Interventions to Reduce Pain during Vaccination in Infancy

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Objective To investigate interventions that affect pain reduction during vaccination in infants and children attending a well-child unit.

Study design A consecutive sample of 243 children between age 0 and 48 months receiving their routine vaccinations was randomly assigned to 1 of the study groups. A total of 158 infants under age 6 months were randomly assigned to breast-feeding or no breast-feeding during immunization, and 85 children age 6 to 48 months were randomly assigned to receive 12% sucrose solution, lidocaine-prilocaine cream, or no intervention. All children were evaluated for crying time and pain score by a pediatrician using the Neonatal Infant Pain Scale (NIPS) for those under age 12 months and the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) for those over age 12 months.

Results Breast-feeding in infants under age 6 months and use of sucrose or lidocaine-prilocaine in children age 6 to 48 months significantly reduced crying time and pain scores compared with controls. No difference in outcome was seen between the sucrose and lidocaine-prilocaine treatment groups.

Conclusions Here we expand on previous findings by demonstrating that breast-feeding may have an analgesic effect up to age 6 months and that in older children, both sucrose and lidocaine-prilocaine reduce vaccination pain. *(J Pediatr 2009;154:385-90)*

In the developed world, the most common painful procedure performed in infants is vaccination, a process involving repeated injections in the first 2 years of life.[1] Even young children have a pain memory, causing them to anticipate painful procedures and to react more intensely if they have undergone previous painful procedures with inadequate analgesia.[2-5]

To meet stricter requirements for gentle handling, evaluating various pain- reduction strategies is important.[6] Recent studies have shown that breast-feeding has an analgesic effect during acute, short-lasting, repetitive painful procedures in term newborns.[7-11] To the best of our knowledge, there has been no study investigating the analgesic effect of breast-feeding on pain reduction during minor procedures beyond the newborn period.

Sucrose water (12% to 50%) and other sweet solutions administered just before a procedure have been shown to decrease the pain associated with procedures in neonates.[10-12] It has been suggested that sucrose loses its efficacy by age 4 to 6 months, however.[13]

Topical anesthetics have been shown to reduce the pain of both subcutaneous and intramuscular injections. Lidocaine-prilocaine is safe and does not alter the immunogenicity of vaccines.[14,15] Unfortunately, however, the delayed onset of action of lidocaine-prilocaine cream (~1 hour) limits its applicability during routine vaccinations.

The primary aims of the present study were to investigate the analgesic effect of breast-feeding in infants age 0 to 6 months and to compare the analgesic effects of sucrose solution and lidocaine-prilocaine cream in children 6 to 48 months. The secondary aim was to investigate the possible risk factors associated with higher pain scores, such as age, sex, maternal education, socioeconomic level, previous pain experience, maternal distraction, injection site and technique, needle length, and number of injections.

METHODS

Approval to perform the study was granted by the Ethics Committee of Ankara Training and Research Hospital. The aim, risks, and possible benefits of the study were explained to the mothers, and informed consent was obtained from each.

CHEOPS	Children's Hospital of Eastern Ontario Pain Scale	NIPS	Neonatal Infant Pain Scale
CI	Confidence interval	OR	Odds ratio

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Inclusion Criteria

A total of 250 healthy infants and children receiving their regular vaccinations between age 0 and 48 months attending the well-child unit of the Department of Pediatrics were recruited and randomized for the study. Overall, 243 infants were analyzed. In Turkey, the routine vaccination schedule includes single injections at 0 to 2 weeks, 1 month, 6 months (hepatitis B vaccine), and 12 months (measles-mumps-rubella vaccine) and multiple injections at 2 months (bacillus Calmette-Guérin vaccine, diphtheria-tetanus-pertussis and inactive polio vaccine, and *Hemophilus influenzae* b vaccine), 4 months, 6 months, and 16 to 24 months (diphtheria-tetanus-pertussis, inactivated polio virus vaccine, and *H influenzae* b vaccine). Although pneumococcus, varicella, influenza, and hepatitis A vaccines are not included in routine vaccination schedule, these vaccines can be purchased by the parents and administered according to American Academy of Pediatrics recommendations.

Exclusion Criteria

Infants with intercurrent illness born at less than 37 completed weeks' gestation who were unable to tolerate fluids by mouth, had an allergy to any component of the anesthetic used in the study, or had a diagnosis of cerebral palsy (in whom the response to painful stimuli may be difficult to interpret) were excluded.

