconds of administration of the spray; 3) BO group or control group: in this group infant was breastfed only.

After randomization and allocation, two persons (NG&AA) would come in the immunization room. "NG" administered 0.5 mL of wDPT vaccine by a 2-mL syringe with 23-gauge 1-inch needle at 90 degree angle on the anterolateral aspect of thigh (left/right) after cleaning the skin with sprit swab. For giving DPT, baby was made to lie in mother lap, with exposed thigh. During this procedure, "NG" called "in" when he inserted the needle and "out" when he removed the needle. All events were recorded by "AA" on digital video camera for total a duration of 3 minutes from removal of the needle. The fourth person (AU) analyzed the outcome variables from the video recording in all babies.

All the four persons (AD, NG, AA, and AU) were same throughout the study and performed the same role in all the enrolled babies. NG, AA, and AU were blinded to intervention given to the baby.

No active intervention other than breastfeeding was given while wDPT was being administered. In all three groups, babies were breastfed for at least 2 minutes prior to wDPT vaccination and it was continued throughout the procedure. One person (AA) followed up all the infants for 24 hours after vaccination by telephone. Parents were asked to provide a description of any unexpected events at the site of vaccination in infants. She also asked specific closed questions (presence and timing of any pain, redness, swelling). At least three attempts were made to contact each patient.

Assessment of outcome measures

Primary outcome measure: duration of first cry

It was defined as the duration from start of crying (defined as continuous distress vocalization after needle insertion) to the period of silence of more than 5 seconds, excluding this period of 5 seconds. As video recording was done only for 3 minutes, the duration of cry was taken as 180 seconds only for babies who were still crying even after 3 minutes.

Secondary outcome measures

1) Latency of onset of cry (in seconds) was defined as the period between insertion of needle, marked by the sound "in" and the onset of vocalization, in the form of cry; 2) Modified Facial Coding Score (MFCS): a composite score was obtained from the sum of brow bulge, eye squeeze, nasolabial furrow, open mouth, chin quiver and trunk movement. Each parameter was scored "0" if absent and "1" if present, and the total composite score was obtained; 3) Neonatal Infant Pain Scale (NIPS): a composite score was obtained from the sum of facial expression, cry, breathing, arm and leg movements, and alertness. Each parameter was scored "0" if absent and "1" if present except cry which was scored 0, 1 and 2. Maximum add up score was 7 and a score of more than 3 was considered pain.

The MFCS and NIPS were recorded immediately and 1 and 3 minutes after needle insertion.

During breastfeeding, only half of the face was visible, so all parameters were based on the facial side which the observer could see. If however, for some reason any parameter could not be seen on both sides, a zero score was given.

In order to avoid confounding by other pain-relieving methods, the following steps were ensured. All enrolled babies should have been fed within the last 3 hours but had not received a feed in the last 30 minutes. All babies were held in mother's lap during vaccination. The mothers were allowed to hold, talk to, or rock the baby during the procedure in all the groups. Since the state of wakefulness could have modified the response, the procedure was done in awake babies. If babies were sleeping, they were gently awakened; if they cried, they were soothed to quite wakefulness before the procedure. Nonnutritive sucking was not done during the procedure. All the tests were performed between 10 a.m. to 2 p.m. to avoid diurnal variation in pain response.

Sample size and statistical analysis

Duration of cry was the primary outcome variable and sample size was calculated using this variable. Sample size calculation was done on the basis of previous study from our institute.[12] Median [interquartile range (IQR)] duration of cry in breastfed babies was used from that study. Assuming 25% reduction in duration of cry with use of EMLA cream or vapocoolant spray, 30 cases in each group were required to attain a power of 80% with test significance of 0.05. Results were analyzed by using Stata 11.0 software. Analyses of continuous data with normal distribution were done by one-way ANOVA followed by Bonferroni correction for multiple analyses of data. Nonnormally distributed data was analyzed by Kruskal-Wallis test. Categorical data was analyzed by Chi-square test or Fisher's exact test, where applicable.

