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ORIGINAL ARTICLE

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

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Abstract The primary objective was to evaluate the analgesic effect of a eutectic mixture of local anesthetics (EMLA) during whole cell DPT vaccination. The secondary objective was to evaluate if the analgesic effect of EMLA was synergistic to breastfeeding. A randomized, placebo-controlled trial was done to include infants of up to 3 months of age who came for their first DPT vaccination. The outcome variables were duration of cry, latency of onset of cry, and Modified Facial Coding Score. Thirty babies were enrolled in each of three groups. The groups did not differ significantly in baseline characteristics. Median (interquartile range) of duration of cry was least [34.6 (24.1–72.2)s] in babies receiving EMLA cream with breastfeeding (EB group), followed by 94.2 (46.1–180)s in babies receiving EMLA cream with oral distilled water (EW group), as compared to 180.0 (180–180)s in babies receiving placebo cream with oral distilled water (PCW group) ($p<0.05$). Mean (SD) of latency of cry was significantly greater in EB group [2.4 (1.14)s] and EW group [1.9 (0.62)s] as compared to babies in PCW group [1.5 (0.47)s] ($p<0.05$), but the difference between EB and EW groups was not significant. Modified Facial Coding Score was significantly lower in EB group as compared to the other groups ($p<0.05$). *Conclusions*: Topical EMLA is effective in reducing pain and has a synergistic effect in analgesia when combined with breastfeeding during vaccination in infants.

Keywords Duration of cry · DPT vaccination · EMLA · Pain · Infant

Abbreviations

ANOVA	Analysis of variance
SD	Standard deviation
IQR	Interquartile range
MFCS	Modified Facial Coding Score
wDPT	Whole cell DPT vaccine
EMLA	Eutectic mixture of local anesthetics
EB group	Babies receiving EMLA cream with breastfeeding
EW group	Babies receiving EMLA cream with oral distilled water
PCW group	Babies receiving placebo cream with oral distilled water

Introduction

Infants undergo painful procedures like heel pricks, venipuncture, and immunization. Such procedures may inflict physiological, behavioral, hormonal, and metabolic changes [1, 6]. Routine intramuscular vaccination is among the most common source of pain in infants. Intramuscular injection for whole cell DPT vaccine can cause significant pain and sustained cry, which can result in families even opting out of the vaccination program due to fear of pain. Acellular pertussis vaccine causes lesser pain [4] but is considerably costlier. Methods to alleviate this pain are highly desirable, but we still do not know the best way to do so. A number of pharmacological and nonpharmacological interventions have been evaluated to reduce the pain inflicted by vaccination and minor

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procedures. Pretreatment with 5 % lidocaine–prilocaine cream (eutectic mixture of local anesthetics (EMLA), Astra Pharma Inc.) has been shown in pediatric clinical trials to decrease the pain due to venipuncture [8, 10, 13, 17], lumbar puncture [8], removal of molluscum contagiosum lesion [11, 18], and DPT [26, 27] or MMR immunization [9].

Expressed breast milk and breastfeeding have been demonstrated to be effective analgesic in minor painful OPD procedures like heel prick [14], venipuncture [23, 28], and immunization [5, 24] in neonates and infants. We planned to combine these two noninvasive interventions and see if their analgesic effects are synergestic. The objective of our study was to compare the pain-relieving efficacy of topical EMLA cream combined with breastfeeding, topical EMLA cream with distilled water, and topical placebo cream with distilled water for their analgesic effect during first DPT vaccination in term infants of up to 3 months of age.

Methods

Setting

The present study was carried out in the immunization clinic in the Department of Pediatrics, LLRM Medical College, Meerut from October 2009 to September 2010.

Participants/inclusion criteria

Healthy term infants of less than 3 months of postnatal ages, who were on exclusive or partial breastfeeding and attended the immunization clinic for first whole cell DPT (wDPT) vaccine with their mothers, were included in the study.

Exclusion criteria

Babies with any of the following were excluded: Infants who have required hospital admission more than 48 h, perinatal asphyxia (5-min Apgar score <5 or delayed cry >5min, if born at home), small for gestational age (birth weight <10th percentile for gestational age), preterm babies (delivery before 37 weeks of gestation), obvious neurological abnormality, and previous surgery.

Design

This study was designed as a randomized, placebo-controlled trial.