Randomization

A consecutive sample of 243 infants and children age 0 to 48 months receiving routine vaccinations were randomly assigned by the first assistant to 1 of the study groups, stratified by age using sealed envelopes. All infants under age 6 months who were exclusively breast-fed were randomly assigned to breast-feeding or no breast-feeding during immunization. Masking of the intervention was not possible. Children age 6 to 48 months were randomly assigned to receive 12% sucrose solution, lidocaine-prilocaine cream, or no intervention (Figure). The subjects were not allowed to receive anything orally (eg, sucrose, water, juice, formula, pacifier) during the procedure. The mothers were not allowed to breast-feed the older infants.

The pediatrician responsible for recording the crying time and pain score was not present during the interventions and was blinded to each subject's allocation except to the breast-feeding group.

Sociodemographic and Clinical Characteristics

The subjects' age and sex were recorded. Participating mothers were asked questions about educational and socioeconomic level. Educational attainment was classified as "no formal schooling: illiterate," "primary education," "secondary education," or "university education." Socioeconomic level was classified according to monthly household income and the official 2004 poverty thresholds of the Turkish Statistical Institute (http://www.tuik.gov.tr). Pain experience during previous vaccination was noted.

Procedures

The mother was seated with the infant or child in her arms. All infants and children were awake during the procedure. Any verbal distraction by the mother during vaccination was recorded. Injection site, injection technique, needle length, and injection number also were recorded on prepared forms by the research assistant.

Breast-feeding group. The study was initiated when the infant maintained a good latch, as determined by a large amount of areola in the mouth, flanged lips, and active jaw movement. Achieving this generally took 30 to 60 seconds. The mother was asked to continue breast-feeding the infant during the procedure. Four infants failed to complete the study because they did not resume feeding.

Sucrose group. The mother was instructed to hold the infants across her lap in a cross-cradle position while ensuring that the infant's arms or thighs were accessible throughout the procedure. Sucrose solution (12%) was placed in oral syringes by a pharmacist. Two minutes before the injection, the sucrose-allocated group received 2 mL of 12% sucrose solution orally, as described by Allen et al.[15]

Lidocaine-prilocaine group. One gram of lidocaine-prilocaine was applied to the vaccination area (lateral region of the right thigh or deltoid) 1 hour before vaccination.[16] The cream was covered with an occlusive dressing (Tegaderm; 3M, Minneapolis, Minnesota) for 1 hour. Vaccinations and related interventions were performed in a separate warm and quiet room. All vaccinations were performed by the same experienced nurse.

Outcome Measures

Crying time. Crying from the moment of needle insertion until all crying activity had ceased was recorded by the pediatrician.

Pain responses. Two pain scales were used to assess vaccination pain on an objective scale[17,18]:

- Neonatal Infant Pain Scale (NIPS). Pain responses were assessed with the NIPS in infants under age 12 months.[19] The tool consists of 6 categories (facial expression, cry, breathing pattern, arm and leg movements, state of arousal), scored dichotomously, with 2 descriptors in each category. The NIPS was translated into Turkish by Akdovan, and the validity and reliability of the scale was confirmed by the same author in a study on 180 infants.[19-21] NIPS forms were completed by the pediatrician. A score above 3 indicates pain; the maximum score is 7.
- Children's Hospital of Eastern Ontario Pain Scale (CHEOPS). This scale, developed in 1985 by McGrath et al,[22] is used for