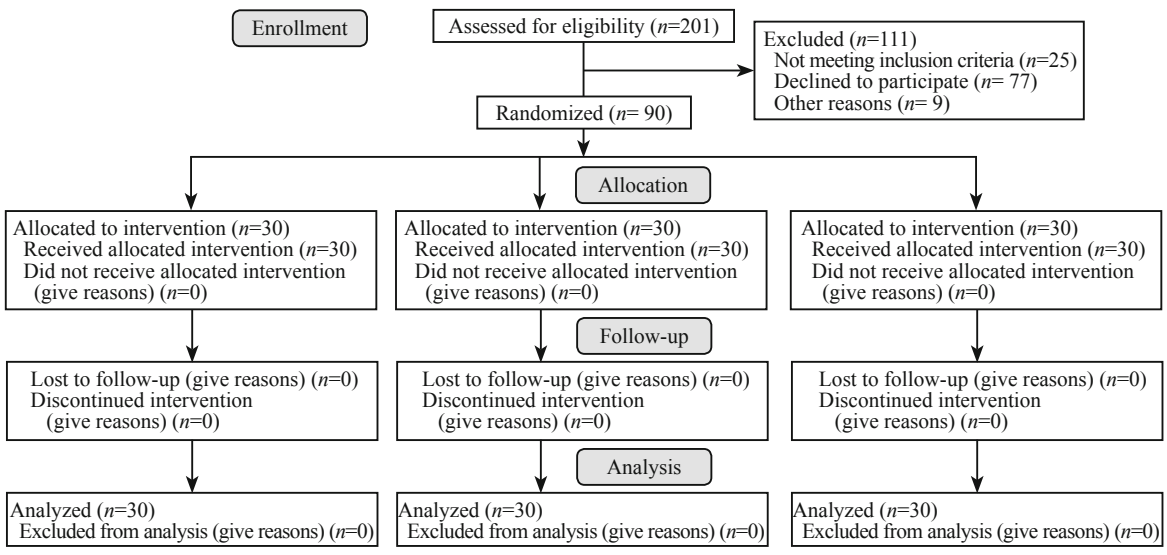

Fig. 1. Consort flow diagram of participant's enrollment.

Table 1. Baseline characteristics of babies in the three groups

Parameters	EB group (*n*=30)	VB group (*n*=30)	BO group (*n*=30)	*P* value
Sex (male)*, *n* (%)	14 (46.7)	19 (63.3)	16 (53.3)	>0.05
Age (mon)	1.7 (0.34)	1.6 (0.45)	1.9 (0.40)	>0.05
Weight (kg)	4.3 (0.83)	4.3 (0.63)	4.4 (0.70)	>0.05
Length (cm)	54.1 (4.2)	54.6 (3.6)	54.6 (4.4)	>0.05
Head circumference (cm)	37.2 (1.7)	37.6 (1.5)	37.6 (1.5)	>0.05
Time since last feed (min)	54.2 (16.7)	54.5 (29.4)	50.3 (17.0)	>0.05
Duration of needle insertion (s)	3.6 (0.37)	3.7 (0.45)	3.7 (0.45)	>0.05

Values are presented as mean (standard deviation). *: Data are reported as number with the corresponding percentage in parentheses. EB: babies receiving EMLA cream with breast feeding; VB: babies receiving vapocoolant spray with breast feeding; BO: babies receiving only breast feedingbabies receiving only breast feeding.

Results

Out of the total of 201 eligible participants, 111 babies were excluded for various reasons (Fig. 1) and 90 babies were randomized and analyzed in three groups of 30 each. The baseline characteristics of the three groups were comparable (Table 1).

Duration of cry

The median (IQR) duration of cry was 35.86 (21.07-107.75) seconds in the EB group, followed by 32.58 (21.25-106.21) seconds in the VB group as compared with 67.5 (27.6-180) seconds in the BO group. This difference was not statistically significant (*P*=0.147) (Fig. 2).