Randomizations

Details of name, age, sex, weight, height, and head circumference were recorded on a prestructured proforma. Any other painful procedures experienced by the neonate before study entries were noted. Babies were brought to the room where vaccination was to be done. 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 (SNOSE method). The three groups were (1) babies receiving topical EMLA cream with breastfeeding (EB group), (2) babies receiving topical EMLA cream with oral distilled water 2 min prior to vaccination (EW group), and (3) babies receiving topical placebo cream with oral distilled water 2 min prior to vaccination (PCW group).

Allocation, intervention, observation, and blinding

Babies were allotted a serial number, which was recorded on the proforma. All the babies received the intervention from one person only (NG). Recruitment was done in an immunization room; NG opened the sealed envelope and allocated the group and intervention in all the babies. The three groups were as follows: (1) In the EB group, 1 g of EMLA cream was applied at the site of injection. It was then covered with the occlusive dressing (Tegaderm, 3M) for approximately 60 min. The dressing and cream were removed by the investigator after 60 min by using tissue paper. A water-soluble marker (sketch pen) was used to mark four dots on the skin where the cream had been applied. Breastfeeding started 2 min prior to vaccination and continued throughout the procedure. (2) In the EW group, 1 g of EMLA cream was applied at the site of injection by the same method and for same duration described in the previous group. But in this group, 2 ml distilled water had been given orally by a sterile syringe 2 min prior to wDPT vaccination, instead of breastfeeding. (3) In the PCW group, 1 g of placebo cream was applied at the site of injection by the same method and for same duration, which was described in the previous group. Placebo cream "Vaseline" was visually and cosmetically identical to EMLA cream, but does not have known analgesic properties. It is a total moisture-nourishing cream, containing soya, glycerin, and vitamin E. Two milliliters of distilled water was also given orally by a sterile syringe 2 min prior to wDPT vaccination as oral placebo.

After randomization and allocation, two persons (AA and JK) would then come in the immunization room. AA administered 0.5 ml of wDPT vaccine by using a 2-ml syringe with a 23-gauge 1-in. needle on the anterolateral aspect of the thigh (left/right) after cleaning the skin with sprit swab. When DPT was given, the baby was made to lie supine in the mother's lap, with the thigh exposed. During the procedure, AA called "in" when she inserted the needle and "out" when she removed the needle. All events were recorded by JK on a digital video camera (model Sony CCD-TRV238E) for a total duration of 3 min from just before needle insertion. The fourth person (AU) analyzed the outcome variables from the video

recording. All the four persons were same throughout the study and performed the same role in all the enrolled babies. AA, JK, and AU were blinded to the pharmacological intervention given to the baby. However, no investigator could be blinded to the intervention of breastfeeding. One person (AA) followed up all the infants for 24 h after vaccination by telephone. Parents were asked to provide a description of any unexpected events at the site of vaccination in infants. In case of any untoward incidence, the baby was examined. He 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 variables

Primary outcome variable

Primary outcome variable was the duration of cry (in seconds) after vaccination. It was defined as the duration of continuous distressed vocalization (cry) after needle insertion to the period of silence of more than 5 s, excluding this 5 s. As video recording was done only for 3 min, the duration of cry was taken as 180 s only for babies who were still crying even after 3 min.

Secondary outcome variable

Secondary outcome variable was the latency of onset of cry and Modified Neonatal Facial Coding Score (MFCS) [28].

Latency of onset of cry 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.

MFCS MFCS was calculated immediately and after 1 and 3 min of needle insertion. This was a composite score obtained from the sum of the following: 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 score was obtained. One observer (AU) was responsible for giving the scores in all the babies after analyzing the video. 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 to that parameter. All outcome variables were recorded from the video recording by one person (AU) only.

In order to avoid confounding by other pain-relieving methods, the following steps were ensured: All enrolled babies had been fed within the last 3 h, but not sooner than 30 min. 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 the baby was sleeping, he was gently awakened; if he was crying, he was soothed to quite wakefulness before the procedure. Nonnutritive sucking was not done during the procedure. All the tests were performed between 10 a.m. and 1 p.m. to avoid diurnal variation in pain response.

Written informed consent was obtained from the parents, and ethical clearance was taken from the ethical committee of the institution.

Sample size

To calculate the average means (standard deviation, SD) of the three groups, we conducted a pilot study of eight babies each. The mean duration of cry was 110, 70, and 150 s in the three groups with a common SD of 60 s. A one-way analysis of variance (ANOVA) would have 90 % power to detect a significant difference in means at 5 % level of significance, when the sample size in each group was 16. Similarly, the latency of cry was 2.3, 2.0, and 1.5 s in the three groups (EB, EW, PCW) with a common SD of 0.8 s. A one-way ANOVA would have 90 % power to detect a significant difference in means at 5 % level of significance, when the sample size in each group was 28. So a sample size of 30 in each group was thought to be adequate to study all the parameters to correct for some dropouts and video-recording error. This was similar to the sample size used in previous studies as well [12, 21].