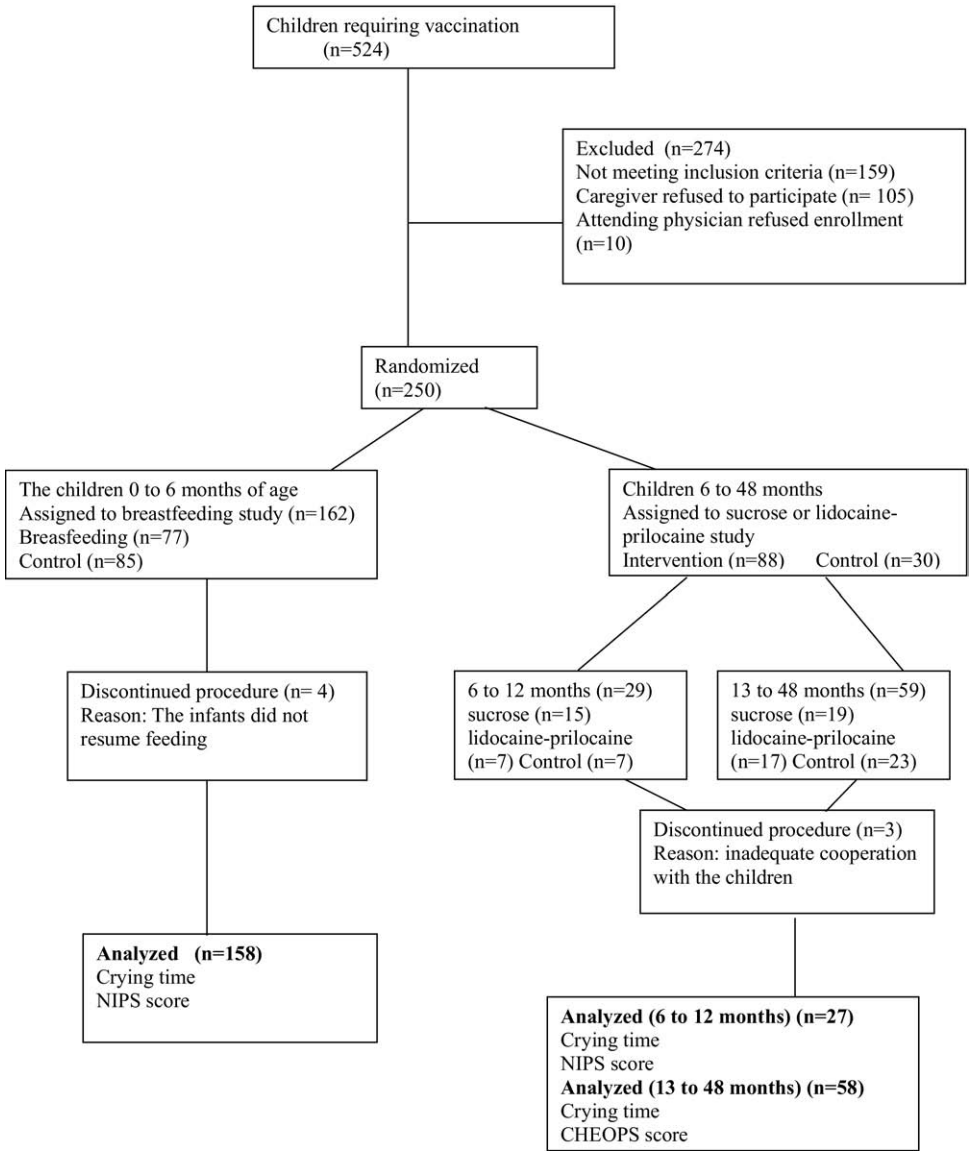

Figure. Randomization, follow-up, and data analysis.

children age 1 to 7 years.[22-24] The scale includes 6 categories of pain behavior: cry, facial expression, verbal, torso, touch, and legs. The CHEOPS forms were completed by the same pediatrician. A score above 4 indicates pain; the maximum score is 13.

Data Analysis

SPSS version 15.0 (SPSS Inc, Chicago, Illinois) was used to perform all statistical analyses. We obtained frequency distributions and cross-tabulations of variables of interest. Because the groups did not exhibit normal distribution according to the Kolmogorov-Smirnov test, they were analyzed using the Mann-Whitney U test, Kruskal-Wallis test, or χ^2 test as appropriate. Multivariate analysis was used to define the factors associated with higher pain scores. A P value $<.05$ (2-tailed tests) was considered to indicate statistical significance.

RESULTS

Demographic and clinical characteristics of the study subjects are summarized in Table I. A total of 243 children were enrolled, of whom 158 were younger than 6 months, 142 (58.4%) were male, and 101 (41.6%) were female. Of the 158 infants under age 6 months, 73 (46%) were breast-fed during vaccination. Crying time and NIPS score were significantly higher in the control group (Table II).

In the infants age 6 to 12 months, crying time and NIPS score were significantly higher in the control group compared with the sucrose and lidocaine-prilocaine intervention groups. A separate analysis revealed no statistically significant difference between the sucrose and lidocaine-prilocaine groups (Table II).