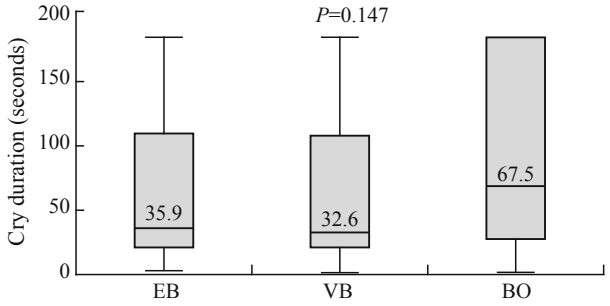

Fig. 2. Box and Whisker plot for duration of cry showed median, inter quartile range (edge of boxes) and range (horizontal bars). EB: babies receiving EMLA cream with breast feeding; VB: babies receiving vapocoolant spray with breast feeding; BO: babies receiving only breast feedingbabies receiving only breast feeding; EMLA: eutectic mixture of lidocaine 2.5% and prilocaine 2.5%.

Latency of onset of cry

The median (IQR) latency of cry in the EB, VB, and BO groups was 1.26 (1.06-1.8), 1.84 (1.25-2.21) and 1.48 (1.13-1.92) seconds, respectively (*P*>0.05).

MFCS

At 1 minute and 3 minutes, MFCS was significantly lower in the EB and VB groups babies as compare with the BO group (*P*<0.05). There was no significant difference in MFCS immediately after needle insertion (*P*>0.05) (Table 2).

NIPS

At 1 minute and 3 minutes, NIPS was significantly lower in the EB and VB groups babies as compare to BO group (*P*<0.05). There was no statistically significant difference in NIPS immediately after needle insertion (Table 2).

All the babies who demonstrated significant pain on MFCS also demonstrated significant pain on NIPS at both 60 and 180 seconds. There was strong co-relation between MFCS and NIPS with Spearman's rho co-relation coefficient between them at 60 seconds among 3 groups, being EB (*r*=0.95), VB (*r*=0.98) and BO (*r*=0.92), and similar at 180 seconds among 3 groups, being EB (*r*=1.00), VB (*r*=0.94) and BO (*r*=0.94).

Table 2. Primary and secondary outcomes measures

Outcomes	EB group (*n*=30)	VB group (*n*=30)	BO group (*n*=30)	*P* value
MFCS				
Immediate	5.7 (0.3)	5.9 (0.3)	5.9 (0.3)	>0.05
After 1 min	1.4 (2.4)	1.8 (2.5)	3.2 (2.6)	<0.05
After 3 min	0.9 (1.9)	0.6 (1.5)	2.3 (2.7)	<0.05
NIPS				
Immediate	6.7 (0.3)	6.9 (0.3)	6.8 (0.6)	>0.05
After 1 min	1.9 (3.1)	2.3 (3.0)	3.2 (2.6)	<0.05
After 3 min	0.9 (1.9)	0.6 (1.5)	2.3 (2.7)	<0.05

Values are presented as mean (standard deviation). EB: babies receiving EMLA cream with breast feeding; VB: babies receiving vapocoolant spray with breast feeding; BO: babies receiving only breast feedingbabies receiving only breast feeding; EMLA: eutectic mixture of lidocaine 2.5% and prilocaine 2.5%; MFCS: Modified Facial Coding Score; NIPS: Neonatal Infant Pain Scale.

There was also a strong Pearson coefficient co-relation between NIPS and MFCS at 60 seconds (*r*=0.98) and 180 sec (*r*=0.99) among the babies.

Side effects of EMLA cream and vapocoolant spray usually observed are erythema, paleness, swelling and pruritis. However, erythema and swelling may appear after wDPT vaccination itself. In our study, they were observed immediately in 17%, 20%, and 15% of babies in the EB, VB, and BO groups, respectively (*P*>0.05).

After 24 hours, through a telephone interview, they were present in 5%, 8%, and 6% of babies in the EB, VB, and BO groups, respectively (P>0.05).