Statistical analysis

Results were analyzed by Stata 11.0 software. Continuous data with normal distribution were analyzed by one-way ANOVA followed by Bonferroni correction for multiple analyses of data. Nonnormally distributed data were analyzed by Kruskal–Wallis test. Any difference in MFCS over the period of time was calculated by a generalized estimating equation (GEE) model. Categorical data were analyzed by chi-square test.

Observation and results

A total of 111 babies were screened. Twenty-one babies were excluded for various reasons (Fig. 1). A total of 90 babies were randomized in three groups of 30 each. The groups did not differ significantly in baseline characteristics (Table 1).

Outcome variables

Primary outcome (duration of cry)

Median (interquartile range, IQR) was significantly lower in EB group [34.6 (24.1–72.2)s] and EW group [94.2 (46.1–180)s] as compared to PCW group [180.0 (180–180)s] ($p<0.05$) (Fig. 2). The duration of cry was shorter in the babies in EB group by about 50 s when compared to EW

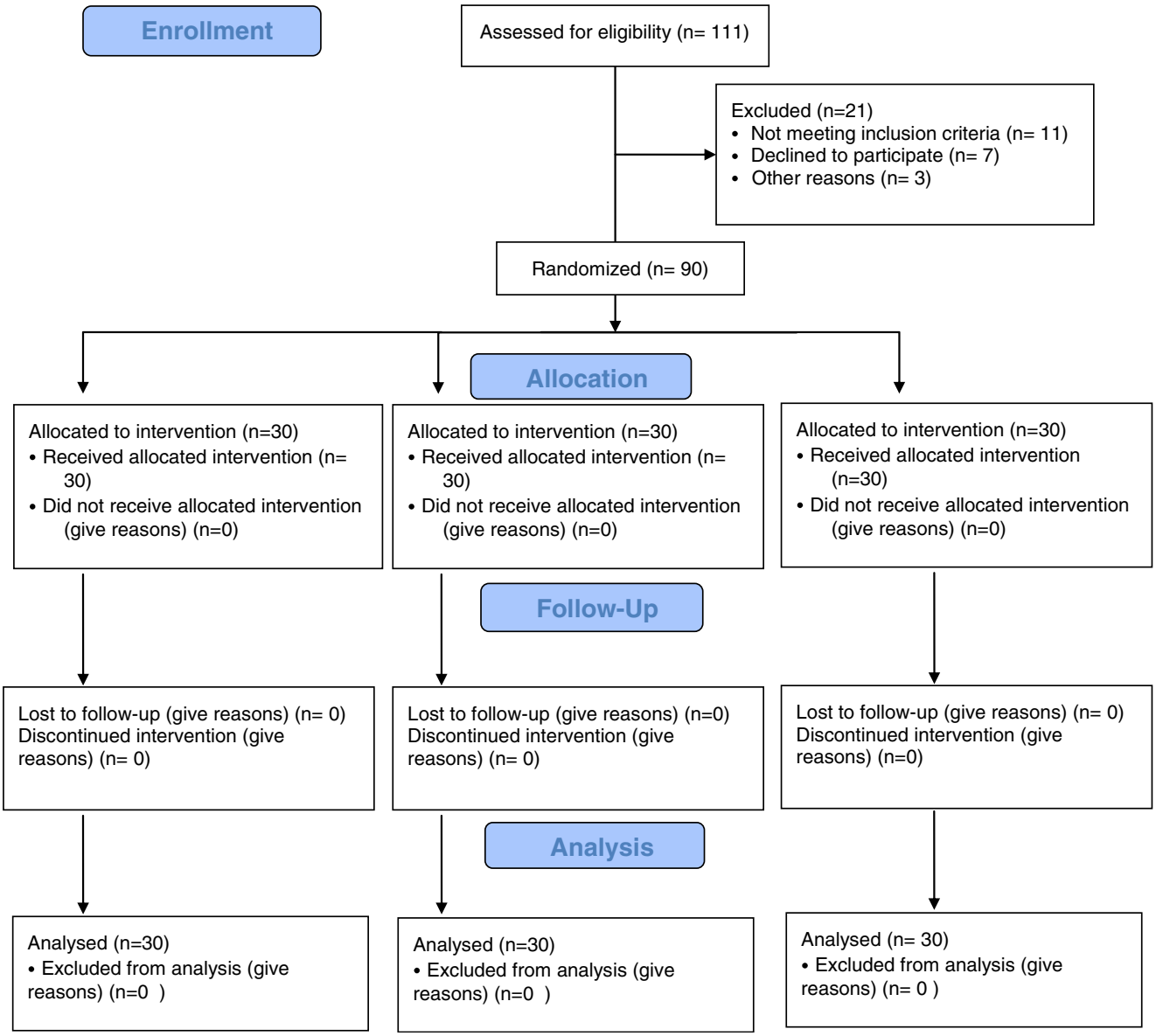

Fig. 1 Consort flow diagram of participants' enrollment

group and by about 100 s ($p<0.05$) when compared to PCW group. In PCW group, 23/30 (76.66 %) babies cried for more than 180 s, as compared to 2/30 (6.66 %) in EB group and 11/30 (36.66 %) in EW group ($p<0.05$) (Fig. 2). Mean (SD) also was significantly lower in EB and EW groups as compared to PCW group ($p<0.05$) (Table 2).