Of the 58 children age 13 to 48 months, 19 received sucrose, 16 received lidocaine-prilocaine, and 23 received no intervention. The CHEOPS scale was used to assess pain. Cry-

Table I. Demographic and clinical characteristics of the study subjects (n = 243)

Age, months, median (range)	3 (0-48)
Sex, n (%)	
Female	101 (41.8)
Male	142 (58.4)
Maternal education, n (%)	
Illiterate	5 (2.1)
Primary education	164 (67.4)
Secondary education	59 (24.3)
University	15 (6.2)
Socioeconomic level, n (%)	
Low	122 (50.2)
Medium	81 (33.3)
High	40 (18.5)
Previous pain experience, n (%)	
Yes	189 (77.8)
No	54 (22.2)
Maternal distraction performed, n (%)	
Yes	118 (48.6)
No	125 (51.4)
Injection site, n (%)	
Vastus lateralis	214 (88.1)
Deltoid	29 (11.9)
Needle length, n (%)	
16 mm	96 (39.5)
25 mm	147 (60.5)
Injection technique, n (%)	
Intramuscular	203 (83.5)
Subcutaneous	40 (16.5)
Injection, n (%)	
Single	175 (72.0)
Multiple	68 (28.0)

ing time and CHEOPS score were higher in the control group than in the sucrose and lidocaine-prilocaine groups ($P = .002$ and .001, respectively). A separate analysis found no significant difference between the sucrose and lidocaine-prilocaine groups.

In 108 of the 243 infants (44.4%), pain scores were greater than the cutoff values (>3 for NIPS and >4 for CHEOPS). Multivariate analysis was used to define the factors associated with higher pain scores during vaccination. Age, sex, maternal education, socioeconomic level, injection site and technique, needle length, and having previous pain experience were seen to have no effect on pain score; however, lack of maternal distraction was associated with higher pain scores during vaccination ($P = .02$; odds ratio [OR] = 1.8; 95% confidence interval [CI] = 1.0 to 3.0) (Table III).

DISCUSSION

The pain experienced by infants and young children often is underestimated and undertreated.[25,26] This prospective controlled study has demonstrated effective pain reduction during routine vaccination from breast-feeding in infants up to age 6 months and from administration of 12% sucrose solution in children age 6 to 48 months. In the latter group, both sucrose and lidocaine-prilocaine provided better pain

Table II. Total duration of crying time and NIPS score in infants under age 12 months according to pain reduction method

	Age 0 to 6 months (n = 158)			Age 6 to 12 months (n = 27)			
	Breast-feeding (n = 73)	Control (n = 85)	P value	Sucrose (n = 13)	Lidocaine-prilocaine (n = 7)	Control (n = 7)	P value
Crying time, seconds, median (range)	20.0 (0-120)	150.0 (0-180)	.001	40.0 (0-130)	30.0 (0-45)	120.0 (75-180)	.001 Sucrose-lidocaine-prilocaine = .53 Sucrose control = .001 Lidocaine-prilocaine control = .001
NIPS score, median (range)	3.0 (0-6)	6.0 (0-7)	.001	3.0 (0-7)	2.0 (1-5)	6 (5-7)	.001 Sucrose-lidocaine-prilocaine = .43 Sucrose control = .001 Lidocaine-prilocaine control = .001
NIPS score > 3%	12 (16.4)	64 (75.3)	.001	4 (30.8)	1 (14.3)	7 (100.0)	.01