Discussion

Our study demonstrated that addition of topical EMLA or vapocoolant spray to breastfeeding during wDPT vaccination did not significantly reduce the duration of cry, but lowers the pain assessment scores at 1 minute and 3 minutes. The present study failed to demonstrate significant synergistic or additive analgesic activity between breastfeeding and EMLA cream or vapocoolant spray. Gupta et al,[12] from our institute, had earlier demonstrated that breastfeeding acted synergistically with EMLA cream in pain reduction, when compared with no intervention during the 1st DPT vaccination. However, our study failed to show any such synergistic effect. This could be because of the difference in control groups tested in both studies. Previous study[12] used no intervention in the control group, while our study used breastfeeding as control group, which itself has been shown to be a pain reliever and thus an intervention in itself. We used breastfeeding in the control group as well, as with the current evidence, it was considered unethical to give no medication.[5] Previous studies, including one by our group, have demonstrated that breastfeeding during painful procedure result in pain relief.[13,14] Eff and Ozer[4] have reported that breast feeding reduced pain during intramuscular vaccination. Gupta et al,[12] Taddio et al,[7] and Uhari et al[8] have demonstrated that use of topical EMLA before DPT/measles, mumps, and rubella vaccination results decrease in pain response. Lindh et al[15] also demonstrated that visual analogue scale and modified behavioral pain scale were significantly lower in the EMLA-glucose group compared with the placebo group during DPT vaccination.

Prior topical vapocoolant spray has been reported to quickly and effectively reduce pain due to vaccination[16] and intravenous cannulation.[17,18] Cohen Reis and Holubkov[10] have demonstrated that vapocoolant spray significantly reduces immediate vaccine-associated pain compared with distraction alone, and it is equally effective, less expensive, and faster-acting than EMLA cream in children. However, not all studies have reported reduction in pain with use of vapocoolant spray. Two previous studies have reported no reduction in pain due to intravenous canulation in children.[19,20] The reason for difference in results could be difference in the product composition (refrigerant), application process, speed of evaporation and even the trial methodologies. However, there was no previous trial comparing the synergetic analgesic effect of EMLA or vapocoolant sray with breastfeeding and breastfeeding alone. In infants, a limited number of facial actions have been studied, but they have been found to be consistent across ages and situations. The most widely used measures are behavior scores like MFCS and NIPS. Duration of first cry has been widely used in various studies as a marker of severity of pain, as it is very easy to measure, reliable, validated and has good inter-observer and intra-observer correlation.[21] Our study did not demonstrate decrease in duration of cry but showed reduction in pain score. Kataria et al[22] also reported decrease only in Preterm Infant Pain Profile scores without affecting duration of cry.

Lack of measurements of physiological parameter of pain assessment (heart rate, respiratory rate, oxygen saturation) can be perceived as a limitation. We avoided them because pulse oxymeters often do not give readings in crying and vigorous babies and attaching electrocardiograph leads for heart rate monitoring to healthy babies in immunization rooms can be intimidating and stressful for the parents. However, we used other multidimensional assessment tools to overcome lack of these parameters. In this study, babies were allowed to be hold, talk to, or rocked because it was considered unethical to not do above pacifying measures in a crying baby. This can be considered a limitation of this study. However all the groups the pacifying measures were similar, they are unlikely to be the confounding. We took considerable efforts to ensure allocation concealment and blinding of participants and observer. A number of parents refused to stay back for an extra 60 minutes and refused for participation in trial. However, there is no reason to believe that excluded subjects would have differed significantly from those who were enrolled.

In conclusion, addition of topical EMLA application or vapocoolant spray to breastfeeding during wDPT vaccination does not reduce duration of cry in infants up to 3 months of age. However they are able to show reduction in pain score and further studies are warranted to assess their efficacy as pain relief measures in infants and children.

Funding: None.

Ethical approval: The study has been approved by ethical commitee of Government Medical College, Meerut, India (Lala Lajpat Rai Memorial Medical College, Meerut, India).

Competing interest: None.

Contributors: Upadhyay A planned, supervised the study and reviewed manuscript. Gupta NK and Dwivedi AK conducted study, prepared manuscript, reviewed literature and collected data. Agarwal A collected data and followed up the infants. Singh A and Jaiswal V critically revised the manuscript for important intellectual content. Upadhyay A is the guarantor.