Table 1 Baseline characteristics of babies in the three groups

Parameter	EB group ($n=30$)	EW group ($n=30$)	PCW group ($n=30$)	p value
Sex (male)[a]	16 (53 %)	15 (50 %)	16 (53 %)	>0.05
Age (months)	2.0 (0.54)	2.2 (0.62)	2.2 (0.55)	>0.05
Weight (kg)	4.3 (0.69)	4.5 (0.76)	4.6 (0.75)	>0.05
Height (cm)	57.6 (2.7)	58 (4.3)	57.3 (4.4)	>0.05
Head circumference (cm)	38 (1.8)	37 (1.3)	38.6 (1.5)	>0.05
Time since last feed (min)	40.1 (7.5)	39 (6.2)	42.3 (7.2)	>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 (SD)

[a] Data are reported as number with the corresponding percentage in parentheses

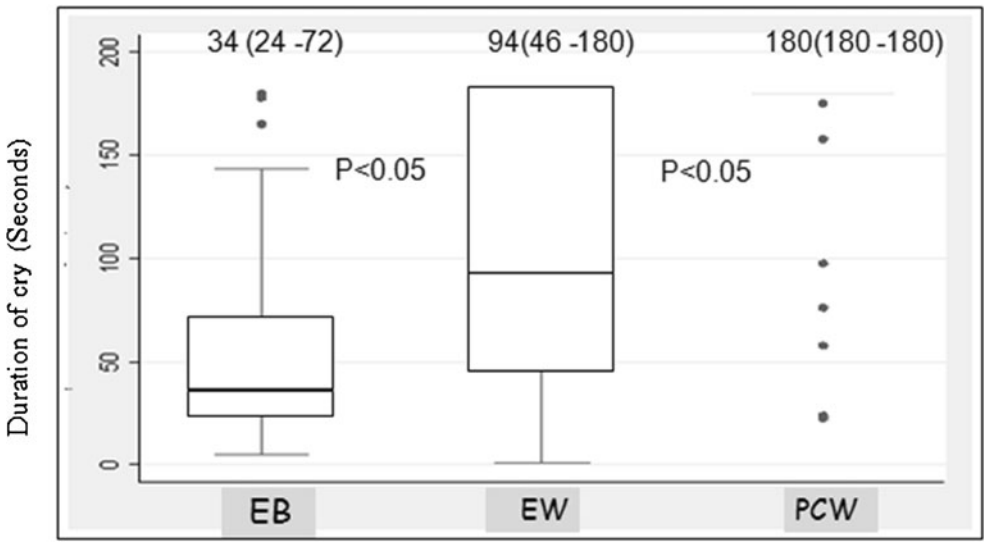

Fig. 2 Box and whisker plot of duration of cry (median, IQR, minimum and maximum range, and outliers)

Secondary outcomes

Latency of onset of cry The mean (SD) of latency of cry in EB, EW, and PCW groups was 2.4 (1.14), 1.9 (0.62), and 1.5 (0.47)s, respectively (Table 2). The latency was significantly more in EB and EW group as compared to PCW group ($p<0.05$).

MFCS Mean (SD) of MFCS of the three groups is given in Table 2. At 1 and 3 min, MFCS was significantly lower in EB group than in EW group, which in turn was lower than that in PCW group ($p<0.05$).