Table III. Risk factors associated with higher pain score during vaccination

Variables	Pain score category		*P* value	OR	95% CI
	Higher (n =108)	Lower (n =135)			
Age, months, median (range)	3.0 (0-48)	3.0 (0-48)	.15	0.9	0.9-1.0
Sex, n (%)					
Female	53 (49.1)	48 (35.6)			
Male	55 (50.9)	87 (64.4)	.42	1.2	0.7-2.1
Mother's education, n (%)					
Illiterate	3 (2.8)	2 (1.5)			
Primary school	76 (70.4)	88 (65.2)			
High school	21 (19.4)	38 (28.1)			
University	8 (7.4)	7 (5.2)	.68	3.7	0.3-37.5
Socioeconomic level, n (%)					
Low	52 (48.1)	70 (51.9)			
Medium	36 (33.3)	45 (33.3)			
High	20 (18.5)	20 (14.8)	.16	1.6	0.8-3.5
Previous pain experience, n (%)					
Yes	86 (79.6)	103 (76.3)			
No	22 (20.4)	32 (23.7)	.59	0.8	0.3-1.7
Maternal distraction performed, n (%)					
Yes	58 (53.7)	60 (44.4)			
No	50 (46.3)	75 (55.6)	.02	1.8	1.0-3.0
Injection site, n (%)					
Vastus lateralis	90 (83.3)	124 (91.9)			
Deltoid	18 (16.7)	11 (8.1)	.20	2.0	0.6-6.4
Needle length, n (%)					
16 mm	38 (35.2)	58 (43.0)			
25 mm	70 (64.8)	77 (57.0)	.10	0.5	0.2-1.1
Injection technique, n (%)					
Intramuscular	89 (82.4)	114 (84.4)			
Subcutaneous	19 (17.6)	21 (15.6)	.12	1.9	0.8-4.5
Injection number, n (%)					
Single	67 (62.0)	108 (80.0)			
Multiple	41 (38.0)	27 (20.0)	.44	1.2	0.6-2.4

reduction than no intervention. The lack of statistical difference between the 2 intervention groups does not necessarily imply similarity, however. Moreover, the sucrose group cried for about 30% longer and had a higher proportion of children with elevated pain scores. The study group had a male preponderance (58.4%), possibly because in Turkey, males are more likely than females to be brought for vaccination.

Some recent studies have demonstrated analgesic effects of breast-feeding during acute, short-lasting, repetitive painful procedures in term newborns.[8,27] Phillips et al[9] suggested that the mother holding the infant during such procedures may be of benefit. Some other studies have compared the analgesic effects of sucrose and breast-feeding; for example, Carbajal et al[10] suggested that sucrose administration and pacifier use together showed a trend toward lower pain scores compared with pacifier use alone. Gradin et al[11] reported an association between combined oral glucose administration and breast-feeding with the lowest pain scores and significantly shorter duration of crying. Örs et al[28] found that 25% sucrose solution had superior pain-reducing effects to breast milk. Similarly, Skogsdal et al[29] reported that strong sweet solutions, such as sucrose and 30% glucose, alleviated pain successfully, whereas breast milk did not. In the present study, we used breast-feeding for pain reduction in infants up to age 6 months. Although we did not compare breast-feeding with nonnutritive sucking and sucrose, we found that breast-feeding reduced vaccination-related pain in infants up to age 6 months.

The use of sucrose analgesia for immunization-related pain has been studied previously.[15] Recently, Hatfield et al[30] reported that administration of 2 mL of 24% oral sucrose solution 2 minutes before routine vaccination reduced pain in infants age 2 and 4 months. Barr et al[31] suggested that sucrose loses its efficacy by age 4 to 6 months; however, in the present study, we used sucrose for pain reduction in children age 6 to 48 months and found that sucrose was effective beyond age 6 months.

Topical anesthetics are known to reduce the pain of both subcutaneous and intramuscular injections. Lidocaine-prilocaine cream is the most widely studied topical anesthetic for use during vaccinations.[32-34] In our study, we did not combine lidocaine-prilocaine with glucose or sucrose. In children age 6 to 48 months, we found that both lidocaine-prilocaine and sucrose were more effective in reducing pain compared with no intervention.

It has been suggested that parental behavior during vaccination significantly influences the amount of pain and distress that children experience. One study found that children whose mothers provided verbal distraction exhibited less distress and shorter crying time than other children.[35] Those findings concur with our results, although the confidence interval for our study includes 1.0.

Various technical factors associated with the injection itself have been examined to determine their impact on injection pain. An association between longer needle length and less pain has been suggested;[36,37] however, we found no associations among injection technique, needle length, and higher pain scores. This may be related to the small number of subjects in our study.

Our study has several limitations. First, our sample size was small, especially regarding older children. Masking of the intervention was not possible in the breast-feeding group. Given considerations of expense and time, topical anesthetic use should be reserved for children who are phobic or particularly anxious about a pending injection. Sucrose, which is inexpensive and easily administered by individuals without professional training, may be preferred and used during immunization in young children.

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