References

1 Kennedy RM, Luhmann JD. Pharmacological management of pain and anxiety during emergency procedures in children. Paediatr Drugs 2001;3:337-354.
2 Iturriaga GS, Unceta-Barrenechea AA, Zárate KS, Olaechea IZ, Núñez AR, Rivero MM. Analgesic effect of breastfeeding when taking blood by heel-prick in newborns. An Pediatr (Barc). 2009;71:310-313.
3 Osinaike BB, Oyedeji AO, Adeoye OT, Dairo MD, Aderinto DA. Effect of breastfeeding during venepuncture in neonates. Ann Trop Paediatr 2007;27:201-205.
4 Efe E, Ozer ZC. The use of breast-feeding for pain relief during neonatal immunization injections. Appl Nurs Res 2007;20:10-16.
5 Shah PS, Aliwalas L, Shah V. Breastfeeding or breast milk to alleviate procedural pain in neonates: a systematic review. Breastfeed Med 2007;2:74-82.
6 Rosdahl I, Edmar B, Gisslen H, Nordin P, Lillieborg S. Curettage of molluscum contagiosum in children: analgesia by topical application of lidocaine/prilocaine cream (EMLA). Acta derm venereol 1998;68:149-153.
7 Taddio A, Nulman I, Goldbach M, Ipp M, Koren G. Use of lidocaine-prilocaine cream for vaccination pain in infants. J Pediatr 1994;124:643-648.
8 Uhari M. A eutectic mixture of lidocaine and prilocaine for alleviating vaccination pain in infants. Pediatrics 1993;92:719-721.
9 Abbott K, Fowler-Kerry S. The use of a topical refrigerant anesthetic to reduce injection pain in children. J Pain 1995;10:584-590.
10 Cohen Reis E, Holubkov R. Vapocoolant spray is equally effective as EMLA cream in reducing immunization pain in school-aged children. Pediatrics 1997;100:E5.
11 Maikler VE. Effects of a skin refrigerant/anesthetic and age on the pain responses of infants receiving immunizations. Res Nurs Health 1991;14:397-403.
12 Gupta NK, Upadhyay A, Agarwal A, Goswami G, Kumar J, Sreenivas V. Randomized controlled trial of topical EMLA and breastfeeding for reducing pain during wDPT vaccination. Eur J Pediatr 2013;172:1527-1533.
13 Goswami G, Upadhyay A, Gupta NK, Chaudhry R, Chawla D, Sreenivas V. Comparison of analgesic effect of direct breastfeeding, oral 25% dextrose solution and placebo during 1st DPT vaccination in healthy term infants: a randomized, placebo controlled trial. Indian Pediatr 2013;50:649-653.
14 Singh VB, Mishra SK, Singh T, Upadhyay A. Antinociceptive effect of exclusive breast feeding in healthy term infants during vaccination. Early Hum Dev 2008;84:50-51.
15 Lindh V, Wiklund U, Blomquist HK, Håkansson S. EMLA cream and oral glucose for immunization pain in 3-month-old infants. Pain 2003;104:381-388.
16 Mawhorter S, Daugherty L, Ford A, Hughes R, Metzger D, Easley K. Topical vapocoolant quickly and effectively reduces vaccine-associated pain: results of a randomized, single-blinded, placebo-controlled study. J Travel Med 2004;11:267-272.
17 Farion KJ, Splinter KL, Newhook K, Gaboury I, Splinter WM. The effect of vapocoolant spray on pain due to intravenous cannulation in children: a randomized controlled trial. CMAJ 2008;179:31-36.
18 Hijazi R, Taylor D, Richardson J. Effect of topical alkane vapocoolant spray on pain with intravenous cannulation in patients in emergency departments: randomised double blind placebo controlled trial. BMJ 2009;338:b215.
19 Costello M, Ramundo M, Christopher NC, Powell KR. Ethyl vinyl chloride vapocoolant spray fails to decrease pain associated with intravenous cannulation in children. Clin Pediatr 2006;45:628-632.
20 Ramsook C, Kozinetz CA, Moro-Sutherland D. Efficacy of ethyl chloride as a local anesthetic for venipuncture and intravenous cannula insertion in a pediatric emergency department. Pediatr Emerg Care 2001;17:341-343.
21 Upadhyay A, Aggarwal R, Narayan S, Joshi M, Paul VK, Deorari AK. Analgesic effect of expressed breast milk in procedural pain in term neonates: a randomized, placebo-controlled, double-blind trial. Acta Paediatr 2004;93:518-522.
22 Kataria M, Narang S, Chawla D, Sood S, Gupta PC. Oral dextrose for pain management during laser treatment of retinopathy of prematurity under topical anesthesia. Indian J Pediatr 2015;82:694-697.

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