Side effects of EMLA cream were erythema, paleness, swelling, and pruritus. These were observed soon after in 18, 21, and 17 % of babies in EB, EW, and PCW groups, respectively. After 24 h, through a telephone interview, they were present in 5, 8, and 6 % of babies in EB, EW, and PCW groups, respectively ($p<0.05$).

Discussion

Our study demonstrated that babies who were breast-fed, along with the application of topical EMLA cream 60 min prior to DPT vaccination, had significantly shorter duration of cry and lower pain scores at 1 and 3 min after needle insertion, as compared to EMLA alone or no intervention. Young infants react to pain with crying, change in facial expression, and alteration in heart rate, saturation, and sleep wake cycle [6, 16, 25]. Numerous pharmacological interventions have been tried to reduce pain of vaccination and minor procedures. Prior use of topical EMLA has been shown to reduce the pain due to venipuncture [13], lumber puncture [12], and DPT [26, 29] or MMR vaccination [9]. Similar to our study, Eff and Ozer had reported that breastfeeding during wDPT vaccination reduces pain [5]. Previous studies by our group have demonstrated that expressed breast milk [28] or breastfeeding [23], 2 min prior to venipuncture, reduced pain in term infants. Possible reasons for analgesia due to breastfeeding include synergistic action of relaxation and distraction due to skin-to-skin contact, release of opiates and antistress hormone (oxytocin) [7], and lesser release of stress hormone [15]. The mechanism of relaxation and analgesia probably works synergistically [3, 19, 22]. Addition of breastfeeding to topical EMLA almost halved the duration of cry when compared that when EMLA was used alone. During breastfeeding, though only half of the face was visible, facial scores could be interpreted due to symmetrical facial responses [5]. Cochrane review also concluded that if available, breastfeeding or breast milk should be used to alleviate procedural pain in neonates undergoing a single painful procedure compared to placebo, positioning, or no intervention [20]. Biran et al. revealed a higher analgesic effect of a

Table 2 Primary and secondary outcomes measures

Outcomes	EB group (n=30)	EW group (n=30)	PCW group (n=30)	p value
Duration of cry	59.31 (54.17)	109.73 (65.56)	158.37 (48.43)	<0.05
Latency of onset of cry	2.40 (1.14)	1.95 (0.62)	1.50 (0.47)	<0.05
MFCS				
Immediate	5.9 (0.40)	6 (0)	6 (0)	>0.05
After 1 min	2.06 (2.71)	4.23 (2.66)	5.26 (1.83)	<0.05
After 3 min	0.40 (1.52)	1.96 (2.68)	4.13 (2.51)	<0.05

Values are presented as mean (SD)

combination of sucrose and EMLA cream than sucrose alone during venipuncture in these preterm infants [2]. However, there was no previous trial combining the analgesic effect of breastfeeding and EMLA. Our study is the first one to demonstrate that these two already well-documented measures act synergistically when given together. Singh et al. have shown that exclusively breast-fed babies perceive lesser pain during intramuscular injection than partially or non-breast-fed babies, even without any physiological or medical intervention during vaccination [24]. The numbers of exclusively breast-fed babies were in similar proportion in the three groups. One limitation of our study was that it was not possible to "blind" the subjects who were breastfeeding during the IM injection, as it was clearly visible in video recording. We did not keep a group with babies given only exclusively breastfeeding as previous studies have unequivocally documented efficacy of breastfeeding [20, 23]. Also, our objective of evaluating the synergistic effect between breastfeeding and EMLA cream could be reasonably achieved by having the three above-mentioned groups. Lack of physiological parameters of pain assessment (heart rate, respiratory rate, oxygen saturation) could be another limitation. We however avoided it because pulse oximeters often do not give readings in crying and vigorous babies and attaching ECG leads (for heart rate monitoring) to healthy babies in immunization room can be intimidating and stressful for the parents. Previous studies also have also used pure behavioral scales in children [6]. Erythema and swelling associated the use of EMLA and may also be present after wDPT vaccination itself. But no significant adverse events have been reported in previous study.

Conclusion

Prior topical EMLA application, pain reduces due to DPT vaccination in infants of up to 3 months of age. It has a synergistic effect when combined with breastfeeding during vaccination.

What is already known? Measures like expressed breast milk feeding, breastfeeding, and topical EMLA have pain-relieving effects in minor OPD procedures and intramuscular and intravenous injections and DPT vaccination

What this study adds? Prior EMLA application along with concomitant breastfeeding during DPT vaccination provides synergistic relief in pain due to vaccination

Conflict of interest None

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